

Prenatal whole exome sequencing

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1 Prenatal Whole Exome Sequencing; the Views of Clinicians, Scientists, Genetic
2 Counsellors and Patient Representatives

3

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32 Results and Choices (ARC), Genetic Alliance UK, SWAN (Syndromes Without A
33 Name) and Unique (the rare chromosome disorder support group).

34 **Conflict of interest**

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

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

- 37 • Prenatal WES generates variants of uncertain significance (VUS) and
38 incidental findings (ICFs).

39 **What does this study add?**

- 40 • Consent-takers require training.
41 • An overview of the findings that will/won't be reported should be provided.
42 • Patient Representative Groups (PRGs) felt women want access to all
43 information and re-interpretation of results over time.

- 44 • Clinical Professionals (CPs) felt that interpretation should be at the point of
45 testing only.

46

47 **Abstract**

48 **Objective**

49 Focus groups were conducted with individuals involved in prenatal diagnosis to
50 determine their opinions relating to WES in fetuses with structural anomalies.

51 **Method**

52 Five representatives of patient groups/charities (PRGs) and eight clinical
53 professionals (CPs) participated. Three focus groups occurred (the two groups
54 separately and then combined). Framework analysis was performed to elicit themes.
55 A thematic coding frame was identified based on emerging themes.

56 **Results**

57 Seven main themes (consent, analysis, interpretation/reinterpretation of results,
58 prenatal issues, uncertainty, incidental findings, and information access) with sub-
59 themes emerged. The main themes were raised by both groups, apart from
60 'analysis' which was raised by CPs only. Some subthemes were raised by PRGs
61 and CPs (with different perspectives). Others were raised either by PRGs or CPs,
62 showing differences in patient/clinician agendas.

63 **Conclusions**

64 Prenatal consent for WES is not a 'perfect' process but consent takers should be
65 fully educated regarding the test. PRGs highlighted issues involving access to
66 results feeling that women want to know all information. PRGs also felt that patients

67 want re-interpretation of results over time whilst CPs felt that interpretation should be
68 performed at the point of testing only.

69 **Key words:** Prenatal; genetic testing; whole exome sequencing.

70

71 **Introduction**

72 Standard chromosome testing (G-band karyotyping) undertaken prenatally has been
73 largely superseded by the use of chromosomal microarrays (CMAs)¹ identifying sub-
74 microscopic rearrangements undetectable by conventional cytogenetic methods².

75 Next generation sequencing (NGS) technologies represent a further development in
76 terms of the quantity of genetic data obtainable and the bioinformatics needed to
77 fully utilise and interpret results³. NGS offers knowledge, but comes with
78 challenges⁴. Genome wide testing produces huge quantities of information, some of
79 which may be uncertain and/or unanticipated, raising ethical concerns about
80 disclosure and stimulating debate regarding how best to integrate such testing into
81 prenatal clinical practice⁵.

82 Within the postnatal/paediatric setting parents value being able to choose the types
83 of genetic information they wish to receive and their understanding of the different
84 options for the return of findings (and the implications of receiving different kinds of
85 results) can be facilitated by the consent process⁶. Parents do not express desire to
86 know any and all genetic findings⁷, rather they prefer to receive information that they
87 consider to be actionable, allowing them to balance the possible benefits and harms
88 of learning their children's genetic results⁸. Parents can sometimes find themselves

89 in uncharted territory needing to decide which types of findings (beyond primary
90 variants) to receive⁷.

91 There is little guidance relating to the process and content of informed consent for
92 whole genome sequencing (WGS) and whole exome sequencing (WES) in the
93 prenatal setting or the means by which results should be reported back to families⁹.

94 Despite uncertainties, sequencing technologies are being introduced to clinical
95 practice and reduction in cost is focusing the need to evaluate the balance of
96 potential benefits and harms for patients undergoing prenatal genetic diagnosis¹⁰. A
97 significant barrier to the integration of WES/WGS into clinical care involves the
98 management of incidental findings (results that are not related to the patient's clinical
99 indication for testing)⁹. The issue is compounded by the biological time-frame of
100 pregnancy, which creates a sense of time pressure¹¹. It is essential that we seek to
101 understand the impact WGS/WES (and the uncertainty associated with it) has on
102 families, if not we risk, potentially incorrectly, assuming families are making properly
103 informed decisions¹².

104 As a first step to gain insight into the opinions of individuals with personal or
105 professional experience of WES within the prenatal setting, focus group sessions
106 were conducted with representatives of patient groups/charities (PRGs) that support
107 families undergoing genetic testing and genetic diagnosis, and clinical professionals
108 and clinical genetic scientists (CPs) involved in prenatal diagnosis to discuss the
109 issues. The aim of the focus group sessions with PRGs and CPs reported here was
110 to gain information to subsequently inform ethical guidance relating to prenatal
111 genetic sequencing and to help design an interview schedule to be used to

112 understand the experiences of families undergoing prenatal WES as a further phase
113 of the work.

114

115 **Method**

116 To identify participants for the PRG and CP focus groups members of the Prenatal
117 Assessment of Genomes and Exomes (PAGE) Study working group used
118 convenience sampling¹³ to contact individuals known to be experts in their field.
119 Three groups were held in succession during the afternoon of 9th October 2014.
120 The first focus group consisted of five PRGs from the charities; Antenatal Results
121 and Choices (ARC), Genetic Alliance UK, SWAN and Unique. The second focus
122 group consisted of eight CPs (two fetal medicine consultants, two genetic
123 counsellors, two consultant clinical geneticists and two clinical genetic scientists).
124 The third focus group combined all thirteen participants of the first and second focus
125 groups. The focus groups were conducted by SH, EQJ and MP using a topic guide;
126 the main areas covered are shown in Table 1. We held separate focus groups of
127 PRGs and CPs first in order to allow for any topics to be discussed that might not be
128 discussed in the presence of the other group. The third group used the same topic
129 guide, but focused on areas that had been felt by the facilitators to be areas of
130 differences of opinion (between the CPs and PRGs) during focus groups one and
131 two. The size of the focus groups was limited by the number of professionals we
132 could assimilate geographically on the same day. All participants gave written
133 consent. Ethical approval for the focus groups was provided by the NRES
134 Committee West Midlands –South Birmingham (14/WM/0150).

135

136 **Analysis**

137 The focus groups were voice recorded and then transcribed verbatim. Data was
138 analysed using a thematic approach^{14,15}. To gain familiarization with the data the
139 transcripts were read and re-read by SH and EQJ. Throughout this process key
140 ideas and recurrent themes were noted. A coding frame was then identified based
141 on the emerging themes. The coding frame was refined as transcripts were added.
142 This was agreed between three authors (SH, EQJ and SG). All text was indexed
143 numerically, with numbers placed in the margin beside the text. The original pieces
144 of data were charted using Excel (©Microsoft Office 2010). Charts were developed
145 using themes and subthemes.

146

147 **Results**

148 The thirteen participants came from four different charities and six healthcare sites
149 within three geographical areas of the UK (Table 2). Seven main themes with sub-
150 themes were identified. With the exception of theme two, 'Analysis', which was
151 raised by CPs only (FG1) all themes were discussed by both PRGs and CPs (FG1
152 and FG2). Within those seven main themes some similar subthemes were either a)
153 raised by both groups (with similar or different opinions) or b) different subthemes
154 were raised by the separate groups, showing a difference in the patient and clinician
155 agenda (Table 3). Quotations with their focus group identifier (FG1, FG2, and FG3)
156 are used to reflect the themes and sub-themes.

157 **Theme One: Consent**

158 The first theme, consent, was discussed by PRGs and CPs. Much of the discussion
159 focused on the problem of consenting for a complicated test and the time/resources
160 that facilitating informed consent would require. In addition, the possibility of an 'opt
161 in' consent form was discussed whereby patients could give different levels of
162 consent depending on the results they wanted to receive.

163 Both PRGs and CPs expressed concern about how much detailed information
164 should be given in the consent process:

165 *CP "There seems to be a variation and divergence of opinion between clinical*
166 *geneticists and the clinicians that deal with the parents as to how much information*
167 *needs to be provided about problems that are clearly not related to the indication or*
168 *reason for testing and I think that is my major concern" FG2*

169 Both expressed concern about who would obtain consent and the possibility of an
170 'education gap' if those taking consent did not have a full understanding of the
171 testing:

172 *PRG "Who is going to be doing all this counselling? It can't possibly be Geneticists,*
173 *it's going to be non-genetics professionals and I think there is a huge education gap*
174 *there which needs filling" FG1*

175 Both also expressed concern about adding pressure to 'overstretched services' and
176 the time it would take to consent for prenatal WES given the scope of what it could
177 report:

178 *PRG "I think there is a worry too about the pressure it puts on genetics, pressure on*
179 *genetic counsellors, because it is all, certainly in the first instance, going to be*
180 *focused on them and they are already stretched" FG1*

181 Finally both PRGs and CPs discussed the option of an 'opt in' consent form whereby
182 patients could choose to receive findings of incidental significance in addition to
183 results relating to the primary reason for testing. PRGs felt this was something
184 patients would welcome. CPs however felt that this type of consent would need to
185 be taken by a clinical geneticist or genetics counsellor.

186 An area discussed by PRGs only was motivation for testing. PRGs felt the most
187 common motivation for testing was reassurance. Other motivators were recurrence
188 risk, 'for extra information' and wanting a genetically perfect baby:

189 *PRG "maybe there would be pressure for people to make sure their baby is*
190 *perfect...it is a bit of a nightmare really" FG1*

191 **Theme Two: Analysis**

192 This theme was only discussed by the CP group. This is not surprising given that
193 the CP group contained clinical scientists. The potential to 'target' the testing to
194 relevant genes was discussed. It was felt this would negate the problem of
195 incidental findings but in practice would be difficult to achieve given the current limits
196 of genetic knowledge:

197 *CP "I kind of assume that you are going to do a target interpretation of that data and*
198 *what you target is going to affect how you consent so if you are not going to look at*
199 *BRCA1 and BRCA2 then you don't need to consent about it" FG2*

200 **Theme Three: Interpretation/reinterpretation of results**

201 Although this was discussed by both PRGs and CPs, there was a difference of
202 opinion between the groups regarding reinterpretation of results over time. CPs felt

203 results should be reviewed at the time of testing only. PRGs felt that patients would
204 want information as and whenever it became available:

205 *PRG “Our families that we support, they live without knowing for years and years,*
206 *some of them, and their need for that diagnosis never goes away...if something five*
207 *years down the line came up and suddenly they could link that then those families*
208 *would most definitely want to know” FG3*

209 *CP “it is a unique situation in medicine where we might have to reinterpret a test that*
210 *was done for an entirely different reason five years ago in the context of what is*
211 *known now...if the mother or father had not reported it [a medical concern] and the*
212 *child hasn’t been presented to a medical practitioner, do we have a right to go along*
213 *[contact the family] and say okay we found this relationship [genetic variation] exists*
214 *and disrupt this family when they have perceived no medical problem at all?” FG3*

215 Only PRGs discussed access to the generated genetic data:

216 *PRG “a high percentage of families said if you had knowledge about me, my child or*
217 *my baby, that is my knowledge and I want it, even to the point of wanting the raw*
218 *sequencing data” FG1*

219 PRGs felt that women and their families wanted ‘all’ the information possible but that
220 when the test became a reality fewer may choose to receive results of uncertain
221 significance or incidental findings:

222 *PRG “Experience from when the Huntington’s test was made available on the NHS*
223 *was that the community wanted it and everyone would go for it and then in practice I*
224 *think it’s about a third go for it...we think maybe this (WES) is the same thing again”*
225 *FG1*

226 **Theme Four: Issues specific to prenatal WES**

227 The reasons that prenatal exome sequencing is different from postnatal sequencing
228 were explored by both PRGs and CPs. Both agreed that pregnancy is a uniquely
229 stressful situation with a 'biological timeframe':

230 *PRG "Your mind is jelly. It takes you weeks to get your mind working properly, even*
231 *if you are in the business, so God help people who have not even got the basic*
232 *knowledge of what genetic testing is and what it means" FG1*

233 The PRGs alone discussed non-agreement between partners. They also discussed
234 the difficulties that couples have prenatally making an 'imaginary leap' as to what
235 they would do with results:

236 *PRG "a lot of people they will nod their heads and make the right noises but they*
237 *might not have thought the consequences through and they are the ones when*
238 *something anomalous is picked up who will need the most time and concentration in*
239 *helping them to work out what the result means to them" FG1*

240 The CPs group raised the issue that there is a more ambiguous phenotype
241 antenatally, for instance you cannot see neurodevelopment, and this is an obvious
242 limitation to counselling.

243 **Theme Five: Uncertainty**

244 There is often uncertainty in prenatal counselling for structural fetal anomalies as the
245 full phenotype may not be detectable on scan and a genetic diagnosis maybe
246 associated with variable penetrance. Additionally WES detects variants where there
247 is not enough definitive information to say that the genetic difference is the cause of

248 the scan findings. These variants of uncertain significance (VUS) present difficulties
249 in the counselling of women if they are reported.

250 Both the CPs and PRGs agreed that reporting VUS to patients can have a negative
251 impact on the patient and potentially the doctor-patient relationship:

252 *CP "The time that I have had patients really angry has been when I have been*
253 *reporting back uncertainty. They are in the middle of this situation where they are*
254 *trying to make a decision and I tell them something and then say "but I don't know*
255 *what that means" and I have had really angry reactions" FG2*

256 However both groups also agreed that VUS should not be withheld:

257 *PRG "there is a tremendous pressure when they (CPs) are giving information for*
258 *which they can give no real certainty...but I would not want that to take away from*
259 *the autonomy of that woman from making a decision to end the pregnancy if that is*
260 *what they [she would] want because the potential we have at the moment is to*
261 *potentially be paternalistic about the information given because of what might be*
262 *done with it" FG1*

263 There was also consensus between the groups that VUS should be recorded in
264 databases to build up a picture of whether the variants are benign or pathological.

265 **Theme Six: Incidental findings and prenatal WES**

266 WES is capable of detecting 'incidental findings' which are mutations which can
267 sometimes associate with pathology. These findings are incidental because they are
268 unrelated to the reason for testing. Reporting incidental findings will have
269 implications for CPs' time and healthcare resources, and there was a difference

270 between the views of CPs and PRGs. Some CPs felt that incidental findings should
271 not be reported:

272 *CP “We don’t have a national screening program [to identify incidental findings] (for*
273 *adults) so why are we doing screening by subterfuge [to detect such findings]*
274 *through the fetus” FG2*

275 Other CPs discussed that there appears to be a progression to the reporting of
276 incidental findings postnatally if there is treatment for the condition available.

277 PRGs highlighted the potential injury to the relationship between patients and
278 medical professionals if an incidental result was revealed subsequently and it was
279 felt this information had been withheld.

280 **Theme Seven: Access to prenatal WES information**

281 Both the PRGs and CPs agreed on the need for clear detailed written information to
282 take away after the consultation. The PRGs suggested more detailed signposting or
283 information sharing, particularly in relation to patient charities that could provide
284 focused support to families. CPs also highlighted the need for national reporting
285 guidance:

286 *CP “There should be some written information. Ideally in this day and age and*
287 *definitely in 10 years there should be a dedicated website that they (parents) can*
288 *access and find out information” FG2*

289 *CP “I think the ideal scenario would be to have national or even better international*
290 *criteria for what is a definite [pathological variant] and what is a VUS and therefore*
291 *you minimise the possibility [of uncertainty] for the parents” FG2*

292

293 **Conclusions**

294 All themes, with the exception of 'Analysis', were discussed by both CPs and PRGs.

295 Both groups generally had similar opinions. The process of consent for prenatal

296 WES was considered and concerns were raised regarding the current lack of clinical

297 geneticists/counsellors available to facilitate consent in prenatal clinical practice

298 within the UK National Healthcare System.

299 They also discussed the depth of the consent prior to the test, particularly when

300 taken under stressful circumstances. Previously authors have commented "*that it is*301 *virtually impossible to counsel in these circumstances*"¹⁶. When pregnant women

302 find themselves in a stressful position, they may cope by complying with what they

303 believe is the health professional's recommendations¹⁷. It was generally agreed that

304 clinicians should do the best job possible pre-test but understand that the process

305 will not be perfect and that more detailed information should be provided to families

306 when genetic anomalies are found.

307 The issue of access to results was highlighted by the PRGs who felt that women

308 would want to know all information generated as it was '*their genome*'. PRGs also

309 felt that patients would ideally want reinterpretation of genetic information over time,

310 for instance if a VUS was recorded and was later found out to be pathological.

311 Conversely some CPs felt that interpretation should be performed at the point of

312 testing only and that on-going review was unsustainable. This is in contrast to the

313 views of Yu et al that propose "*results should be viewed as a dynamic, sustained*

314 *resource of information that is available to an individual not only at a single point in*
315 *time, but over many years and even possibly a lifetime”¹⁸.*

316 It was felt that conveying uncertain information could create tension in the doctor
317 patient relationship. In these circumstances patients require rapid follow up with a
318 consultant clinical geneticist. Even when this has occurred people may make
319 incorrect conclusions to fit with their own schemata¹². Bernhardt et al interviewed
320 women with VUS. Many of them considered uncertainty to be information that they
321 wished they did not have (“toxic knowledge”)². Women were left feeling anxious,
322 and these concerns lingered into worries about their child’s development. This
323 would be in opposition to recent research showing that patients consider all
324 information very important¹⁹.

325 Some CPs felt that we should not report genes relating to adult onset conditions and
326 allow the sequencing to become a screening test. However there has been
327 progression towards reporting of adult onset conditions in the postnatal arena (as per
328 guidance by the ACMG²⁰) and it seems possible that this may transfer into the
329 prenatal setting. Srebniak et al found that 55% of future parents want to be informed
330 about adverse health effects at an adult stage but did not make a distinction between
331 treatable and non treatable conditions²¹.

332 The potential contrast in views of the CPs and PRGs is also highlighted in the recent
333 publication of views of nearly 7000 people on the return of incidental results from
334 genetic sequencing²². Here compared with the public, genetic health professionals
335 were five times more likely to think that incidental findings should not be returned.
336 Participants were more interested in learning about conditions that were preventable
337 and less interested in receiving information that is uncertain and cannot be

338 interpreted at the moment. It maybe that genetic health professionals anticipate a
339 vast increase in workload with the seemingly rapid progression towards the use of
340 sequencing in the prenatal and postnatal setting²². Recently Kalynchuk et al
341 surveyed parental attitudes to WES and found that 83% felt it should be offered and
342 54% would potentially accept it. Only 2.2% were opposed to the testing. However
343 over 70% reported an increased risk of adult onset conditions or a variant of
344 uncertain significance would cause them anxiety²³.

345

346 **Limitations**

347 The number of focus group participants was limited by the number of CPs and PRGs
348 who could be brought together geographically. Therefore this is a relatively small
349 study. However it has been suggested that in qualitative work a small sample can
350 provide useful information about participants' experience²⁴. The number of focus
351 groups we carried out accords with guidance for a 'small' study²⁵, in which we were
352 seeking information to inform further work and we did not aim or claim to reach data
353 saturation²⁶. We cannot comment on the extent to which the views expressed reflect
354 those of CPs and PRGs as a whole, and further themes such may have arisen had
355 we carried out further focus groups. There are a number of stakeholder groups
356 involved in WES. This paper has presented the views of two such groups and
357 although the patients' opinions themselves were not included in this study, we were
358 able to gain useful insights into the topic area to inform further work to explore
359 families' experiences. Using the themes which emerged from our focus groups a
360 semi-structured interview has been designed and patients will be interviewed to
361 determine their opinions on prenatal exome sequencing as part of the PAGE project

362 (<http://www.pageuk.org>). The opinions of obstetricians and gynaecologists, who are
363 not specialists in fetal medicine, were not explored in this research and the
364 perspectives of this particular group of clinical professionals may well have revealed
365 some additional insights. There may also be details of significance that participants
366 might have been willing to share more privately rather than in a focus group setting
367 ²⁷. As private feedback was not sought from participants following the focus groups
368 we are unable to comment on this, and as such the authors accept this as limiting
369 aspect of this research.

370 It is premature to make concrete recommendations from these qualitative data but
371 our findings suggest that consent in the prenatal arena is not a 'perfect' process.
372 Consent-takers should be fully educated regarding the test. This work did not seek to
373 fully explore the characterisation of the information that should be conveyed to make
374 consent valid. We feel that further qualitative work needs to explore this and in
375 particular capture the views of women and their families.

376

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