Chapter 3

Empowerment and anxiety of patients and parents during genetic counseling for epilepsy

Manuscript ready to submit

Danique RM Vlaskamp[1,2], Patrick Rump[1], Petra MC Callenbach[2], Jan S Voorwinden[3], Eva H Brilstra[4], Mary E Velthuizen[4], Oebele F Brouwer[2], Adelita Ranchor[3], Conny M.A. van Ravenswaaij-Arts[1]

[1] University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen, the Netherlands. [2] University of Groningen, University Medical Center Groningen, Department of Neurology. Groningen, the Netherlands. [3] University of Groningen, University Medical Center Groningen, Department of Health Psychology, the Netherlands. [4] University Medical Center Utrecht, Department of Genetics, Utrecht, the Netherlands.

Acknowledgements. We thank all patients and their parents for their participation in our study. We are thankful for the help of all research assistants, especially Rianne Lieben, Denise Blom, Elise Boersma and Sumalai Sompitak, with data collection and input. We thank Kate Mc Intyre for editing our manuscript.

Disclosures. None of the authors have any conflicts of interest to disclose.

ABSTRACT

Purpose. To study the patient-reported outcome of genetic counseling before and after genetic testing for epilepsy by evaluating empowermenta combination of cognitive, decisional and behavioral control, emotional regulation and hope—and anxiety.

Methods. Patients or their parents (if <16 years old or intellectually disabled) referred to two university hospitals for genetic testing for epilepsy between June 2014 and 2017 were asked to complete three questionnaires: one before pre-test counseling, one after, and one following post-test counseling. Empowerment was measured with the Genetic Counseling Outcome Scale (GCOS-18), anxiety with the short State Trait Anxiety Inventory (STAI-6).

Results. Of 106 participants who had genetic testing, 63 completed all three questionnaires and were included in our study. Empowerment significantly increased during the genetic counseling trajectory with a medium effect size ($p<0.001$, $d=0.57$), and a small but significant increase in empowerment was already seen after pre-test counseling ($p=0.038$, $d=0.29$). Anxiety did not change significantly during the counseling trajectory ($p=0.223$, $d=-0.24$).

Conclusion. Patients with epilepsy or their parents show a clinically relevant increase in empowerment after genetic counseling, which is a key outcome goal of genetic counseling. Empowerment was already increased after pre-test counseling, indicating the importance of counseling before initiating genetic testing for epilepsy.

INTRODUCTION

The increasing use of genetic testing in individuals with epilepsy is transforming epilepsy care. Finding a genetic cause for epilepsy, even though this is still only possible for the minority of patients, precludes unnecessary further diagnostic investigations and leads to a better understanding of epilepsy etiology, comorbidities, prognosis and recurrence risks.[1–4] For a very few cases, finding the genetic variant for epilepsy may even improve treatment and outcome.[5] Genetic testing in epilepsy is therefore increasingly part of routine diagnostic care.[6,7] However, little is known about the psychological outcomes of genetic services from the patient or parent perspective.[8–10]

Previous qualitative studies showed that patients with epilepsy or their parents have a strong hypothetical interest in genetic testing, if offered, especially in a scenario where knowing the genetic change would improve medical care.[11–13] Study participants mentioned both potential benefits (such as better understanding and care in children at risk and more sense of control and less guilt, blame and anxiety with negative test results) and potential concerns (including increased blame, guilt, stigma, discrimination, self-imposed limitations on life goals, and alterations in fundamental conceptions of 'what epilepsy is').[13] Individuals with a familial epilepsy for which a genetic cause has been identified also expressed both positive and negative feelings on receiving a genetic diagnosis.[14] To date, the psychological outcomes of genetic services for epilepsy have not been studied systematically.

In our current clinical practice, genetic testing for epilepsy is preceded and followed by genetic counseling. During pre-test counseling, counselors first obtain a medical and family history to decide which genetic test would be most suitable. Subsequently, they inform the patients and their families about genetic testing and encourage them to make an informed choice about whether this testing should be done. During post-test counseling, the test results are explained to the patients and families. The overall aim of genetic counseling is helping people to understand and adapt to the medical, psychological and familial implications of identifying genetic contributions to disease.[15] By this means, genetic counseling can lead to increased knowledge, increased perceived personal control, positive health behavior, improved risk perception accuracy and decreased decisional conflict, anxiety and worry.[16] Studying the psychological outcome of genetic services for epilepsy may help counselors to improve the counseling trajectory in accordance with patient's and their families' needs.

These psychological outcomes can be measured by evaluating the change in 'empowerment' and anxiety. Empowerment is an all-encompassing patient-reported outcome of genetic counseling, defined as the set of beliefs that a person can make important life decisions (decisional control), has sufficient information about the condition (cognitive control), can make effective use of health and social care systems (behavioral control), is able to manage feelings about having a

genetic condition in the family (emotional regulation) and has hope for a fulfilling family life (hope).[17–19] We aimed to study the outcome of genetic counseling before and after genetic testing for epilepsy by evaluating empowerment and anxiety of patients or their parents.

METHODS

Study cohort and design

Our research was part of a larger study on the Dutch version of the Genetic Counseling Outcome Scale (GCOS) and followed the same study design.[20] All patients who were referred to a clinical geneticist in the outpatient clinics of the University Medical Center Groningen (UMCG) or the University Medical Center Utrecht (UMCU) in the Netherlands were eligible for inclusion in the study. For our study, all patients who were referred for genetic counseling and testing for epilepsy between June 2014 and June 2017 were eligible for inclusion.

The research had a pre-post observational study design. All patients were asked to complete three questionnaires during the genetic counseling trajectory: 1. before pre-test counseling (T0), 2. around 1-2 weeks after pre-test counseling (T1), and 3. around 1-2 months after genetic testing and post-test counseling (T2, Figure 1). If patients were under 16 years of age or intellectually disabled, one of their parents or caretakers was asked to complete the questionnaires for their child, but from their own perspective. We will use the term 'participants' for those patients or parents who completed the questionnaires. For one patient, a legal representative who was not a parent completed the questionnaires, but was included as a parent. We excluded the participants who declined genetic testing or who did not complete all three questionnaires.

Measurement instruments

We used two patient-reported outcome measures that were included in the questionnaires. Empowerment was measured using the validated Dutch version of the Genetic Counseling Outcome Scale (GCOS). The Dutch version includes 18 of the original 24 English questions (GCOS-24), categorized into six subscales: hope and coping, knowledge about the condition, knowledge about genetic services, uncertainty about genetic services, negative emotions, and uncertainty about heredity (Supplemental Table 1 and 2).[20] The GCOS-18 shows a satisfactory internal consistency (Cronbach's $\alpha = .77$) and excellent test-retest reliability (ICC = .92).[20] Anxiety was measured with the short 6-item version of the Spielberger State-Trait Anxiety Inventory (STAI), which is a validated questionnaire that can be used to measure the psychological outcome of genetic counseling.[16,21,22] Questions on baseline characteristics were included in the first questionnaire.

After obtaining the participants' consent for extracting information from medical records, we evaluated the pre- and post-test counseling letters from the clinical geneticists for the referral

reasons, the presence of seizures, the results from genetic testing performed before and during our study, and the initiation of further genetic testing after completion of our study. The results from genetic testing were categorized into three groups: a disease-associated pathogenic variant, a variant of unknown significance, or normal test results.

Outcome

Our primary outcomes were empowerment (GCOS) and anxiety (STAI) scores throughout the genetic counseling trajectory. Secondary outcomes concerned the six subscales of empowerment.

Statistical analysis

The total and subscores on the GCOS and STAI were calculated by adding all item scores after reversing item scores for negatively formulated questions. STAI scores were converted to the 20-item STAI questionnaire to allow comparison with reference values, as recommended in the manual.[21] Missing items of the GCOS or STAI were imputed using the mean of the other GCOS item scores for that individual if ≤20% of the items were missing. If >20% items of the GCOS or STAI were missing, the participant was excluded from the analyses on this questionnaire.

We first studied the change in empowerment and anxiety scores during the genetic counseling trajectory in the total study group using repeated measurements ANOVA tests. Indicators for change were statistical significance and effect sizes. Effect sizes were calculated with the formula $x = \frac{Mean_{T2} - Mean_{T0}}{pooled\ SD}$ with pooled SD $\sqrt{(SD_{T2}{}^2 + SD_{T0}{}^2 / 2)}$. An effect size ≥0.2 was considered small, ≥0.5 medium, and ≥0.8 large.[23] An effect size of >0.5 was considered as the threshold for a minimal clinically important change for our patient-reported outcome measurements.[24,25] To evaluate the outcome of genetic counseling on an individual level, we calculated the changes in GCOS and STAI scores between T2 and T0 and their effect sizes for each individual using the formula $\frac{\text{Score at T2} - \text{Score at T0}}{pooled\ SD\ in\ the\ total\ study\ group}$. Individual changes with an effect size >0.5 were considered a clinically relevant increase, changes with an effect size between 0.5 and -0.5 as stable, and changes with an effect size <-0.5 as a clinically relevant decrease.[24,25]

Second, we compared the total GCOS and STAI scores at baseline (T0) between participants with different demographic characteristics or genetic testing results using ANOVA tests.

Third, a full-factorial repeated measures ANOVA test was used to evaluate the influence of demographic characteristics and genetic testing results on the course of the GCOS and STAI scores over time. We also compared the number of participants with clinically relevant increased, stable, or decreased GCOS and STAI scores between subgroups of participants based on these same demographic characteristics and genetic testing results using Fisher's exact tests.

Lastly, Fisher's exact tests were also used to compare categorical baseline characteristics and independent T-tests for continuous baseline characteristics between participants who accepted

and participants who declined genetic testing and between participants who did and participants who did not complete all follow-up questionnaires.

We used SPSS Statistics Version 23.0 (IBM Corporation, NY, USA). Analyses were two-tailed. A p-value <0.05/2 was considered statistically significant for our two primary outcomes, and a p-value <0.05/6 as statistically significant for our two secondary outcomes. In the post-hoc analyses for comparisons between T0-T1, T1-T2, and T0-T2, Bonferroni corrections were applied and p-values <0.05 were considered statistically significant.

Ethical statement

The Institutional Medical Ethical Committee of the University Medical Center Groningen gave permission for this study (M13.139274). All participants gave written consent for participation in the study.

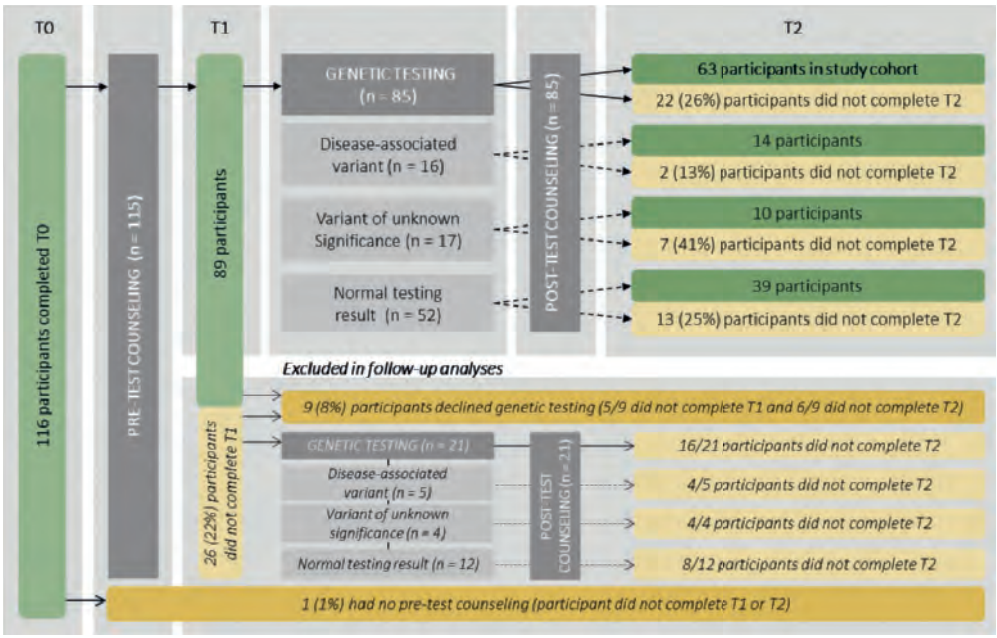
RESULTS

Characteristics of the study cohort

In total, 116 initial participants who were referred for genetic counseling and testing for epilepsy agreed to participate. Of these, 106 (91%) decided to do genetic testing and 63/106 (59%) completed all questionnaires and were included in our study (Figure 1). Table 1 shows the characteristics of all initial participants (n = 116), participants who decided to do genetic testing (n = 106), and participants included in our study cohort (n = 63).

Participants who declined genetic testing had a higher baseline empowerment compared to those who decided to perform genetic testing (p = 0.003). Furthermore, participants who declined genetic testing were more often from the UMCU (p = 0.014), more often a patient (p = 0.001) and lived more often without children (p = 0.016). Among the participants who had genetic testing, follow-up questionnaires were significantly more often completed by participants who had a higher education (p = 0.030). Other demographic characteristics, genetic testing results and baseline empowerment and anxiety scores did not differ between those who did and did not decide to do genetic testing and those who did and did not complete the follow-up questionnaires (data not shown).

Figure 1: Inclusion and exclusion of participants in our study cohort.



Empowerment

The mean empowerment score significantly increased during the genetic counseling trajectory ($p < 0.001$; Figure 2A, Table 2). The overall change in empowerment had a medium effect size ($d = 0.57$), indicating a clinically relevant increase. Empowerment was already increased after pre-test counseling compared to baseline ($p = 0.038$), and a further increase was seen after post-test counseling compared to after pre-test counseling ($p = 0.033$). Both changes had a small effect size ($d = 0.28$ and $d = 0.30$, respectively). On an individual level, 32/63 (50.8%) participants showed a clinically relevant increase in empowerment and 6/63 (9.5%) a clinically relevant decrease. In the remaining 25/63 (39.6%), empowerment scores remained stable throughout the counseling trajectory.

Anxiety

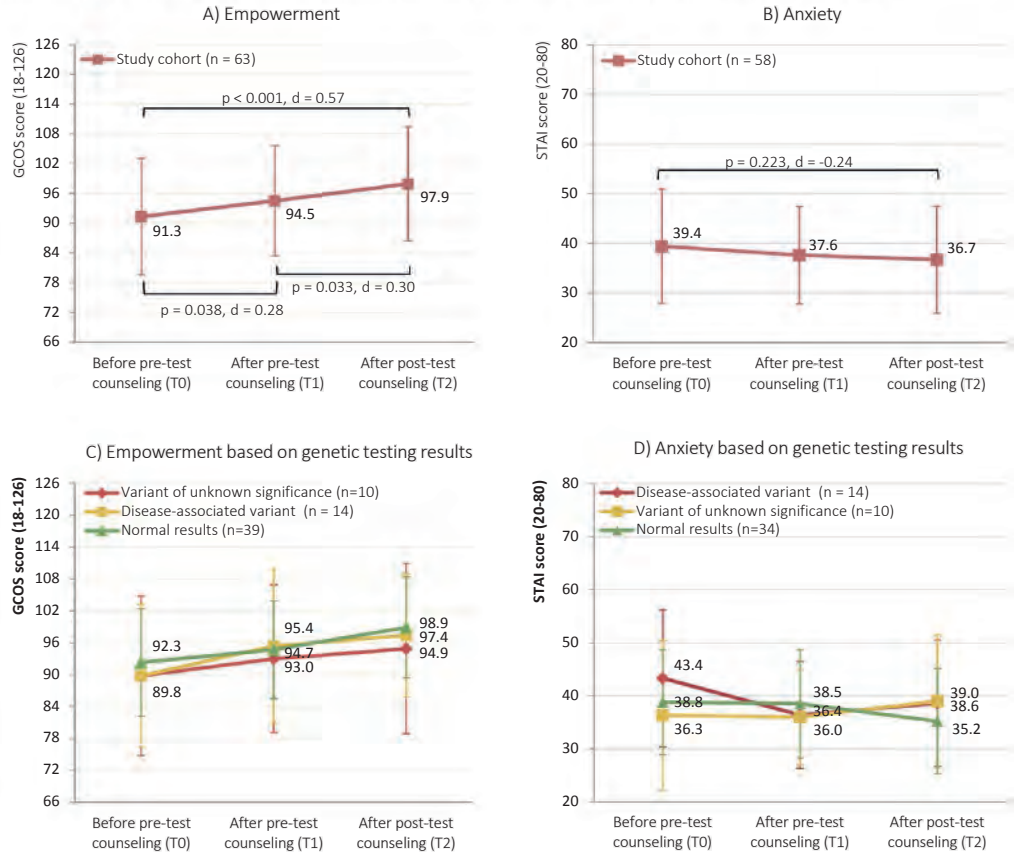
The mean anxiety score decreased during the genetic counseling trajectory, but the effect size was small ($d = -0.24$) and the differences were not statistically significant ($p = 0.223$; Figure 2B, Table 2). These results were based on 58/63 participants with <20% missing STAI items. On an individual level, we observed a clinically relevant decrease in anxiety in 23/58 (39.7%) participants, a clinically relevant increase in anxiety in 14/58 (24.1%) participants, and a stable score in the remaining 21/58 (36.2%) participants.

Table 1: Characteristics of participants

Demographic characteristics		All initial participants (n = 116)	Participants who had genetic testing (n = 106)	Study cohort (n = 63)
Hospital [1]	- UMCG (%) - UMCU (%)	70 (60.3) 46 (39.7)	68 (64.2) 38 (35.8)	45 (71.4) 18 (28.6)
Participants	- Patient (%) - Parent (%) * Mother * Father	24 (20.7) 92 (79.3) 76 (65.5) 16 (13.8)	17 (16.0) 89 (84.0) 74 (69.8) 15 (14.2)	8 (12.7) 55 (87.3) 46 (73.0) 9 (14.3)
Marital status	- Living together with children - Living together without children - Living alone with children - Single - Different situation [2]	77/115 (67.0) 16/115 (13.9) 7/115 (6.1) 5/115 (4.3) 10/115 (8.7)	74/105 (70.5) 12/105 (11.4) 5/105 (4.8) 5/105 (4.8) 9/105 (8.6)	44 (69.8) 6 (9.5) 4 (6.3) 4 (6.3) 5 (7.9)
Employment status	- Working - Studying - Unemployed - Unable to work (disabled) - Retired	64/108 (59.3) 7/108 (6.5) 25/108 (23.1) 9/108 (8.3) 3/108 (2.8)	58/98 (59.2) 6/98 (6.1) 22/98 (22.4) 9/98 (9.2) 3/98 (3.1)	34/57 (59.6) 3/57 (5.3) 14/57 (24.6) 4/57 (7.0) 2/57 (3.5)
Education level [1]	- Low (%) - Intermediate (%) - High (%)	24/110 (21.8) 56/110 (50.9) 30/110 (27.3)	21/100 (21.0) 52/100 (52.0) 27/100 (27.0)	9/58 (15.5) 28/58 (48.3) 21/58 (36.2)
Seizures	- Patient is symptomatic - Patient is pre-symptomatic [3]	114 (98.3) 2 (1.7)	104 (98.1) 2 (1.9)	61 (96.8) 2 (3.2)
Genetic testing characteristics				
Genetic testing	- Genetic testing performed between T1 and T2 (%) - Follow-up genetic testing after T2 (%)	106 (91.4) 16/109 (14.7)	106 (100) 16/105 (15.2)	63 (100) 8/62 (12.7)
Results from genetic testing	- Disease causing variant (%) - Variant of unknown significance (%) - Normal (%)	21/106 (19.8) 21/106 (19.8) 64/106 (60.4)	21 (19.8) 21 (19.8) 64 (60.4)	14 (22.2) 10 (15.9) 39 (61.9)
Baseline empowerment and anxiety				
Empowerment	- Mean total score on GCOS at T0 (SD, n)	92.3 (12.4, 115)	91.3 (12.0, 105)	91.3 (11.7, 63)
Anxiety	- Mean total score on STAI at T0 (SD, n)	40.1 (13.0, 113)	40.8 (13.0, 103)	39.6 (11.2, 62)

[1] Characteristics differed significantly between participants who were (n=63) and were not (n=57) included in the study cohort (data not shown). [2] Different situation includes living with one parent or assisted living. [3] In these participants, a disease-causing gene variant for epilepsy that was already known in the family was tested in a pre-symptomatic relative.
Abbreviations: GCOS-18 = genetic counseling outcome scale, STAI = Spielberger State-Trait Anxiety Inventory

Figure 2: Empowerment and anxiety during the genetic counseling trajectory in the study cohort (Figure A and B) and in three subgroups based on genetic testing results (Figure C and D).



The mean ± SD scores for empowerment and anxiety are presented. Empowerment significantly increased in the study cohort between T0, T1 and T2 (**A**). Anxiety scores did not decrease significantly in the study cohort (**B**). The results of genetic testing did not seem to significantly influence the course of empowerment and anxiety during the genetic counseling trajectory (**C and D**).

Of the 23 participants with a clinically relevant decreased anxiety score, 15 (65.2%) also had an increased empowerment score, 6 (26.1%) had a stable empowerment score, and only 2 (8.7%) participants had a decreased empowerment score. Furthermore, of the 14 participants with a clinically relevant increased anxiety score, only 2 (14.3%) also had a decreased empowerment score, while 8 (57.1%) had a stable empowerment score and 4 (28.6%) had an increased empowerment score.

Empowerment subscales

During the genetic counseling trajectory, significant increases in scores were seen in 3/6 subscales of the GCOS-18: knowledge about genetic services ($p = 0.008$, $d = 0.44$), uncertainty about genetic services ($p = 0.006$, $d = 0.38$), and uncertainty about heredity ($p < 0.001$, $d = 0.63$) (Table 2). Higher

scores indicated more knowledge and less uncertainty. In line with this, more participants had relevant increases in these three subscales compared to other subscales on an individual level (Table 2).

Empowerment and anxiety in subgroups of participants

At baseline, empowerment and anxiety scores did not differ between subgroups of participants based on demographic and genetic testing characteristics (see Table 1 for tested characteristics, data not shown), except that baseline anxiety scores were significantly higher in participants with a low (48.3, SD 15.0) versus an intermediate (37.2, SD 9.5) or high (37.6, SD 9.1) education level ($p = 0.020$).

The changes in empowerment and anxiety scores during the genetic counseling trajectory were not significantly influenced by the genetic testing results (Figure 2C and 2D) or other demographic or genetic testing characteristics (data not shown). Also, the number of participants with relevant increases, decreases, or stable empowerment and anxiety scores did not differ significantly between participants with different demographic and genetic testing characteristics (data not shown).

DISCUSSION

With the increasing use of genetic testing for epilepsy, there is a need to study the outcome of genetic services from the perspective of patients and their parents. We found that patients and their parents show a clinically relevant increase in empowerment after genetic counseling before and after genetic testing for epilepsy, while their feelings of anxiety did not change significantly. Some of the increase in empowerment was already seen after pre-test counseling, suggesting that pre-test counseling is an important part of the genetic counseling trajectory.

Empowerment

Empowerment is a validated overarching construct that represents many specific outcomes of genetic counseling.[19] Empowerment in our participants significantly increased on three of six subscales: knowledge about the genetic services, uncertainty about the genetic services, and uncertainty about heredity. Higher scores indicate more empowerment and less uncertainty. Translating these subscales into theoretical concepts of empowerment, our results indicate that during the genetic counseling trajectory participants made gains in behavioral control (making effective use of health and social care systems) and emotional regulation (managing feelings about having a genetic condition). Decisional control was increased in those who declined genetic testing after pre-test counseling. Knowledge about the disorder had not increased significantly, possibly because the participants had already received a lot of information about epilepsy from the referring clinicians. Also, feelings of hope about the future did not increase or decrease significantly after counseling.

Since our study was part of a larger study on the Dutch version of the GCOS-18 (n=2.194), and followed the same study design, we were able to compare our results.[20] We found similar baseline

Table 2: Effects of genetic testing and counseling on empowerment and anxiety in the study cohort

Questionnaires scores (minimum - maximum possible score)	N	Mean total scores (SD)			P-value for differences between T0, T1 and T2	Effect sizes between T0 and T2		
		Baseline (T0)	After pre-test counseling (T1)	After post-test counseling (T2)		Group level	Individual level	
							Participants with clinically relevant increase (%)	Participants with clinically relevant decrease (%)
Total GCOS score (18-126)	63	91.3 (11.7)	94.6 (11.1)	97.9 (11.5)	**<0.001***	**0.57 *****	32 (50.8)	6 (9.5)
Total STAI score (20-80)	58	39.4 (11.4)	37.6 (9.8)	36.7 (10.8)	0.180	-0.24	14 (24.1)	23 (39.7)
GCOS score on subscales [1]								
- Hope and coping (4-28)	63	22.6 (4.0)	23.2 (3.2)	23.4 (3.6)	0.222	0.21	25 (39.7)	12 (19.0)
- Knowledge condition (3-21)	63	17.7 (2.8)	17.4 (3.1)	18.0 (2.3)	0.321	0.12	17 (27.0)	16 (25.4)
- Knowledge genetic services (3-21)	63	18.2 (2.5)	18.9 (2.2)	19.2 (2.0)	**0.008 ****	0.44	23 (36.5)	6 (9.5)
- Uncertainty genetic services (3-21)	63	13.1 (4.0)	14.2 (3.4)	14.5 (3.3)	**0.006 ****	0.38	26 (41.3)	9 (14.3)
- Negative emotions (3-21)	63	13.4 (4.2)	13.5 (3.7)	14.2 (4.1)	0.092	0.19	20 (31.7)	6 (9.5)
- Uncertainty heredity (2-14)	63	6.4 (3.7)	7.4 (3.6)	8.7 (3.6)	**<0.001 ****	**0.63 *****	33 (52.4)	12 (19.0)

[1] A higher score means more empowerment for the six subscales: more hope and coping, more knowledge about the condition, more knowledge about genetic services, less uncertainty about genetic services, less negative emotions, and less uncertainty about heredity. * P-value is <0.05/2. ** P-value is <0.05/6. *** Medium effect size (d>0.5). Abbreviations: GCOS = genetic counseling outcome scale (scale for empowerment), STAI = Spielberger State-Trait Anxiety Inventory (scale for anxiety).

empowerment scores in our subcohort (mean 91.3, SD 11.7, n = 63) to those seen in the total Dutch cohort (91.7, SD 12.1, n = 2.194), as well as similar increases in empowerment in both cohorts (d = 0.57 and d = 0.52, respectively).[20,26] To date, three other studies evaluating the outcome of genetic counseling using the GCOS have also shown increased empowerment in people referred for genetic counseling and/or testing for any reason,[27] attendees at a psychiatric counseling clinic[28], and in participants with suspected inherited retinal dystrophy.[29] Further comparison with their results is not possible, since they used the GCOS-24 and not the GCOS-18.

Anxiety

Our participants had normal anxiety levels for their situation, and their anxiety did not significantly change during the genetic counseling trajectory. Although their mean baseline anxiety score (39.4) were higher compared to those in the normal adult population (30-35)[30–32], they were still at the proposed cut-off point for clinically significant anxiety symptoms (39-40).[33] Further comparison of our results with those in the literature (available for females only) shows that the mean baseline anxiety score in the females in our cohort (39.6) was slightly higher than in females making non-invasive health care decisions such as whether genetic testing should be performed (36-39) and far below scores for females making invasive health care or difficult treatment decisions (50-62).[34]

Anxiety was not well captured in the concept of empowerment. A third of the participants with decreased anxiety did not feel more empowerment, and 85% of participants with increased anxiety did not experience less empowerment. Previous studies found contrary correlations between anxiety and empowerment.[18,20] We therefore recommend also taking anxiety into account in evaluating the outcome of genetic counseling for epilepsy. Although anxiety levels did not change on a group level in our study, individual changes could occur during the genetic counseling trajectory.

The importance of pre-test counseling

The results of our study indicate that genetic counseling before initiating genetic testing for epilepsy is important. First, about half of the increase in empowerment was already seen after pre-test counseling aimed at informed decision making. In line with this, a similar increase in empowerment after the first counseling session was also seen in the total Dutch GCOS study cohort.[20] Second, our participants were not becoming more anxious when they approached genetic testing, while clinically significant anxiety scores were observed both before (47) and after (50) genetic testing in a previously published cohort without genetic counseling.[35] We therefore emphasize the importance of counseling together with genetic testing. Lastly, 9/115 (8%) of the eligible participants who had pre-test counseling decided not to do genetic testing after pre-test counseling, while they initially agreed with referral to the genetic outpatient clinic. Notably, these participants had higher baseline empowerment scores compared to those who did not decline genetic testing. It is possible that participants with higher baseline empowerment scores feel that their psychological wellbeing would benefit less from genetic testing or they are better equipped to refrain from testing after counseling.

Influence of genetic testing results on empowerment and anxiety

Empowerment was not significantly influenced by the genetic testing results. Clinicians might be worried about decreasing participant empowerment by reporting a variant of unknown significance, but all ten participants in our cohort with a variant of unknown significance showed increased empowerment after genetic counseling. However, we did observe a trend towards more anxiety in participants with a variant of unknown significance or disease-associated variant.[34] Further studies are warranted to confirm whether there is a difference in anxiety between participants with different genetic testing results, since we had relatively small subgroups and saw a large variation in anxiety scores within these subgroups.

Two previous studies have reported the outcome of genetic services in parents of children with developmental problems of whom only a minority had epilepsy. One study reported a higher quality of life in mothers of children with a diagnostic result from microarray versus those with inconclusive array results.[36] Another study identified that the experiences of parents of children with epilepsy with genetic testing vary and are associated with the genetic testing results and the presence of parental depression and anxiety after receiving these results.[37]

Limitations

We have to address two important limitations of this study. First, this study aimed at reporting the outcome of genetic counseling for epilepsy in a single cohort of participants who all underwent the same genetic counseling trajectory. We had no control group of participants who had genetic testing without counseling. Therefore, we cannot exclude the effect of other individual factors (such as life events) apart from the genetic counseling itself on the empowerment of participants during the genetic counseling trajectory. Still, empowerment was measured with the GCOS-18, which has shown to be very stable over time if no counseling occurs with an excellent test-retest reliability.[20] The changes in empowerment over time therefore likely reflect the effect of counseling (possibly together with other factors) and not of time itself. Further randomized controlled trials with different forms of counseling in different groups may help to identify which parts of counseling are most effective in terms of gaining empowerment.

Second, although we had an average responder rate of 58% (n=70/120) in the participants of one hospital (UMCG) and an unknown responder rate in the other (UMCU),[38] a significant proportion of the responders did not complete the follow-up questionnaires and were not included for the study. This drop out seemed partially explained by education level, since participants with a higher education were more likely to complete the questionnaires, but not by any other demographic or genetic testing variable or by baseline empowerment and anxiety scores. Participants more often completed the last questionnaires if they had a disease-associated variant (87%) or normal test results (75%) compared to having a variant of unknown significance (56%). Although these differences were not statistically significant, the genetic test results may have influenced the willingness of participants to complete the last questionnaire. In addition, parents mentioned

that filling out the questionnaires was time-consuming, and this may also have contributed to a lower response rate. As a result of this drop out, the size of our remaining study cohort may have been too small to detect significant differences in the effect of genetic services on empowerment and anxiety between patient subgroups, based on demographic characteristics and genetic testing results.

CONCLUSION AND FUTURE RESEARCH DIRECTIONS

Our study provides insight into the outcomes of genetic counseling before and after genetic testing for epilepsy, which may help genetic counselors of patients with epilepsy. Patients with epilepsy or their parents show increased empowerment after genetic counseling both before and after genetic testing, especially in the domains knowledge about genetic services, uncertainty about genetic services, and uncertainty about heredity. This change is independent of the results of genetic testing. Anxiety remained stable during the genetic counseling trajectory. On an individual level, half of the participants showed a clinically relevant increased empowerment. Further research is warranted to identify the individual differences in the outcome of genetic services based on demographic characteristics and genetic testing results and to identify which aspects of counseling are most effective in terms of increasing empowerment. Such studies may help to further improve the genetic counseling trajectory personalized to the participants' needs.

REFERENCES

1. Scheffer IE. Epilepsy genetics revolutionizes clinical practice. Neuropediatrics 2014; 45: 70-74.
2. Berkovic SF. Genetics of epilepsy in clinical practice. Epilepsy Curr 2015; 15: 192-196.
3. Myers CT, Mefford HC. Advancing epilepsy genetics in the genomic era. Genome Med. 2015; 7: 91.
4. Mei D, Parrini E, Marini C, Guerrini R. The Impact of Next-Generation Sequencing on the Diagnosis and Treatment of Epilepsy in Paediatric Patients. Mol Diagn Ther 2017; 21: 357-373.
5. Balestrini S, Sisodiya SM. Pharmacogenomics in epilepsy. Neurosci Lett 2018; 667: 27-39.
6. Miller DT, Adam MP, Aradhya S, et al. Consensus Statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies. Am J Hum Genet 2010; 86: 749-764.
7. Mefford HC. Clinical Genetic Testing in Epilepsy. Epilepsy Curr 2015; 15: 197-201.
8. Haddow J, Palomaki G. ACCE: A model process for evaluating data on emerging genetic tests. In: Khoury M, Little J, Burke W, eds. Human Genome Epidemiology: A Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease. Oxford: Oxford University Press; 2004.
9. Shostak S, Ottman R. Ethical, legal, and social dimensions of epilepsy genetics. Epilepsia 2006; 47:1595-1602.
10. Ottman R, Hirose S, Jain S, et al. Genetic testing in the epilepsies—Report of the ILAE Genetics Commission. Epilepsia 2010; 51: 655-670.
11. Caminiti CB, Hesdorffer DC, Shostak S, et al. Parents' interest in genetic testing of their offspring in multiplex epilepsy families. Epilepsia 2016; 57: 279-287.
12. Okeke JO, Tangel VE, Sorge ST, et al. Genetic testing preferences in families containing multiple individuals with epilepsy. Epilepsia 2014; 55: 1705-1713.
13. Shostak S, Zarhin D, Ottman R. What's at stake? Genetic information from the perspective of people with epilepsy and their family members. Soc Sci Med 2011; 73: 645-654.
14. Vears DF, Dunn KL, Wake SA, Scheffer IE. "It's good to know": Experiences of gene identification and result disclosure in familial epilepsies. Epilepsy Res 2015; 112: 64-71.
15. Resta R, Biesecker BB, Bennett RL, et al. A new definition of genetic counseling: National Society of Genetic Counselors' Task Force report. J Genet Couns 2006; 15: 77-83.
16. Madlensky L, Trepanier AM, Cragun D, Lerner B, Shannon KM, Zierhut H. A Rapid Systematic Review of Outcomes Studies in Genetic Counseling. J Genet Counsel 2017: 26; 361-378.
17. Mcallister M, Payne K, Macleod R, Nicholls S, Dian Donnai, Davies L. Patient empowerment in clinical genetics services. J Health Psychol 2008; 13: 895-905.
18. Mcallister M, Wood A, Dunn G, Shiloh S, Todd C. The Genetic Counseling Outcome Scale: A new patient-reported outcome measure for clinical genetics services. Clin Genet 2011; 79:413-424.
19. McAllister M, Dearing A. Patient reported outcomes and patient empowerment in clinical genetics services. Clin Genet 2015; 88: 114-121.
20. Voorwinden JS, Plantinga M, Krijnen W, et al. A validated PROM in genetic counseling: the psychometric properties of the Dutch version of the Genetic Counseling Outcome Scale. Manuscript under review.
21. Marteau TM, Bekker H. The development of a six item short form of the state scale of the Spielberger State Trait Anxiety Inventory (STAI). Br J Clin Psychol 1992; 31: 301-306.
22. Otten E, Birnie E, Ranchor A V, Tintelen JP Van, Langen IM Van. A group approach to genetic counselling of cardiomyopathy patients : satisfaction and psychological outcomes suf fi cient for further implementation. Eur J Hum Genet 2015; 23: 1462-1467.
23. Cohen J. editor. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. New York, USA: Academic Press,1988.
24. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol 2008; 61: 102-109.
25. Angst F, Aeschlimann A, Angst J. The minimal clinically important difference raised the significance of outcome effects above the statistical level, with methodological implications for future studies. J Clin Epidemiol 2017; 82: 128-136.
26. Voorwinden JS, Plantinga M, Ausems M, et al. a large outcome study on genetic counseling in the Netherlands: empowerment and emotional functioning. Manuscript in Preparation.
27. Costal Tirado A, McDermott AM, Thomas C, et al. Using Patient-Reported Outcome Measures for Quality Improvement in Clinical Genetics: an Exploratory Study. J Genet Couns 2017; 26: 1017-1028.
28. Inglis A, Koehn D, Mcgillivray B, Stewart SE, Austin J. Evaluating a unique, specialist psychiatric genetic counseling clinic: uptake and impact. Clin Genet. 2016; 87: 218-224.
29. Davison N, Payne K, Eden M, et al. Exploring the feasibility of delivering standardized genomic care using ophthalmology as an example. Genet Med 2017; 19: 1032-1039.
30. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA, editors. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press, 1983.
31. Forsberg C, Bjiirvell H. Swedish population norms for the GRHI, HI and STAI-state. Qaulity life Res 1993; 2: 349-356.
32. Knight RG, Waal-Manning HJ, Spears GF. Some norms and reliability data for the State-Trait Anxiety Inventory and th eZung Self-Rating Depression scale. Br J Clin Psychol 1983; 22: 245-249.

33. Julian LJ. Measures of Anxiety. Arthritis Care 2011; 63: 1-11.
34. Bekker HL, Legare F, Stacey D, O'Connor A, Lemyre L. Is anxiety a suitable measure of decision aid effectiveness: A systematic review? Patient Educ Couns 2003; 50: 255-262.
35. Dinc L, Terzioglu F. The psychological impact of genetic testing on parents. J Clin Nurs 2006; 15: 45-51.
36. Lingen M, Albers L, Borchers M, et al. Obtaining a genetic diagnosis in a child with disability: Impact on parental quality of life. Clin Genet 2016; 89: 258-266.
37. Wynn J, Ottman R, Duong J, et al. Diagnostic exome sequencing in children: A survey of parental understanding, experience and psychological impact. Clin Genet 2017; 93: 1039-1048.
38. Baruch Y, Holtom BC. Survey response rate levels and trends in organizational research. Hum Relations 2008; 61: 1139-1160.

SUPPLEMENTAL DATA

Supplemental Table 1: The English version of the Genetic Counseling Outcome Scale

The Genetic Counseling Outcome Scale (GCOS-24)

Using the scale below, circle a number next to each statement to indicate how much you agree with the statement. Please answer all the questions. For questions that are not applicable to you, please choose option 4 (neither agree or disagree).

	1 = Strongly disagree 2 = Disagree 3 = Slightly disagree 4 = Neither disagree nor agree 5 = Slightly agree 6 = Agree 7 = Strongly agree	**Strongly disagree**	**Disagree**	**Slightly disagree**	**Neither disagree nor agree**	**Slightly agree**	**Agree**	**Strongly agree**
1	I am clear in my own mind why I am attending the clinical genetics service.	1	2	3	4	5	6	7
2	I can explain what the condition means to people in my family who may need to know.	1	2	3	4	5	6	7
3	I understand the impact of the condition on my child(ren) / any child I may have.	1	2	3	4	5	6	7
4	When I think about the condition in my family, I get upset.	1	2	3	4	5	6	7
5	I don't know where to go to get the medical help I / my family need(s).	1	2	3	4	5	6	7
6	I can see that good things have come from having this condition in my family.	1	2	3	4	5	6	7
7	I can control how this condition affects my family.	1	2	3	4	5	6	7
8	I feel positive about the future.	1	2	3	4	5	6	7
9	I am able to cope with having this condition in my family.	1	2	3	4	5	6	7
10	I don't know what could be gained from each of the options available to me.	1	2	3	4	5	6	7
11	Having this condition in my family makes me feel anxious.	1	2	3	4	5	6	7
12	I don't know if this condition could affect my other relatives (brothers, sisters, aunts, uncles, cousins).	1	2	3	4	5	6	7
13	In relation to the condition in my family, nothing I decide will change the future for my children / any children I might have.	1	2	3	4	5	6	7
14	I understand the reason why my doctor referred me to the clinical genetics service.	1	2	3	4	5	6	7
15	I know how to get the non-medical help I / my family needs (e.g. educational, financial, social support).	1	2	3	4	5	6	7
16	I can explain what the condition means to people outside my family who may need to know (e.g. teachers, social workers).	1	2	3	4	5	6	7
17	I don't know what I can do to change how this condition affects me / my family.	1	2	3	4	5	6	7
18	I don't know who else in my family might be at risk for this condition.	1	2	3	4	5	6	7
19	I am hopeful that my children can look forward to a rewarding family life.	1	2	3	4	5	6	7
20	I am able to make plans for the future.	1	2	3	4	5	6	7
21	I feel guilty because I (might have) passed this condition on to my children.	1	2	3	4	5	6	7
22	I am powerless to do anything about this condition in my family.	1	2	3	4	5	6	7
23	I understand what concerns brought me to the clinical genetics service.	1	2	3	4	5	6	7
24	I can make decisions about the condition that may change my child(ren)'s future / the future of any child(ren) I may have.	1	2	3	4	5	6	7

(For the GCOS-18 item 6,7,13,15,22,24 need to be removed; all the items of the negative emotions and the two uncertainty scales need to be reversed to calculate a total score for empowerment)

Supplemental Table 2: The subscales of the Dutch version of the GCOS

Subscale	Question
Hope and coping (HC)	8. I feel positive about the future. 20. I am able to make plans for the future. 9. I am able to cope with having this condition in my family. 19. I am hopeful that my children can look forward to a rewarding family life.
Knowledge about the condition (KC)	2. I can explain what the condition means to people in my family who may need to know. 3. I understand the impact of the condition on my child(ren) / any child I may have. 16. I can explain what the condition means to people in my family who may need to know.
Knowledge about genetic services (KG)	1. I am clear in my own mind why I am attending the clinical genetics service. 23. I understand what concerns brought me to the clinical genetics service. 14. I understand the reasons why my doctor referred me to the clinical genetics service.
Uncertainty about genetic services (UG)	17. I don't know what I can do to change how this condition affects me/my children. 5. I don't know where to go to get the medical help I/my family need(s). 10. I don't know what could be gained from each of the options available for me.
Negative emotions (NE)	4. When I think about the condition in my family, I get upset. 11. Having this condition in my family makes me feel anxious. 21. I feel guilty because I (might have) passed this condition on to my children.
Uncertainty about heredity (UH)	12. I don't know if this condition could affect my other relatives (brothers, sisters, aunts, uncles, cousins). 18. I don't know who else in my family might be at risk for this condition.

PART II

Genotype-phenotype studies