

Parental experiences of prenatal whole exome sequencing (WES) in cases of ultrasound diagnosed fetal structural anomaly

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1 Parental Experiences of Prenatal Whole Exome Sequencing (WES) in Cases of
2 Ultrasound Diagnosed Fetal Structural Anomaly

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26 those of the Department of Health or Wellcome Trust.

27 **Conflict of interest**

28 The authors are unaware of any potential conflict of interest.

29 **What is already known about this topic?**

- 30 • Prenatal WES for genetic diagnosis is possible, but little is known regarding
31 parental experiences of prenatal sequencing

32 **What does this study add?**

- 33 • Parents require specific information to help them decide whether to undergo
34 WES for prenatal diagnosis
- 35 • Appropriate counselling is essential for informed consent
- 36 • Parents require explanation about what WES might identify, and how and
37 when findings are returned

38 **Abstract**

39 **Objective**

40 To explore parental experiences of WES for prenatal diagnosis, and ascertain what
41 influenced their decision-making to undergo testing.

42 **Method**

43 Twelve women comprised a purposeful sample in a series of semi-structured
44 interviews. All had received a fetal anomaly diagnosis on ultrasound. A topic guide
45 was used, and transcripts were thematically analysed to elicit key themes.

46 **Results**

47 Five main themes (parental experiences of prenatal WES, need for information,
48 consent/reasons for prenatal WES, sources of support for prenatal WES, and return
49 of WES findings to families) emerged, some with multiple sub-themes.

50 **Conclusions**

51 Parents desired as much information as possible and appreciated information being
52 repeated, and provided in various formats. Many struggled with clinical uncertainty
53 relating to the cause and prognosis following a fetal anomaly diagnosis, and found it
54 difficult to balance the risks of invasive testing against their need for more definitive
55 information. Parents trusted their clinicians and valued their support with decisions
56 in pregnancy. Testing was sometimes pursued to reassure parents that their baby
57 was 'normal' rather than to confirm an underlying genetic problem. Parents were
58 motivated to undergo WES for personal and altruistic reasons but disliked waiting
59 times for results, and were uncertain about what findings might be returned.

60 **Key words:** Prenatal; whole exome sequencing; parents views

61 **Introduction**

62 Structural anomalies are diagnosed by ultrasound in up to 3% of pregnancies^[1].
63 Fetal outcome is variable depending on the type of abnormalities identified, and the
64 underlying genetic aetiology^[2]. Determining the potential cause of fetal anomalies
65 enables a more accurate diagnosis and provides prognostic information relating to

66 the pregnancy and the likely risk of recurrence^[2]. Genetic testing is available for
67 parents following the identification of a fetal anomaly and recent advances in
68 molecular genetics are enabling increasingly detailed prenatal genetic
69 investigation^[3]. Prenatal genetic diagnosis is of significant value to parents and can
70 assist with prospective planning for optimal perinatal management^[4]. It may also
71 provide a means to inform parental decisions regarding the continuation or
72 termination of an affected pregnancy. **Currently in the UK prenatal genetic testing**
73 **involves increasingly routine QF-PCR (Quantitative Fluorescence-Polymerase Chain**
74 **Reaction) and CMA (Chromosomal Microarray) to identify chromosomal differences**
75 **and variations in copy number (CNVs). Targeted genetic sequencing of exonic**
76 **regions is used to detect single nucleotide variants (SNVs) associated with various**
77 **single gene disorders, but this modality has limited potential to identify CNVs.**
78 **Whole genome sequencing (WGS) approaches are beginning to be used and have**
79 **the ability to detect CNVs.**

80 ***Next-Generation Sequencing (NGS) and the Prenatal Application of Whole***
81 ***Exome Sequencing (WES) Approaches***

82 NGS applications are broadening the scope of prenatal diagnosis to identify the
83 genetic aetiology of sporadic and inherited disease^[5] and are revolutionising current
84 practice in prenatal diagnostics^[6]. Sequencing analysis of trio (fetal and biparental)
85 DNA can identify genetic alterations that are potentially causative of fetal
86 abnormalities, but this technology is only recently being evaluated within prenatal
87 medicine. WES captures the majority of regions that encode proteins to identify
88 SNVs and small insertions and deletions (indels)^[5]. As a technique it has proved
89 useful to the diagnosis of known genetic disease and to the discovery of novel

90 disorder genes,^[7] and is increasingly being used to diagnose rare Mendelian
91 conditions (when standard tests are uninformative)^[8]. The use of WES in prenatal
92 diagnosis is potentially advantageous as its accuracy enables personalised care,
93 prospective risk assessment and preventative fertility treatment, reproductive genetic
94 counselling and family planning^[9]. As such, if a definitive diagnosis is made this
95 testing may aid understanding of aetiology, potential co-morbidities and risk of
96 recurrence. However, NGS, in the prenatal setting, presents potential challenges
97 around the interpretation of results, especially if positive results are not thought to be
98 'causative' or are of unknown significance. The detection of these secondary and/or
99 incidental findings (ICFs), may have significant and morbid emotional effects on the
100 parents and also impact negatively on parental decision making in the prenatal
101 setting.

102 Several studies involving WES in patients with Mendelian disease have
103 demonstrated a diagnostic yield in the order of 25%^[10-11]. This indicates that WES is
104 complementary to conventional prenatal diagnostic techniques^[12]. Research relating
105 to the use of genetic sequencing for prenatal diagnosis in on-going pregnancy is
106 limited,^[4] however, the feasibility of WES in prenatal diagnostics has been
107 demonstrated in small case series^[3,12,13]. Survey data involving 186 expectant
108 parents in the USA demonstrated that 83% thought that prenatal WES should be
109 offered,^[14] and research into the views of fifteen women with non-continuing
110 anomalous pregnancies found that they had high hopes and expectations of WES,
111 despite testing enabling a diagnosis in only 1 in 3 (30% of cases)^[15].

112 Successful implementation of WES for prenatal diagnosis would require rigorous
113 health economic assessment, and would be dependent upon the development of

114 rapid analytical and interpretation pipelines^[12]. Sequencing findings would need to
115 be available within a timeframe that would assist parents to make informed decisions
116 relating to the affected pregnancy, and this will only be possible when the knowledge
117 base relating to the genetic causes of prenatal structural anomalies is significantly
118 developed^[12]. The challenge of prenatal WES will be the integration of sequencing
119 analysis into prenatal diagnostics as part of a responsible and ethical framework for
120 clinical practice^[2]. Currently, the PAGE consortium project funded by the Department
121 of Health/Wellcome Trust is prospectively recruiting parent/fetus trios across the UK
122 to investigate the prenatal use of WES as a diagnostic tool in structurally abnormal
123 fetuses^[16]. The study will analyse ~1000 trio whole exomes with the aim to elucidate
124 the relative contribution of different forms of genetic variation to prenatal structural
125 anomalies.

126 As the use of WES increases, and transfers from the research setting to routine
127 care, it will be important to ensure a streamlined approach to the integration of
128 genomic analysis to existing prenatal care pathways. This transition will require an
129 understanding of parental acceptability and expectations around sequencing
130 analysis for prenatal diagnosis following discussion with parents who have personal
131 experience of this type of genetic testing in pregnancy. These parents will provide a
132 unique perspective on their experiences as it is important to ensure that this
133 technology is translated into clinical care because parents consider it to be of value.
134 The views of parents who have undergone genetic sequencing for prenatal diagnosis
135 have not been formally explored using qualitative interview methodology. The aim of
136 this research was to gain insight into the experience of parents who have undergone
137 prenatal WES following a fetal anomaly diagnosis, to understand more about what

138 influenced their decision-making to have testing, and elicit their beliefs around how
139 they perceived WES to be of potential benefit. Qualitative methods allow for
140 exploration of parental experiences, beliefs and feelings around the use of prenatal
141 WES in a way that quantitative methodology cannot. It is important to understand
142 parental views around prenatal sequencing to inform the routine use of these
143 technologies in the future.

144 **Method**

145 A purposeful sample^[17] (i.e. parents who had undergone WES for prenatal diagnosis
146 following enrolment in the PAGE Study^[16]) was selected to participate in this
147 research. All parents had received focussed pre-test counselling for approximately
148 one hour from a fetal medicine specialist regarding standard invasive prenatal testing
149 options (QF-PCR and CMA), non-invasive prenatal testing (NIPT) for common
150 aneuploidy, and WES as part of the PAGE Study. All were informed prior to testing
151 that trio analysis (biparental/fetus) would be performed and that results would not be
152 available within the timeframe of their pregnancy. It was also explained that only
153 pathological findings considered to have contributed to the fetal phenotype would be
154 returned, and that no uncertain, secondary or incidental information would be
155 reported. They were also told that WES could potentially detect up to 10% more
156 causes for fetal structural anomalies above standard testing based on existing
157 evidence. Fifteen women were approached at random by EQJ (research midwife)
158 during their appointments at the Birmingham Women's Hospital Fetal Medicine
159 Centre and asked to participate in an interview, three of whom declined without
160 giving a reason, thus the study sample composed twelve women (Figure 1). It was
161 anticipated that if data saturation was not reached after twelve interviews then more

162 interviews would continue until data saturation was achieved. Interviews were
163 undertaken either at the hospital or at home depending on parental preference. A
164 topic guide was used to guide questioning, and interviews were carried out by EQJ
165 with each interview lasting approximately 30 to 45 minutes. Development of the
166 topic guide was informed by related focus group research with stakeholders
167 undertaken by EQJ and others^[18]. Women were interviewed alone, or with their
168 partner/or other close family member. All women spoke English although this was
169 not a criterion for inclusion. **The timing of interviews varied, but all were carried out**
170 **within two weeks of parents giving consent for WES.** Issues explored with parents
171 included their personal experience of prenatal genetic testing and diagnosis, and
172 what they remembered and understood regarding WES. Parents were asked about
173 their expectations and concerns relating to prenatal genetic sequencing, and about
174 the factors that influenced them to undergo testing, including the information they
175 required to inform their decision. Interviews were digitally recorded and transcribed.
176 National Research Ethics Service approval to undertake this study was granted by
177 West Midlands - South Birmingham Committee (REC Reference 14/WM/0150).

178 **Analysis**

179 Analysis of the interview data followed a standard thematic approach^[19]. Transcripts
180 were read by EQJ to enable familiarisation. Using an inductive process^[20] the
181 transcripts were then coded for similarities and differences in content to develop a
182 coding frame. Encompassing key themes with underpinning sub-themes were
183 produced by combining the identified codes. Two transcripts were independently
184 read by SCH (clinical co-facilitator for aforementioned focus groups and interview
185 design) who similarly used thematic analysis to elicit themes^[19]. The coding frame

186 developed by EQJ was shared with SCH and was subsequently modified. The
187 coding frame and agreed themes were shared with SMG (medical sociologist). Two
188 further transcripts were analysed by SMG using the established coding frame.
189 Further amendments to the coding frame were not thought necessary as a result of
190 this analysis. All three researchers met to reach a consensus that the themes
191 identified were indeed reflective of the accounts provided. A rapid analysis of the
192 interview transcripts was then undertaken by EQJ to ensure completeness and
193 assess for data saturation^[19]. A consensus decision by the three researchers was
194 made that data saturation had occurred and that no further interviews were required.

195 **Results**

196 Participants were diverse with regard to age, ethnicity, parity and gestation, and had
197 varying diagnoses of both isolated and multiple fetal structural anomalies (Figure 1).
198 Women were aged between 21 and 38, and identified themselves as Caucasian,
199 Black African or Asian, with Caucasian women comprising 75% of the sample. Of
200 the 12 women interviewed 7 (58%) were multiparous and gestational ages ranged
201 from 12 to 38 weeks. There was an equal split between isolated and multiple
202 structural abnormalities and the prognosis for fetuses were variable and sometimes
203 uncertain.

204 Five main themes emerged some with multiple sub-themes (Figure 2).

205 **Theme One: Parental experiences of prenatal WES**

206 Parents sometimes struggled to balance the risks of invasive testing against the
207 perceived benefit of receiving a genetic diagnosis, particularly if there was
208 uncertainty relating to the ultrasound features and the prognosis for the baby (this

209 was especially true if there was a previous history of miscarriage and any associated
210 traumatic memories)

211 *“It was more the risk factor because I had a miscarriage last year and it was*
212 *really horrible so we didn’t want to go through that again, especially as I was*
213 *well over 20 weeks and into my second trimester and the baby was fully*
214 *formed, so that was quite worrying but it wasn’t so much for the results”*

215 *(Interview 4 – Mother)*

216 Parents felt shocked when first told that their baby had a congenital difference, but
217 this initial shock was often replaced with on-going anxiety. Some said it felt as
218 though a ‘heavy weight’ had been placed upon them, and found the experience to be
219 extremely scary. Parents appeared to worry more about the uncertain prognosis for
220 the baby and less about the genetic findings that testing might identify. Many
221 remembered feeling overwhelmed by the different tests available, and felt that their
222 worries and concerns were compounded because they had so much to think about
223 at the time:

224 *“It was scary to be honest with you, all the different tests and constant worry.*
225 *It was worrying because we didn’t know what she (baby) would look like or*
226 *anything like that” (Interview 2 – Father)*

227 Self-blame that they had done something to have caused the fetal anomaly was a
228 common parental concern, thus a desire for reassurance that this was not the case
229 was reported. All parents described that they trusted their clinicians and valued
230 receiving their clear explanations. Parents described that they were assisted in their
231 decision-making when they felt supported by clinicians, and believed that any

232 prenatal testing options discussed by the consultant overseeing their care would be
233 relevant and useful which reassured them:

234 *“We thought that it would give us some reassurance and help us plan and*
235 *prepare for the future” (Interview 4 – Father)*

236 Some parents described how they tried to remain hopeful for a good pregnancy
237 outcome, but also felt that they would love the baby regardless of any disability they
238 may have. Some remembered consciously blocking out their concerns in an attempt
239 to keep positive, believing that searching out more information would only serve to
240 exacerbate their worry. When faced with various options, parents felt that they could
241 make difficult decisions if they were not pressurised and were given enough time:

242 *“I think we’ve tried to blank quite a lot of it because we don’t want to be*
243 *negative. When she is here we will cross that path won’t we?” (Interview 2 –*
244 *Mother)*

245 **Theme Two: Need for information**

246 A desire for information to understand more about the anomaly affecting their baby
247 and the different testing and treatment options available was universally reported by
248 parents. Parents needed to ask lots of questions of their clinicians as they tried to
249 balance the pros and cons of testing:

250 *“More information is all good because it helps us understand whatever it is.*
251 *You can prepare yourself and your family and do what you possibly can with*
252 *the information that you are given” (Interview 1 – Father)*

253 A need for repetition of complex information was also evident as parents found it
254 difficult to fully understand everything that they were told at the initial consultation.
255 Discussion and explanation on more than one occasion was found to be helpful, and
256 parents appreciated receiving clinical details in written format relating to the specific
257 anomalies identified:

258 *“Some things you don’t understand, some of the things the doctor says”*

259 *(Interview 2 – Mother)*

260 *“But when they break it down into smaller (pieces), all these big words like,*
261 *and obviously we don’t know what they mean, but they do break it down”*

262 *(Interview 2 – Father)*

263 **Theme Three: Consent and reasons for prenatal WES**

264 Desiring more information and a wish to rule out as much as possible was a key
265 motivator for parents to undergo prenatal testing. Parents perceived WES as a more
266 detailed assessment to find out additional genetic causes for the anomalies affecting
267 their baby that are not tested for routinely. They considered more information to be
268 the best thing for parents and the baby and this was often the main reason for
269 testing:

270 *“It was going to test for more than everything else, and if there was anything*
271 *rare that it is more likely to pick that up, and he explained that it will take much*
272 *longer” (Interview 10 – Mother)*

273 Parents were aware that testing involved looking for differences and similarities
274 between their individual DNA and the DNA of their baby. It was understood that the
275 testing would not benefit the current pregnancy (because results would not be

276 reported back within the timeframe of pregnancy), but thought that it may be helpful
277 for the baby when older, or if it could provide information for future pregnancy
278 planning:

279 *“It was to try and work out if there is anything between us (parents) that has*
280 *caused the anomalies. I do not know whether it searches for one or both or*
281 *whatever, but just that it is trying to find out if there is anything that is within*
282 *either of us that has made these things happen in the baby” (Interview 3 –*
283 *Mother)*

284 Parents were sometimes uncertain about what was actually being tested for or ruled
285 out and would have appreciated hearing about some example conditions. Most felt
286 that it was better to know about any genetic causes and hoped that the testing would
287 provide answers which would be reported back to them:

288 *“I would like to know about what other things they test for because I asked*
289 *them and they said they would test for over 200 things but I would have liked*
290 *examples because that was still worrying me” (Interview 5 – Mother)*

291 Parents described their decision to have prenatal WES as an opportunity to help
292 others in the future. Altruistic motivations involved feeling that it was important to
293 gather more information on the genetic causes of fetal anomalies, and viewed their
294 participation as a means to contribute to research and the progression of medical
295 knowledge:

296 *“I was kind of contributing to something really, to help others in the future. It is*
297 *the only way you are going to learn and evolve in the medical field. If you can*

298 *achieve anything with it then I would be more than happy” (Interview 7 –*
299 *Mother)*

300 **Theme Four: Sources of support for prenatal WES**

301 Electronic and written sources of support were helpful to parents when faced with the
302 decision of whether to undergo prenatal sequencing. Many opted to avoid the
303 internet due to a perceived risk of inaccurate information. Parents felt that some
304 internet sources showed the extremes of disease and were not always relevant.
305 Some accessed NHS websites and Wikipedia feeling that these were more
306 trustworthy sources. Information leaflets on specific conditions were generally found
307 to be helpful:

308 *“We got advice before we came here as well to steer clear of the internet*
309 *because obviously you get a lot of misinformation, so I kind of took that to*
310 *heart as it sounded quite sensible so I have not really been googling”*
311 *(Interview 1 – Father)*

312 Interactive sources of support were reported to be helpful and parents valued being
313 able to ask questions directly. One couple described that they would have liked to
314 speak to other parents with similar experiences, suggesting that a workshop where
315 they could find out more information and ask questions could be a forum for this:

316 *“Maybe a workshop held by the hospital or midwife that is solely dedicated to*
317 *this as part of their job, where they would have all the knowledge and can*
318 *educate families, and where parents can come together and share their*
319 *experiences” (Interview 4 – Father)*

320 **Theme Five: Return of prenatal WES findings to families**

321 Presently, the prenatal WES 'clinical pipeline' within the PAGE Study^[16] takes up to
322 twelve months. The delay in receiving results was felt by some parents to have
323 prolonged their worry and anxiety. Parents still wished to have WES even though
324 they knew that there would be a significant wait for results believing that they would
325 still rather know than not know about any relevant genetic findings. Many described
326 that having this information eventually would help their understanding and better
327 equip them to cope and prepare for any challenges ahead. Some felt that more
328 information in time relating to the risk of recurrence was worth waiting for and would
329 possibly assist them with future pregnancy planning:

330 *"That was what I hated, just waiting (for results)" (Interview 5 – Mother)*

331 Some parents were uncertain regarding the process by which results would be
332 returned and would have appreciated having this better explained to them. Some
333 parents preferred to return to the hospital and have the results explained by familiar
334 clinicians face-to-face. All were happy for their information to be stored and shared
335 with other clinicians and researchers involved in prenatal diagnosis, and although
336 some said that they preferred their personal information to be anonymised, others
337 were less concerned about protecting their identity:

338 *"If there was anything (genetic results) we would like to come back here*
339 *(hospital) and sit down and discuss it face-to-face with you guys (medical*
340 *team) because we are comfortable with you" (Interview 1 – Mother)*

341 **Conclusions**

342 This is the first qualitative interview study exploring parental experiences of WES for
343 prenatal diagnosis. The findings are important because they are novel in this context

344 and contribute to a limited body of evidence relating to parental experiences of
345 prenatal sequencing in structurally abnormal fetuses. Given the potential for NGS
346 techniques to detect genetic alterations that are causative of various developmental
347 fetal anomalies, it is likely that prenatal sequencing will be integrated into existing
348 prenatal care pathways in the foreseeable future. Transition from the research
349 setting to the clinic will require an assessment of the acceptability of prenatal
350 sequencing for genetic diagnosis to evaluate if testing is desirable to parents. This
351 research has highlighted the views of parents who have undergone WES for prenatal
352 diagnosis, and provided insight in to their decision-making to proceed with testing,
353 and what they perceived the potential benefits of WES to be. Facilitating appropriate
354 consent for testing was highlighted by parents as extremely important, who felt that
355 they needed clearer information regarding what WES might identify, and what, when
356 and how results would be returned. If WES is to be routinely available for prenatal
357 diagnosis this will require the development of national and international guidance
358 that encompass the consent procedure, as well as the option for parents to opt in or
359 out of receiving information which is not directly related to the prenatal findings (i.e.
360 the primary indication for testing) both for the unborn baby and for themselves^[13].
361 Inevitably, prenatal WES and the interpretation of results will become more rapid and
362 clinical usefulness will be significantly improved. Likewise, contribution of parental
363 views around prenatal WES will assist with streamlining the clinical use of the
364 technology for diagnostic purposes. However, CMA research indicates that variants
365 of uncertain significance (VUS) may continue, in a small number of cases, to have
366 morbid emotional consequences^[21,22]. The need for public debate around the use
367 and potential benefits, as well as the drawbacks of prenatal genetic diagnosis is

368 clear, to facilitate the general acceptance and integration of sequencing techniques
369 into routine prenatal care^[23].

370 **Limitations**

371 It is acknowledged that the views expressed by some parents (such as the need for
372 more information to balance risks, feelings of self-blame, and consciously blocking
373 out concerns to remain positive), are likely to be applicable to any couple whose
374 baby has ultrasonographically detected fetal anomalies irrespective of whether they
375 decide to undergo prenatal testing (including WES). As such, these particular
376 findings are not necessarily unique in this context. This research explored the
377 experience of parents who underwent WES for prenatal diagnosis at one large UK
378 fetal medicine centre and parents at other centres (within the UK or internationally)
379 may have different views. The opinions of parents who declined WES are similarly
380 not well represented. It cannot be assumed therefore that the findings are applicable
381 to all parents; moreover they may not reflect the views of parents who decline
382 genetic diagnosis using invasive methods. Further research that considers the
383 opinions of parents who decline prenatal sequencing is needed. Ethical approval for
384 the PAGE Study^[16] only permitted the return of results to families considered to be
385 pathogenic and contributing to the prenatal phenotype, thus it was not possible to
386 explore parental views around the return of VUS and ICFs. Parental opinions
387 regarding the return of VUS and ICFs will be explored in a planned further phase of
388 work.

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