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Parental experiences of rapid exome sequencing in cases with major ultrasound anomalies during pregnancy

Mirjam Plantinga[1] | Lauren Zwienenberg[1] | Eva van Dijk[1] | Hanna Breet[1] | Janouk Diphoorn[1] | Julia El Mecky[1,2] | Katelijne Bouman[1] | Joke Verheij[1] | Erwin Birnie[1] | Adelita V. Ranchor[3] | Nicole Corsten-Janssen[1] | Irene M. van Langen[1]

[1]Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

[2]Clinical Ethics and Law, Faculty of Medicine, University of Southampton, Southampton, UK

[3]Department of Health Psychology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Correspondence
Mirjam Plantinga, Department of Genetics, University Medical Center Groningen, University of Groningen, CB50, PO Box 30.001, 9700 RB, Groningen, The Netherlands.
Email: m.plantinga@umcg.nl

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Abstract

Background: Adding rapid exome sequencing (rES) to conventional genetic tests improves the diagnostic yield of pregnancies showing ultrasound abnormalities but also carries a higher chance of unsolicited findings. We evaluated how rES, including pre- and post-test counseling, was experienced by parents investigating its impact on decision-making and experienced levels of anxiety.

Methods: A mixed-methods approach was adopted. Participating couples (n = 46) were asked to fill in two surveys (pre-test and post-test counseling) and 11 couples were approached for an additional interview.

Results: All couples accepted the rES test-offer with the most important reason for testing emphasizing their hope of finding an underlying diagnosis that would aid decision-making. The actual impact on decision-making was low, however, since most parents decided to terminate the pregnancy based on the major and multiple fetal ultrasound anomalies and did not wait for their rES results. Anxiety was elevated for most participants and decreased over time.

Conclusion: Major congenital anomalies detected on ultrasound seem to have more impact on prenatal parental decision-making and anxiety then the offer and results of rES. However, the impact of rES on reproductive decision-making and experienced anxiety requires further investigation, especially in pregnancies where less (severe) fetal anomalies are detected on ultrasound.

Key points

What is already known about this topic?

- Adding exome sequencing to conventional prenatal genetic tests improves the diagnostic yield.
- Prenatal rapid exome sequencing (rES) with a 2-week turnaround time is feasible.

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What does this study add?

- Insight in the impact of rES offer and communication of rES results during pregnancy, including unsolicited findings, on decision-making and anxiety.
- Most parents did not wait for their rES results in making decisions regarding their current pregnancy because of the severity of the ultrasound anomalies.
- Anxiety was elevated for most participants but decreased over time.

1 | INTRODUCTION

Exome sequencing (ES) is increasingly being used in addition to conventional genetic tests (QF-PCR and SNP-array) when major congenital anomalies are detected in a fetus by ultrasound. ES can increase diagnostic yield by detecting monogenic conditions in addition to chromosomal aberrations detected by QF-PCR and SNP-array. ES can also be applied in prenatal care with a rapid turnaround time.[1-3] In comparison to QF-PCR and SNP-array, ES carries a higher chance of finding variants of uncertain significance (variants with limited evidence for disease association[4]) and unsolicited findings (UFs; unsought variants in genes that reveal information unrelated to the initial clinical question).[5] In addition, the prenatal phenotype is often less clear than the postnatal phenotype and the time-frame for decision-making limited, making implementation of prenatal ES challenging.[1,6-8]

Knowing how parents experience the test-offer is important for the implementation of prenatal ES. Since termination of pregnancy (TOP) upon request is only possible for pregnancies with gestational age <24 weeks in the Netherlands, there is a limited time frame in which decisions need to be made. The limited time frame in combination with the possibility of receiving uncertain and/or unsought results, may complicate decision-making and raise anxiety.[9] To date, only a few studies have investigated parental attitudes[10] and experiences[11-13] regarding prenatal ES. However, these studies did not investigate the impact of the communication of ES results on decision-making during pregnancy, since in these studies ES results were reported back after pregnancy. In addition, UFs were not always reported. Our study investigates the impact of an ES offer and communication of ES results, including UFs, on decision-making during pregnancy. ES was offered in the context of a prenatal rapid ES (rES) implementation study.[14] Using a mixed-methods approach, we evaluated how the rES test-offer was experienced. In doing so, we focused on the process of decision-making and experienced levels of anxiety.

2 | METHODS

2.1 | Implementation study

Participants in the rES implementation study were recruited from March 2018 to December 2019. rES was offered in pregnancies where fetal anomalies were detected on ultrasound and where the following inclusion criteria applied: (a) two or more independent major fetal anomalies, (b) either hydrops fetalis or bilateral renal cysts alone, or (c) one major fetal anomaly and a first-degree relative with the same anomaly. Further inclusion criteria were availability of parental DNA of the biological parents (for trio-analysis), sufficient understanding of Dutch to understand the consent procedure, and informed consent of both partners.

Both pregnancies with gestational age <24 weeks and >24 weeks were included. For pregnancies with gestational age <24 weeks, rES results can impact decision-making of both current and future pregnancies. For pregnancies with gestational age >24 weeks, rES results can only impact decision-making regarding future pregnancies. In this group, a diagnosis may also sometimes improve perinatal management.

In the rES study SNP-array and rES were performed simultaneously, following normal QF-PCR results. rES was performed using a gene panel of ~4000 genes with average turnaround time 14 days (range 8–20 days). Only pathogenic or likely pathogenic variants were reported as were UFs in case of consent. Further details of the study have been reported elsewhere.[14] The rES implementation study was approved by the Medical Ethical Review Committee of the University Medical Center Groningen (GEN14.0117).

2.2 | Unsolicited findings

Four categories of UFs were reported: (1) UFs associated with serious late-onset conditions with potential health benefits for child or parents, (2) UFs associated with developmental delay and/or intellectual disability unrelated to the ultrasound anomalies, (3) heterozygous variants in autosomal recessive (AR) disease genes with a carrier frequency >1:60 in the general population and (4) UFs associated with severe diseases not related to the ultrasound anomalies but with high recurrence risk in future pregnancies.

The consent form included the possibility to opt out of receiving UFs, with two opt-out possibilities: (1) couples could choose to not be informed about any UFs (opt-out for all four UF categories) or (2) couples could choose not to be informed about UFs associated with developmental delay and/or intellectual disability (opt-out for UF category 2). Table 1 shows that UFs were not available (n.a.) in 3/55 pregnancies (5%), meaning that no consent was given to receive UFs. 52/55 couples (95%) chose to be informed about all UFs. During the implementation study, the filtering strategy was adapted to minimize UFs such that AR disease variants detected in one parent (Category 3 UFs) were filtered out.

TABLE 1 Pregnancy characteristics

ID	Gestational age at inclusion	Diagnosis found with array/rES	UF found with array/rES	TOP or continuation	TOP before/after genetic results[a]	Survey response	Interview number
1	20w6d	Yes, rES	Yes, rES	TOP	After	T2: m, f	
2	14w0d	No	Yes, rES	TOP	Before		
3	19w5d	Yes, rES	Yes, rES	TOP	After		
4	19w1d	Yes, rES	No	TOP	After		1
5	21w2d	No	Yes, rES	Continuation	-	T1: f; T2: m, f	
6	31w4d	Yes, array	Yes, rES	Continuation	-		10
7	11w0d	No	No	Miscarriage	-	T1: m, f	
8	21w3d	Yes, array	No	TOP	After	T1: m, f	6
9	21w5d	No	No	Continuation	-	T1: m, f; T2: m, f	2
10	19w3d	Yes, rES	No	TOP	Before	T1: m, f; T2: m, f	
11	19w4d	No	Yes, rES	TOP	Before	T2: m, f	9
12	19w2d	No	N.a.	TOP	Before	T1: m, f; T2: m, f	5
13	34w4d	No	No	Continuation	-	T1: m, f; T2: m, f	
14	16w2d	Yes, rES	No	TOP	Before	T1: m, f; T2: m, f	3
15	14w2d	No	No	TOP	Before	T1: m, f	
16	21w5d	Yes, array	No	TOP	After	T1: m, f; T2: m, f	
17	20w1d	Yes, rES	Yes, rES	TOP	Before	T1: m, f; T2: m, f	
18	20w5d	Yes, array	No	TOP	After	T1: m, f; T2: m, f	8
19	21w5d	No	No	Continuation	-	T1: m, f	
20	19w5d	Yes, rES	Yes, rES	TOP	Before	T1: m, f; T2: m, f	4
21	12w2d	No	Yes, rES	TOP	Before	T1: f	7
22	18w6d	No	No	Continuation	-	T1: m, f; T2: m, f	
23	21w0d	No	No	Continuation	-	T1: m, f; T2: m, f	
24	14w6d	No	No	TOP	Before	T1: m, f; T2: m, f	
25	20w1d	No	Yes, rES	Fetal death	-		
26	20w3d	No	Yes, rES	TOP	Before		
27	28w6d	No	No	Fetal death	-	T1: m, f; T2: m, f	
28	13w0d	No	Yes, rES	Continuation	-	T1: m; T2: m	
29	22w4d	No	No	TOP	Before	T1: m, f	
30	34w4d	No	No	Continuation	-	T1: m, f; T2: m, f	

TABLE 1 (Continued)

ID	Gestational age at inclusion	Diagnosis found with array/rES	UF found with array/rES	TOP or continuation	TOP before/after genetic results[a]	Survey response	Interview number
31	20w1d	Yes, array	No	TOP	After	T1: m, f; T2: f	
32	19w2d	No	No	TOP	Before		
33	20w5d	Yes, rES	Yes, rES	Continuation	-	T1: m, f; T2: f	
34	21w5d	No	No	Continuation	-	T1: m, f; T2: m	
35	20w3d	No	Yes, rES	TOP	Before		
36	13w0d	Yes, rES	Yes, rES	TOP	Before		
37	22w4d	No	No	TOP	Before		
38	27w0d	Yes, rES	No	Continuation	-	T2: m, f	11
39	20w2d	No	No	Continuation	-	T1: m, f	
40	29w0d	No	Yes, array	Continuation	-	T1: m, f	
41	17w1d	No	No	TOP	After	T1: m, f; T2: m, f	
42	21w2d	No	n.a.	Continuation	-	T1: m, f; T2: m, f	
43	21w2d	No	Yes, rES	Continuation	-	T1: m; T2: m	
44	21w5d	No	No	TOP	Before		
45	19w5d	No	No	Continuation	-	T1: m, f; T2: m, f	
46	37w2d	No	No	Continuation	-	T2: m, f	
47	19w2d	No	No	TOP	Before	T1: m, f; T2: m, f	
48	21w3d	Yes, rES	No	TOP	After	T1: m, f	
49	28w2d	No	n.a.	Continuation	-		
50	20w6d	Yes, array	No	TOP	After	T1: m, f; T2: m, f	
51	11w6d	No	No	TOP	Before	T1: m, f; T2: m, f	
52	30w6d	Yes, rES	No	Continuation	-		
53	13w2d	Yes, rES	No	TOP	Before	T1: m, f	
54	19w2d	No	No	TOP	Before	T2: m, f	
55	17w0d	No	No	Fetal death	-		
56	20w3d	With QF-PCR	-	-	-	T1: m, f	
57	21w2d	With QF-PCR	-	-	-	T1: m, f	
58	21w2d	With QF-PCR	-	-	-	T1: m, f	
59	11w6d	With QF-PCR	-	-	-		
60	21w4d	With QF-PCR	-	-	-		
61	24w?d[b]	With QF-PCR	-	-	-	T1: m, f	
62	20w0d	With QF-PCR	-	-	-	T1: m, f	

Abbreviations: d, days; f, female; m, male; n.a., not available (no consent for communication of UFs); rES, rapid Exome Sequencing; TOP, termination of pregnancy; UF, unsolicited finding; w, weeks.

[a]The decision to terminate the pregnancy was made before or after the test-result of the SNP-array and/or rES.

[b]Unknown exact duration of the pregnancy. No reliable data available.

2.3 | Genetic test results

The flowchart of the study is displayed in Figure 1. Of the 62 pregnancies included, a diagnosis was established using QF-PCR in seven cases. In the remaining 55 pregnancies with negative QF-PCR test-results, SNP-array and rES were performed. Table 1 displays the characteristics of all included pregnancies.

A diagnosis was established via SNP-array in 6/55 (11%) pregnancies and via rES in 13/55 (25%) pregnancies (see Table 1). An UF was identified by SNP-array in 1/55 pregnancies (2%) and by rES in 16/55 pregnancies (29%). In two pregnancies, two UFs were found, bringing the total number of UFs found via rES to 18. Most UFs (N = 8, 44%) were category 3 (carrier of AR disease gene with a carrier frequency >1:60 in the general population) (see Table S1).

2.4 | Investigating decision-making and anxiety

All couples participating in the rES implementation study were asked to participate in the parental experience study via an additional consent. Our approach included a structured survey and semi-structured interviews. The survey was created in Dutch using Unipark (www.unipark.de). For the survey study, all participating pregnant women and their partners were asked to both fill in two questionnaires separately from each other: T1 (administered after pre-test counseling but before receiving genetic test results) and T2 (administered after post-test counseling and after receiving genetic test results).

Data collection took place from March 2018 to March 2020 in the Department of Genetics and Prenatal Diagnostics of the UMCG, Groningen, The Netherlands. Part of the patients were recruited at the Department of Obstetrics of the Isala Hospital, Zwolle, the Netherlands, where genetic counseling is offered by counselors from the Department of Genetics and Prenatal Diagnostics of the UMCG The interview study (administered after genetic test results had been received), used a semi-structured approach aimed at more in-depth understanding of the impact of the rES test-offer on decision-making and experienced levels of anxiety. The topic list included the following topics: (1) the perceived pros and cons of rES, (2) the decision to opt out of receiving UFs, (3) people's expectations from rES and reactions to their rES results, (4) the process of decision making regarding rES and terminating or continuing the pregnancy, (5) the impact of the rES result for future pregnancies, (6) counseling experiences (see Supporting Information S1 for the interview guide). In the interview study, a subset of the couples who consented to participate in the parental experience study were approached for an interview after post-test counseling. Couples were selected for interviews via stratified random sampling that considered genetic test result outcomes. Approximately 50% of invited couples agreed to participate in the interview study. Inclusion stopped when data saturation was reached. Interviews were done by different researchers (Hanna Breet, Janouk Diphoorn, Eva van Dijk) between May 2018–July 2019 and lasted 25–75 min. Ethical clearance for the parental experience study was granted (M18.226981) by the Medical Ethical Review Committee of the University Medical Center Groningen.

2.5 | Measures

2.5.1 | Decision-making

Three elements were investigated in the process of decision-making: (1) reasons for accepting and declining rES (including UFs); (2) the role rES plays in the decision to continue or terminate pregnancy; (3) decisional uncertainty concerning the decision to continue or terminate pregnancy. For the investigation of reasons for accepting and declining rES, the survey study was originally set up with separate questionnaires for test-acceptors and test-decliners. However, no test-decliners were included in the implementation study. We therefore only investigated reasons for accepting rES in the survey study. On T1, participants were asked to select the two most important reasons for accepting rES out of a list of five possible reasons: (1) hoping to find a diagnosis in order to enable decision-making concerning continuing or terminating the pregnancy, (2) hoping to find a diagnosis in order to be better prepared during and after the birth of their child, (3) wanting to do everything that is medically possible, (4) wanting to know more about the recurrence risk and (5) other reason specified by the participant. In the interview study, the reasons for participants to accept rES were discussed in-depth and couples were asked if they could retrospectively think of personal reasons for declining rES, which were also discussed in-depth. Participants intention to continue or terminate the pregnancy were investigated in the survey study on T1 and compared with the eventual decisions available from the patient records. In doing so, it was investigated whether a decision was made before or after having received the rES result. In the interviews, the decision to continue or terminate pregnancy and the role rES did or did not play in this decision was extensively discussed. Finally, decision uncertainty was used as a measure to investigate how the decision to continue or terminate the pregnancy was experienced. It was measured at T2 with the validated three-item scale of O' Connor (1995)[15] on a 5-point Likert scale with anchors *strongly agree* (0) and *strongly disagree* (4). These scores were then summed, divided by 3, and multiplied by 25. Final scores range from 0 (feels extremely certain about choice) to 100 (feels extremely uncertain about choice).[16] In addition, the decision-making process was discussed in depth in the interview study.

2.5.2 | Anxiety

On T1 and T2, anxiety was measured using the validated State-Trait Anxiety Inventory (STAI-6).[17] The STAI-6 consists of six items rated on a 4-point scale (1 = not at all, 4 = very much), with the STAI-6 sum score ranging from 4 to 24. A higher score indicates a higher level of

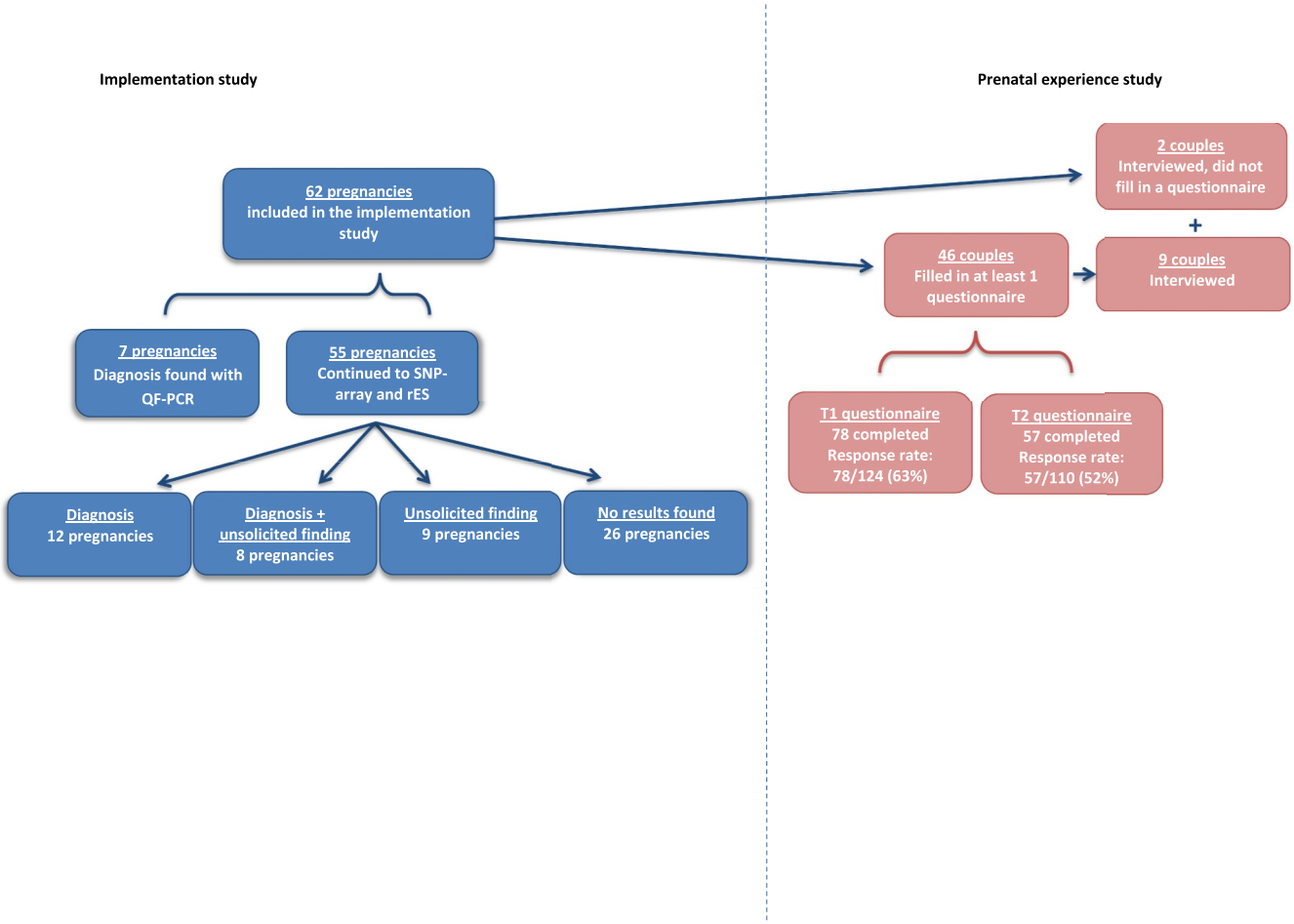

FIGURE 1 Flowchart of the study [Colour figure can be viewed at wileyonlinelibrary.com]

anxiety. Scale reliability was good (Cronbach's alpha 0.82 on T1 and 0.84 on T2). STAI-6 scores were transferred to the prorated STAI by multiplying by 20/6, resulting in a total scale score of 20 (no anxiety) to 80 (very high anxiety). Two cut-off scores have been reported for clinically relevant elevated levels of anxiety. A cut-off of 40 was used in a study among liver transplant candidates during the waiting-list period[18] and a study investigating the psychological outcomes and reproductive intentions of couples in the Dutch general population with couple-based expanded carrier screening.[19] A score of 50 was used in a study investigating women's experiences with non-invasive prenatal testing.[20] We used both cut-offs as reference value.

2.6 | Data analysis

For the survey study, analyses were performed using IBM SPSS version 22. Descriptive analyses were used to summarize participant characteristics, decision-making and anxiety. For the interview study, we developed a topic guide containing open-ended questions to guide the semi-structured interviews. The interviews were audio-taped, and verbatim transcripts were stored anonymously. Thematic analysis was used to analyze the data.[21] Two researchers (Eva van Dijk, Lauren Zwienenberg) independently coded the first two interviews, with coding differences discussed until consensus was reached. Eva van Dijk subsequently coded all interviews, including the first two, in Atlas.ti (version 8.4.3). Themes emerging from the thematic analyses were discussed within the research group until consensus was reached. Outcomes from both the survey and interview study were compared for similarities and differences and integrated in one set of findings for decision-making and anxiety.

3 | RESULTS

3.1 | Participant characteristics

In total, 46 couples participated in the survey study and 11 couples in the interview study (see Figure 1). T1 was sent to all participating parents ($N = 124$). T2 was sent to the parents of pregnancies in which rES was performed ($N = 110$). The response rates were 63% ($N = 78$) at T1 and 50% ($N = 55$) at T2. Figure 2 presents an overview of the interview study participants, their diagnostic results and reproductive decisions. For more details about the pregnancies of participants, their rES test-results, and reproductive decisions, see Table 1 and Table S1.

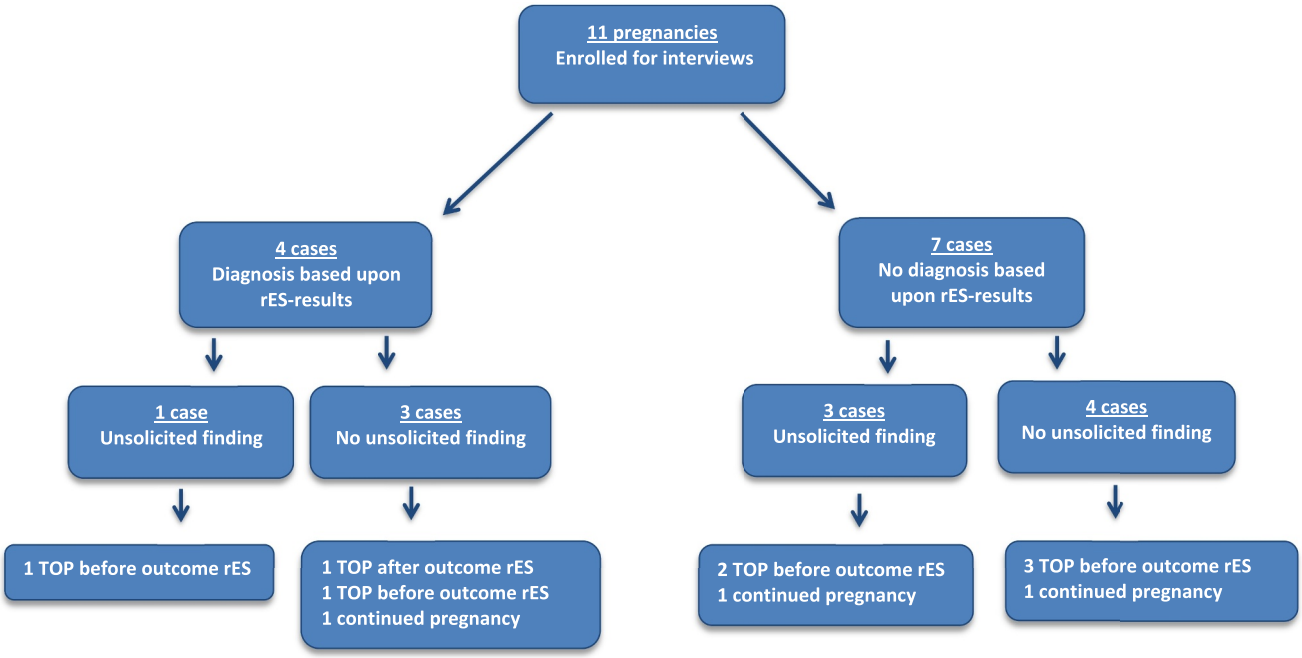

FIGURE 2 Characteristics of the participants in the interview study. rES, rapid exome sequencing; TOP, termination of pregnancy [Colour figure can be viewed at wileyonlinelibrary.com]

3.2 | Decision-making

3.2.1 | Reasons for accepting and declining rES (including UFs)

The two most important reasons for accepting rES, brought forward in the survey study, were wanting to receive all information possible, hoping this would aid decision-making in the current pregnancy as well as provide information of importance for future pregnancies ($N = 38/78$, 49%). This reason was also brought forward in the interview study (quote 1, Table 2). Wanting to do everything medically possible was the next most important reason for accepting rES, brought forward by 23/78 (29%) of the survey participants. In the interview study, this reason was also mentioned (quote 2, Table 2). The interview study revealed an additional reason for accepting rES, not included in the survey study, which was wanting to know to possible consequences for reproduction and/or health of (future) relatives (quote 3, Table 2).

In the interview study, couples were asked if they could, in retrospect, think of reasons for declining rES. The interview study revealed four main reasons for possible decline of rES in the future: (1) if people have a plan to continue the pregnancy no matter what the test result will be, (2) anticipated feelings of guilt (e.g. towards partner in case of carriership) (3) fear of too confronting test-results (e.g. if a fetal anomaly turns out to be genetic), and (4) the positive benefits of rES might not be worth the anxiety that accompanies waiting for test-results (quote 4, Table 2).

Finally, reasons for being or not being informed about UFs were discussed in the interview study. As mentioned, 95% of participating couples chose to be informed about all UFs. Reasons for wanting to be informed about UFs, were wanting to know all available information in the hopes this would aid decision-making, or wanting to gain control (quotes 5 and 6, Table 2). The decision to be informed about UFs was not easy or self-evident for all participants: some found it quite difficult and overwhelming (quote 7, Table 2). Reasons for deciding not to be informed about UFs were wanting to focus on information regarding the initial clinical question and the belief that knowing everything does not make one happy (quotes 8 and 9, Table 2). The timing of receiving the test-result was also important, as shown in quote 10, a case where the male partner learned being a carrier for adrenogenital syndrome while his wife underwent the TOP procedure.

3.2.2 | The role of rES in the decision to continue or terminate pregnancy

Table 3 presents participants' initial intentions to continue or terminate the pregnancy versus their eventual decision. 39/64 (61%) of the participants were unable to express an intended decision based on the fetal anomalies detected on ultrasound. Of these, 9/39 (23%) explicitly mentioned that they wanted to base their decision on the rES test-result. For one participant, due to fetal death, decision-making was not possible anymore. For the participants who expressed an intended decision, 20/64 (31%) intended to terminate the pregnancy because they considered the fetal anomalies detected on ultrasound very severe. In 18/20 (90%) of these cases, the pregnancy was terminated whereas in 2/20 (10%) cases the pregnancy was continued. 4/64 (6%) of the participants intended to continue the pregnancy. In three cases because terminating a pregnancy was not

TABLE 2 Quotations by theme

Theme	Quotation
Reasons for accepting rES	1. "We just wanted to know if her DNA showed an anomaly or if it came from us. If he has something in his genes, or I do, that would be a cause in a future pregnancy. That was the most important thing for us." (Interview 5: no diagnosis, no UF, TOP before test results have been received)
	2. "The more testing you do, the better a decision you can make, the more information you have. It gave us a more complete picture and certainly aided decision making." (Interview 2: no diagnosis, no UF, continuation of pregnancy)
	3. "Yes, I have three sisters who don't have children yet, but if I were a carrier of a gene, then yes it is something for them, even though they don't have children yet, to take into consideration. Now, in our case, it is not genetic, but still." (Interview 11: diagnosis found with rES, no UF, continuation of pregnancy)
Reasons for declining rES	4. "It has just not given us so much. And then I think, well, yes, this adds an uncertain factor that you do take into consideration, the DNA is being investigated, each time results come back that raise anxiety, so you constantly hope for something. And, in our case, it only gained us a little… the result that came out, about that heart condition, is just vague" (Interview 7: no diagnosis, UF found, TOP before test results have been received)
Unsolicited findings	5. "The question was if we wanted to know it [unsolicited findings]. We just said, yes, that is fine, bring it on. If you are well informed, you can act upon it and be able to make good decisions." (Interview 2: no diagnosis, no UFs, continuation of pregnancy)
	6. "We are people who like to be in control. That is why we wanted to know these unsolicited findings. And it also feels strange that people know something about you that you don't know yourself." (Interview 3: diagnosis found with rES, no UFs, TOP before test results)
	7. "I was just busy with all the misery… and then it might come out that something is wrong with yourself or with each other and you just don't want to deal with it.But then, if you think realistically, you figure out that it is better [to know the unsolicited findings]. But at that moment, it was just too much to handle that too" (interview 8, diagnosis found with array, no UF, TOP before test results)
	8. "We did not want to know everything. Whether we have breast cancer in the family, for example, I don't find that essential to know. We were looking for information regarding the fetus, to understand what was happening, what is it, why is it." (Interview 1: diagnosis found with rES, no UFs, TOP after test results)
	9. "We said we did not want to know all these things [unsolicited findings]. If we all would know what we might be afflicted with, I do not think that makes one happy." (Interview 5: no diagnosis, no UF, TOP before test results have been received)
	10. "You were planned to [TOP] and we had to come to the hospital in the morning. Then I needed to inform my family in the middle of that day that I was carrier of AGS. I had difficulty with that. Because it concerned me. And because I had two brothers and sisters who were pregnant and I needed to call them immediately. It is not a very big deal or very bad news, but it is also not nice information to tell." (interview 9: no diagnosis, UF found, TOP before test results have been received)
Decision-making	11. "We did not terminate the pregnancy because the child had Noonan. We terminated the pregnancy because there was so much fluid development [hydrops]. Which was due to Noonan. We have been asked if we want to do amniocentesis the next time, so we can find out of it is Noonan again. We have deliberately said no to this, because if it is a child with Noonan but without fluid development [hydrops], then we are not going to terminate the pregnancy" (Interview 3: diagnosis found with rES, no UFs, TOP before test results)
	12. "It would have made no difference for the child no matter what the test-result would be. It would never be able to live. It was not viable. Because we are both very young and we have a child wish, we wanted to know where it [the structural anomaly detected on ultrasound] comes from, if it is genetic, and if it can happen with a next child" (interview 9: no diagnosis, UF found, TOP before test results have been received)
	13. "On the ultrasound it was already shown that the brain underdeveloped, so a chromosomal aberration was expected. We decided then to terminate the pregnancy.

(Continues)

TABLE 2 (Continued)

Theme	Quotation
	When we found out a few days later that it was a chromosomal aberration, it confirmed our feeling and the choice that we had made" (Interview 4: diagnosis found, UF found, TOP before test results were received)
	14. "We expected a Joubert diagnosis, and if it would have been Joubert we would have continued the pregnancy. Because Zellweger was found, yes, that was so traumatic. I said, no, we are not going to do that" (Interview 1: diagnosis found with rES, no UFs, TOP after test results)
	15. "We appreciated the possibility to participate in this study. That provided us with much clarity and made us feel that at least we have made the right decision" (Interview 1: diagnosis found with rES, no UFs, TOP after test results)
	16. "Yes that sister is quite fanatic with religion and she had big problems with it. It resulted almost in a family crisis. When we knew what was going on, what the prognosis was, she turned around and started supporting us. Yes, that is nice, that you can say, see this is it, look it up yourself" (Interview 1: diagnosis found with rES, no UFs, TOP after test results)
	17. "You want to take it [diagnosis] into consideration, but to what extent? In which form? Mild or severe? Yes, unfortunately, they cannot say anything about that. A heart defect is often found in these children, but this has not been detected on ultrasound so far. So that is good. And for the rest, it is just waiting, and, yes, we are like, we could now get very worried, but you just don't know. And the insecurity that goes together with the diagnosis is less troublesome than not having a diagnosis at all" (Interview 11: diagnosis found with rES, no UFs, continuation of pregnancy)
	18. "The test did not show that something more is going on. You already have a number of things and that no more is added was a great relief." (Interview 2: no diagnosis, no UFs, continuation of pregnancy)
	19. "Now we do not have that choice anymore. That also gives a bit of peace. I found that 24-week deadline tough" (Interview 2: no diagnosis, no UFs, continuation of pregnancy)
Anxiety	20. You receive a message: this is not looking good. So then you are busy with this is not going to go well, so we are going to stop it. And, on the other hand, ok but we need further research, so keep waiting. We need to find out what this is. And that just was very difficult" (Interview 7: no diagnosis, UF found, TOP before test results have been received)
	21. "I think it might be underestimated how anxiety provoking waiting is. Your child keeps growing and your connection changes. Your involvement increases and at a certain point I am convinced that you just can't do it anymore. It becomes increasingly difficult to make that decision. Then I decided, I am just two weeks in this situation, but I can't cope with it. Then we have made the decision. But the DNA research was still ongoing." (Interview 7: no diagnosis, UF found, TOP before test results have been received)

considered as an option in any circumstance, while in one case the pregnancy was continued because the fetal anomaly detected on ultrasound was not perceived as very severe.

Table 1 shows that most couples did not wait for the genetic test-results when deciding about TOP: 31/55 (56%) couples chose for TOP and in 21/31 (68%) cases this was performed before genetic test results had been received. The important role of ultrasound anomalies in couples' decision-making process, was also highlighted in the interview study (quotes 11 and 12, Table 2). Finding a genetic diagnosis, on the other hand, also played a role in decision-making. A genetic diagnose was made in 19 couples using SNP-array or rES. In 15/19 (79%) cases TOP was performed of which in 9/15 (60%) cases after genetic test results were known. The interviews further showed that even when the decision to continue or terminate the pregnancy was made before disclosure of the rES results, the results could still be perceived as valuable as additional confirmation of the decision that had been made (quote 13, Table 2).

In four couples who participated in the interview study, a diagnosis was found with rES (see Figure 2). In two cases, the decision to continue or terminate the pregnancy was influenced by this test result. In the first, rES led to a diagnosis of Zellweger syndrome rather than the previously suspected Joubert syndrome, which led the participants to choose for TOP (quotes 14 and 15, Table 2). For this couple, the rES diagnosis not only provided more information about the (greater) severity of the condition, which affected their decision-making, it also helped them receive understanding from their social environment for their decision to terminate the pregnancy (quote 16, Table 2). In the second case, a diagnosis of Noonan syndrome was established and the

TABLE 3 Intentions versus actual progress of pregnancy

		Actual progress of pregnancy			
		Continuation	TOP	Fetal death	Total
Have you considered the choice you may be faced with (or are already being faced with) about continuing or terminating the pregnancy?	Yes, I want to continue the pregnancy because I find the fetal anomalies detected on ultrasound not so serious	1	0	0	1
	Yes, I want to continue the pregnancy because I would never terminate a pregnancy even if I find the fetal anomaly very serious	3	0	0	3
	Yes, I want to terminate the pregnancy because I find the fetal anomalies detected on ultrasound very serious	2[a]	18	0	20
	No, I have not considered this yet	7	6	0	13
	No, I have not considered this much. My decision depends (largely) on the rES test-result	4	5	0	9
	I am in doubt	7	7	3	17
	Other, namely	0	0	1	1

Abbreviation: TOP, termination of pregnancy.

[a]These two individuals were not a couple and did not participate in the interview study.

couple decided to continue the pregnancy even though the prognosis was difficult to predict (quote 17, Table 2). The interview study further showed that the rES test-result could also impact decision-making even when no underlying genetic diagnosis was established. Quote 18, Table 2 shows that the lack of an underlying genetic diagnosis influenced the decision to continue the pregnancy.

3.2.3 | Decision uncertainty concerning the decision to continue or terminate pregnancy

Decision uncertainty, measured at T2 (see Table 4) was low for most people (mean 26.92, 95% CI: 20.4; 33.5) and significantly lower (mean 12.50, 95% CI: −6.49; 31.49) for participants with gestational age >24 weeks (the cut-off for termination upon request) (see also quote 13, Table 2). Decision uncertainty was higher (significant with $p < 0.10$) for participants who terminated the pregnancy (mean 30.17, 95% CI: 21.68; 38.67) compared to participants who chose to continue the pregnancy (mean 20.42, 95% CI: 8.79; 32.05) and higher (although not significant with p value of 0.12), for participants who received an UF (mean 35.83, 95% CI: 20.69; 50.98) compared to participants who did not (mean 24.80, 95% CI: 17.36; 32.25).

3.3 | Anxiety

Anxiety was elevated (>40/50) for most participants on both T1 (mean for total group of participants 55, 95% CI: 52.3; 57.7) and T2 (mean for total group of participants 43.7, 95% CI: 40.4; 47.0) (Figure 3). Anxiety significantly decreased from T1 (pre-test) to T2 (post-test). On T1, 91% had an anxiety score >40 and 69% >50, whereas these percentages had decreased to 68% and 35%, respectively, on T2. We further found that, on T1, anxiety was significantly lower (mean 50, 95% CI: 46.2; 53.8) for participants with an intended decision to either continue or terminate the pregnancy compared to participants without an intended decision (mean 58.4, 95% CI: 53.8; 63.0). On T1, anxiety was also lower (mean 51.3, 95% CI: 41.2; 61.5) for participants with a gestational age >24 weeks (cut-off for TOP on request) compared to participants with a gestational age <24 weeks (mean 55.5, 95% CI: 52.8; 58.3). This difference was, however, not significant and decreased on T2. Finally, we found a significantly higher level of anxiety among female participants on T1 (mean 59.8, 95% CI: 56.1; 63.5) compared to male participants (mean 50.2, 95% CI: 46.9; 53.5). The difference was no longer significant on T2. The differences in anxiety levels might be an indication that anxiety is lower (especially for women) if the decision to continue or terminate the pregnancy is already made or no longer possible and this was supported by the interview study (quote 19, Table 2). Moreover, it was also brought forward in the interviews that the period of waiting for test-results can be experienced as very anxiety-enhancing and, for some, represented a reason not to wait for their test-results (quotes 20 and 21, Table 2).

4 | DISCUSSION

This is the first study to report on the impact of rES offer and communication of rES results, including the reporting of UFs, during pregnancy on the process of decision-making and experienced levels of anxiety. In our study, all parents accepted the rES offer. The most important motivation being their hope of establishing a diagnosis that would aid decision-making about the current pregnancy. Besides, they valued information that could be relevant for decision-making

TABLE 4 Decision uncertainty measured after post-test counseling (T2)

Group	Total (N = 52)	Gender		Gestational age		Diagnosis		UF		Continuing pregnancy	
		Male (N = 27)	Female (N = 25)	24− (N = 44)	24+ (N = 8)	No (N = 32)	Yes (N = 20)	No (N = 42)	Yes (N = 10)	No (N = 29)	Yes (N = 20)
Median	25.00	25.00	25.00	25.00	4.17	33.33	25.00	20.83	41.67	25.00	8.33
IQR	8.33–41.67	0.00–50.00	8.33–41.67	8.33–47.92	0.00–14.58	0.00–50.00	8.33–31.25	0.00–35.42	20.83–52.08	12.50–41.67	0.00–47.92
Min–Max	0.00–100.00	0.00–66.67	0.00–100.00	0.00–100.00	0.00–66.67	0.00–100.00	0.00–66.67	0.00–100.00	0.00–66.67	0.00–100.00	0.00–75
Group differences (p value)[a]		0.592		0.030*		0.695		0.116		0.090	

Abbreviations: CI, confidence interval (95%); Max, maximum; Min, minimum; N, number of participants; UF, unsolicited finding.

[a]Mann–Whitney U tests are used to compare differences in decision uncertainty between groups (male vs. female; 24− vs. 24+; etc).

*$p < 0.05$.

regarding their and relatives' future pregnancies. Earlier studies investigating parental experiences with genetic testing during pregnancy (ES and SNP-array) found that parents expressed a strong desire to receive as much information as possible for similar reasons.[11,12,22]

Our finding that most of the participating couples in our study (95%) chose to also be informed about possible UFs can also be understood in the context of wanting to know all that could be useful to facilitate decision-making. Since our study was the first to offer the possibility of communication of ES UFs during pregnancy, our findings cannot be directly compared to other empirical studies. Talati et al.[13] communicated ES UFs for medically actionable secondary findings in a parent and heterozygous variants for the same recessive disorder in both parents, although only after decisions about pregnancy continuation were already made and there was no possibility to opt-out of receiving UFs. Our findings, that most participants pursued ES in the hope of receiving information that could explain the findings in the current pregnancy or guide decision-making for future pregnancies, are in line with Talati et al.[13] The studies of Kalynchuck et al.[10] and Brew et al.[23] further surveyed expectant parents and genetic counselors about their attitude towards the (hypothetical) communication of rES UFs during pregnancy. Their findings are also comparable to ours: most expectant parents and genetic counselors expressed the wish to have the option to receive UF information about treatable childhood conditions (96%[10] and 93%,[23] respectively) as well as non-treatable childhood conditions (86%[10] and 80%,[23] respectively).

The low rate of opting-out for returning UFs does not imply that the decision to be informed about UFs was always easy or self-evident. Our interview study showed that some participants felt overwhelmed by the decisions they were confronted with shortly after learning about the fetal anomaly, including the decision to be informed about UFs (quote 16, Table 2). This feeling of being overwhelmed was also highlighted in the PAGE[11] and PPPWES study.[12] Our study further shows that receiving information on UFs is not always perceived as useful and can add further complexity to an already complicated situation (quote 4, Table 2).

Most participants in our study decided to terminate the pregnancy based on the major and multiple fetal anomalies detected on ultrasound and in spite of their wishes to perform rES did not wait for the genetic test-results. Finding a genetic diagnosis did, however, play a role in decision-making in those who decided to wait: in 90% of cases the diagnosis contributed to the decision to terminate the pregnancy. Since most pregnancies had a gestational age >20 weeks, there was little time for decision-making (termination on request is only possible for pregnancies with gestational age <24 weeks) both for accepting or declining rES as well as for deciding to continue or terminate the pregnancy. Earlier detection of ultrasound abnormalities, for example by the implementation of the 13-week anomaly scan,[24] will make it possible to take more time to make a decision about accepting or declining rES and to wait for the rES results in deciding to continue or terminate the pregnancy, which may increase the impact of rES on decision-making.

Elevated anxiety was found after both pre- and post-test counseling, although anxiety decreased over time, in line with findings in

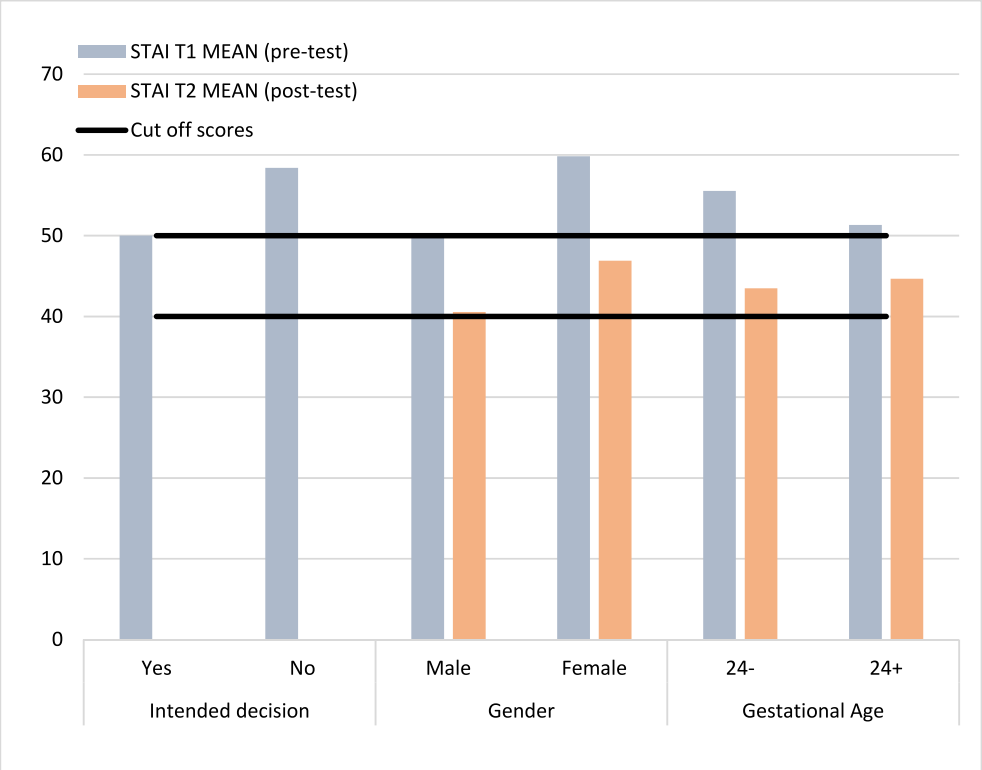

FIGURE 3 Mean anxiety scores (State-Trait Anxiety Inventory) after pre-test (T1) and post-test counseling (T2). The cut-off score indicating clinically relevant elevated levels of anxiety differs depending the population under study. Here we report both 40 (level for healthy population, used by Annema et al.[18]) and 50 (used by Van Schendel et al.[19] in a study investigating women's experiences with NIPT) [Colour figure can be viewed at wileyonlinelibrary.com]

other studies.[13,22,24] Although the study design does not make it possible to attribute the experienced anxiety to the ultrasound anomalies or to the rES offer and communication of rES results, the severity of the fetal anomalies seem to play a large role. Talati et al. (2020) hypothesized that the high levels of anxiety (and the pre- to post-test decrease) might be explained by the (decrease in) mental health burden that accompanies an anomalous pregnancy and the difficult decisions and uncertainty this brings for both current and future pregnancies.[13] Our study also shows that anxiety was lower if parents had already made a decision to continue or terminate the pregnancy or if this choice was no longer possible, indicating that choices concerning continuing or terminating the pregnancy might be anxiety provoking. More research is, however, needed to distinguish the impact of the rES offer and the communication of rES results on parental anxiety levels. In this respect, a fast turnaround time seems important. The long turnaround times in other studies, such as PAGE[11] and PPPWES[12] where test-results were reported back after pregnancy, were evaluated negatively and as prolonging worry and anxiety.

Strengths of this study are that we explored the experiences of both partners and that we used a mixed-methods approach. Our survey study provided an initial overview of patient experiences that could then be explored in depth in the interview study, leading to a more robust understanding of different participant experiences. A limitation of our study is that it only included pregnancies characterized by a high degree of severity. Findings may be different for pregnancies with less severe fetal anomalies. Moreover, many pregnancies were included with a gestational age close to or >24 weeks. For these cases, there was little or no possibility for the genetic test-results to impact decision-making in the current pregnancy. rES results could, however, still impact decision-making regarding future pregnancies. A limitation in the quantitative part of our study is that for some couples we did not receive data from both partners or for both T1 and T2. A further limitation includes a self-selection bias in both the survey study (were the response on T1 and T2 was 63% and 52% respectively) and even more in the interview study where ~50% of the couples who were approached for the interview study were willing to participate. The results may therefore be influenced by selection bias. The timing of the interviews was also not consistent. In some cases more time had passed between receiving the rES results and the interview, which might have impacted recall.

In conclusion, we found that all couples accepted the rES test-offer hoping to find a diagnosis for their severely affected fetus that would aid reproductive decision-making or assist in decision-making regarding future pregnancies. Given the contribution of rES to an increase in diagnostic yield, rES is expected to become a routine offer in all affected pregnancies in the near future. In our study, not the rES test-results, but rather the major congenital anomalies detected on ultrasound seem to have most impacted parental decision-making and anxiety. Given that our study only included pregnancies characterized by a high degree of severity, it is important to further investigate the impact of an rES offer and (the timing of) the communication of rES results (including UFs) on reproductive decision-making and

experienced anxiety, especially in pregnancies where ultrasound abnormalities are detected earlier and where less severe fetal anomalies are detected. Important in this respect is that rES carries a higher chance of finding UFs and our study has shown that receiving information on UFs is not always perceived as useful and can add further complexity to an already complicated situation. For responsible implementation of rES it is of further importance to also investigate information needs, to what extent this may differ between groups (e.g. with different gestational ages), and to what extent adequately addressing information needs through genetic counseling impacts experienced anxiety.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Relevant data included in this paper is available upon request.

ORCID

Mirjam Plantinga https://orcid.org/0000-0003-3350-9842
Nicole Corsten-Janssen https://orcid.org/0000-0002-9438-2374

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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