Prenatal whole exome sequencing

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

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Conflict of interest

The authors are unaware of any potential conflict of interest.

What is already known about this topic?

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

What does this study add?

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

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

Abstract

Objective

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

Method

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

Results

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

Conclusions

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

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

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

Introduction

Standard chromosome testing (G-band karyotyping) undertaken prenatally has been largely superseded by the use of chromosomal microarrays (CMAs)[1] identifying sub-microscopic rearrangements undetectable by conventional cytogenetic methods[2]. Next generation sequencing (NGS) technologies represent a further development in terms of the quantity of genetic data obtainable and the bioinformatics needed to fully utilise and interpret results[3]. NGS offers knowledge, but comes with challenges[4]. Genome wide testing produces huge quantities of information, some of which may be uncertain and/or unanticipated, raising ethical concerns about disclosure and stimulating debate regarding how best to integrate such testing into prenatal clinical practice[5].

Within the postnatal/paediatric setting parents value being able to choose the types of genetic information they wish to receive and their understanding of the different options for the return of findings (and the implications of receiving different kinds of results) can be facilitated by the consent process[6]. Parents do not express desire to know any and all genetic findings[7], rather they prefer to receive information that they consider to be actionable, allowing them to balance the possible benefits and harms of learning their children's genetic results[8]. Parents can sometimes find themselves

in uncharted territory needing to decide which types of findings (beyond primary variants) to receive[7].

There is little guidance relating to the process and content of informed consent for whole genome sequencing (WGS) and whole exome sequencing (WES) in the prenatal setting or the means by which results should be reported back to families[9]. Despite uncertainties, sequencing technologies are being introduced to clinical practice and reduction in cost is focusing the need to evaluate the balance of potential benefits and harms for patients undergoing prenatal genetic diagnosis[10]. A significant barrier to the integration of WES/WGS into clinical care involves the management of incidental findings (results that are not related to the patient's clinical indication for testing)[9]. The issue is compounded by the biological time-frame of pregnancy, which creates a sense of time pressure[11]. It is essential that we seek to understand the impact WGS/WES (and the uncertainty associated with it) has on families, if not we risk, potentially incorrectly, assuming families are making properly informed decisions[12].

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

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

Method

To identify participants for the PRG and CP focus groups members of the Prenatal Assessment of Genomes and Exomes (PAGE) Study working group used convenience sampling[13] to contact individuals known to be experts in their field. Three groups were held in succession during the afternoon of 9th October 2014. The first focus group consisted of five PRGs from the charities; Antenatal Results and Choices (ARC), Genetic Alliance UK, SWAN and Unique. The second focus group consisted of eight CPs (two fetal medicine consultants, two genetic counsellors, two consultant clinical geneticists and two clinical genetic scientists). The third focus group combined all thirteen participants of the first and second focus groups. The focus groups were conducted by SH, EQJ and MP using a topic guide; the main areas covered are shown in Table 1. We held separate focus groups of PRGs and CPs first in order to allow for any topics to be discussed that might not be discussed in the presence of the other group. The third group used the same topic guide, but focused on areas that had been felt by the facilitators to be areas of differences of opinion (between the CPs and PRGs) during focus groups one and two. The size of the focus groups was limited by the number of professionals we could assimilate geographically on the same day. All participants gave written consent. Ethical approval for the focus groups was provided by the NRES Committee West Midlands –South Birmingham (14/WM/0150).

Analysis

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

Results

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

Theme One: Consent

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

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

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

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

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

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

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

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

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

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

Theme Two: Analysis

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

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

Theme Three: Interpretation/reinterpretation of results

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

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

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

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

Only PRGs discussed access to the generated genetic data:

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

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

PRG "Experience from when the Huntington's test was made available on the NHS was that the community wanted it and everyone would go for it and then in practice I think it's about a third go for it…we think maybe this (WES) is the same thing again" FG1

Theme Four: Issues specific to prenatal WES

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

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

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

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

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

Theme Five: Uncertainty

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

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

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

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

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

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

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

Theme Six: Incidental findings and prenatal WES

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

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

CP "We don't have a national screening program [to identify incidental findings] (for adults) so why are we doing screening by subterfuge [to detect such findings] through the fetus" FG2

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

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

Theme Seven: Access to prenatal WES information

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

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

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

Conclusions

All themes, with the exception of 'Analysis', were discussed by both CPs and PRGs. Both groups generally had similar opinions. The process of consent for prenatal WES was considered and concerns were raised regarding the current lack of clinical geneticists/counsellors available to facilitate consent in prenatal clinical practice within the UK National Healthcare System.

They also discussed the depth of the consent prior to the test, particularly when taken under stressful circumstances. Previously authors have commented "*that it is virtually impossible to counsel in these circumstances*"[16]. When pregnant women find themselves in a stressful position, they may cope by complying with what they believe is the health professional's recommendations[17]. It was generally agreed that clinicians should do the best job possible pre-test but understand that the process will not be perfect and that more detailed information should be provided to families when genetic anomalies are found.

The issue of access to results was highlighted by the PRGs who felt that women would want to know all information generated as it was '*their genome*'. PRGs also felt that patients would ideally want reinterpretation of genetic information over time, for instance if a VUS was recorded and was later found out to be pathological. Conversely some CPs felt that interpretation should be performed at the point of testing only and that on-going review was unsustainable. This is in contrast to the views of Yu et al that propose "*results should be viewed as a dynamic, sustained*

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

It was felt that conveying uncertain information could create tension in the doctor patient relationship. In these circumstances patients require rapid follow up with a consultant clinical geneticist. Even when this has occurred people may make incorrect conclusions to fit with their own schemata[12]. Bernhardt et al interviewed women with VUS. Many of them considered uncertainty to be information that they wished they did not have ("toxic knowledge")[2]. Women were left feeling anxious, and these concerns lingered into worries about their child's development. This would be in opposition to recent research showing that patients consider all information very important[19].

Some CPs felt that we should not report genes relating to adult onset conditions and allow the sequencing to become a screening test. However there has been progression towards reporting of adult onset conditions in the postnatal arena (as per guidance by the ACMG[20]) and it seems possible that this may transfer into the prenatal setting. Srebniak et al found that 55% of future parents want to be informed about adverse health effects at an adult stage but did not make a distinction between treatable and non treatable conditions[21].

The potential contrast in views of the CPs and PRGs is also highlighted in the recent publication of views of nearly 7000 people on the return of incidental results from genetic sequencing[22]. Here compared with the public, genetic health professionals were five times more likely to think that incidental findings should not be returned. Participants were more interested in learning about conditions that were preventable and less interested in receiving information that is uncertain and cannot be

interpreted at the moment. It maybe that genetic health professionals anticipate a vast increase in workload with the seemingly rapid progression towards the use of sequencing in the prenatal and postnatal setting[22]. Recently Kalynchuk et al surveyed parental attitudes to WES and found that 83% felt it should be offered and 54% would potentially accept it. Only 2.2% were opposed to the testing. However over 70% reported an increased risk of adult onset conditions or a variant of uncertain significance would cause them anxiety[23].

Limitations

The number of focus group participants was limited by the number of CPs and PRGs who could be brought together geographically. Therefore this is a relatively small study. However it has been suggested that in qualitative work a small sample can provide useful information about participants' experience [24]. The number of focus groups we carried out accords with guidance for a 'small' study[25], in which we were seeking information to inform further work and we did not aim or claim to reach data saturation[26]. We cannot comment on the extent to which the views expressed reflect those of CPs and PRGs as a whole, and further themes such may have arisen had we carried out further focus groups. There are a number of stakeholder groups involved in WES. This paper has presented the views of two such groups and although the patients' opinions themselves were not included in this study, we were able to gain useful insights into the topic area to inform further work to explore families' experiences. Using the themes which emerged from our focus groups a semi-structured interview has been designed and patients will be interviewed to determine their opinions on prenatal exome sequencing as part of the PAGE project

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

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

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