Universiteit Antwerpen

This item is the archived peer-reviewed author-version of:

Attitudes of potential participants towards potential gene therapy trials in autosomal dominant progressive sensorineural hearing loss

Reference:
Levie Camille, Moyaert Julie, Janssens de Varebeke Sebastien, Verdoodt Dorien, Vanderveken Olivier M., Topsakal Vedat, Van Wijk Erwin, de Vrieze Erik, Pennings Ronald, Van de Berg Raymond, ...- Attitudes of potential participants towards potential gene therapy trials in autosomal dominant progressive sensorineural hearing loss
Otology and neurotology - ISSN 1531-7129 - 42:3(2021), p. 384-389
Full text (Publisher's DOI): https://doi.org/10.1097/MAO.0000000000002981
To cite this reference: https://hdl.handle.net/10067/1755180151162165141

uantwerpen.be
Institutional repository IRUA

Attitudes of Potential Participants Towards Potential Gene Therapy Trials in Autosomal Dominant Progressive Sensorineural Hearing Loss.

A hypothetical scenario methodology in DFNA9 patients.

Camille Levie, MD[1]

Julie Moyaert, MSc[1]

Sebastien JanssensdeVarebeke, MD[2,3]

Dorien Verdoodt, MSc[3]

Olivier M. Vanderveken, MD, PhD[1,3]

Vedat Topsakal, MD, PhD[1,3]

Erwin Van Wijk, MSc, PhD[4,5]

Erik Devrieze, MSc, PhD[4,5]

Ronald Pennings, MD, PhD[4,5]

Raymond Van de Berg, MD, PhD[6,7]

Guy Van Camp, MSc, PhD[8]

Peter Ponsaerts, MSc, PhD[9]

Vincent Van Rompaey, MD, PhD[1,3]

[1]Department of Otorhinolaryngology and Head & Neck surgery, Antwerp University Hospital, Edegem, Belgium

[2]Department of Otorhinolaryngology and Head & Neck Surgery, Jessa Hospital, Hasselt, Belgium

[3]Department of Translational Neurosciences, Faculty of Medicine and Health Sciences, University of Antwerp, Belgium

[4]Department of Otorhinolaryngology, Radboud University Medical Center, Nijmegen, the Netherlands.

[5]Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands.

[6]Division of Balance Disorders, Department of ENT, Maastricht University Medical Centre, Maastricht, The Netherlands.

[7]Faculty of Physics, Tomsk State University, Tomsk, Russia.

[8]Centre of Medical Genetics, University of Antwerp and Antwerp University Hospital, Belgium

[9]Laboratory of Experimental Hematology, Faculty of Medicine and Health Sciences, Vaccine and Infectious Disease Institute (VaxInfectio), University of Antwerp, Belgium.

Background: Advances in gene and molecular therapeutic approaches to treat sensorineural hearing loss (SNHL) confront us with future challenges of translating these animal studies into clinical trials. Although restoring hearing up to a certain level has become mainstream because of cochlear implantation, little is known on patient attitudes towards preventing, stabilizing or slowing down progression of SNHL by means of future innovative therapies.

Objective: We aimed to better understand the willingness of patients with progressive SNHL and vestibular function loss of autosomal dominant (AD) inheritance to participate in potential gene therapy trials to prevent, stabilize or slow down hearing loss.

Methods: A survey was performed in carriers of the P51S and G88E pathogenic variant in the *COCH* gene (DFNA9). Various hypothetical scenarios were presented while using a Likert scale to study willingness to participate in potential innovative therapies.

Results: A total of 53 participants were included, incl. 49 symptomatic patients, 1 pre-symptomatic pathogenic variant carrier and 3 participants at risk (hearing loss and positive family history, but no genetic confirmation). Their attitude towards potential trials studying innovative therapies was overall affirmative, even if the treatment would only halt or slow down the decline of hearing and vestibular function, rather than cure the disease. Among the different potential scenarios, the less invasive treatments and those yielding less frequent therapeutic contacts/handlings increased the likelihood to enroll. Daily oral medication and annual intravenous infusion were awarded the highest scores. The more invasive scenario of a single injection in the ear was still likely to be accepted but the willingness to participate decreased if multiple injections would be necessary or the intervention would yield a high risk. The presence of a placebo arm was met with the lowest scores of willingness to participate.

Conclusions: Overall, most symptomatic DFNA9 patients would likely consider participation in future innovative inner ear therapy trials, even if it would only slow down the decline of hearing and vestibular function. However, they were less unequivocal on high-risk treatments or a placebo-controlled study

design. These data can be used to inform the recruitment and consent process into future innovative treatments to treat autosomal dominant nonsyndromic SNHL.

Introduction

Hearing loss has a significant impact on quality of life and society in general. Hearing impairment is the most frequent sensory deficit, affecting 360 million people worldwide. [1] For this reason, it has been listed by the World Health Organization as priority diseases for research into therapeutic interventions to address public health needs. [2, 3] Hearing aids may be used in moderate to severe sensorineural hearing loss (SNHL) [4], while cochlear implantation (CI) can rehabilitate hearing in severe-to-profound SNHL. [5-7]

Nonsyndromic hearing impairment is a partial or total impairment of hearing not associated with other signs and symptoms. Between 75 and 80 percent of cases are inherited through an autosomal recessive (AR) pattern, while another 20 to 25 percent of nonsyndromic hearing impairment have an autosomal dominant (AD) pattern of inheritance, which means one copy of the altered gene in each cell is sufficient to cause the condition. Consequently, the inheritance rate is 50%. Most reported disorders with postlingual nonsyndromic SNHL demonstrate AD inheritance.

DFNA9 is an AD inherited disorder, caused by heterozygous gain-of-function mutations or pathogenic variants in the *COCH* gene. To date, 27 different variants have been identified worldwide, and four of these were described in families from Belgium or the Netherlands. [8] The phenotype is characterized by a progressive SNHL, starting from the 3^{rd}-4^{th} decade, followed by a rapid decline to severe-to-profound SNHL by the 6^{th}-7^{th} decade. [9-11] Progressive vestibular dysfunction eventually evolves towards bilateral vestibular function loss (bilateral vestibulopathy, BVP), which mainly causes oscillopsia and imbalance while walking (especially in the dark). [12-17] The suggested pathophysiology of *COCH* variants is transcription of a mutated isoform of the cochlin protein, the most abundant protein in the inner ear. [18] This pathogenic variant leads to multimeric aggregates that are secreted into the extracellular matrix, while protein deposition or fibrosis can be observed in the semi-circular canals (SCC) on T2-weighted magnetic resonance imaging. [19, 20]

Currently, no treatment is available to prevent or slow down SNHL or BVP in DFNA9 patients. Moreover, the treatment of the established condition of BVP is still unmet, in contrast to SNHL.

More than 100 clinical trials that evaluate novel inner ear are ongoing worldwide, while only one of these trials involves gene therapy. The latter is the first-in-human phase 1/2 clinical trial (supported by the FDA) to upregulate the atonal gene (ATOH1) in supporting cells of the inner ear and to trigger transdifferentiation into functional hair cells. [21] For a review on the current state-of-art on gene therapy for human SNHL, please refer to the following papers. [22, 23] Recently reported rodent studies have generally been aiming (1) to restore hearing in case of congenital SNHL by recovery of gene and protein expression, and subsequent restoration of sensory cell function, e.g. in Usher type 1c [24] or Usher type 1g [25]; (2) to prevent, stabilize or slow down SNHL in case of progressive SNHL in the mature cochlea, e.g. *TMC1*. [26]

Currently, over 40 genes have been described that are implicated in AD nonsyndromic hearing impairment. [27] Unique features in many of these AD disorders include: potential carriers are aware of their family history, including hearing-impaired relatives using HA and CI, and the impact of SNHL on quality of life; potential carriers are able to determine their carrier status by means of routine genetic testing; once carrier status has been achieved, a significant pre-symptomatic interval starts amounting up to several years; and carriers are aware they will likely develop bilateral severe-to-profound SNHL and complete loss of vestibular function.

In the perspective of relatively low adoption rates of hearing rehabilitation options, such as HA and CI among hearing impaired carriers, despite their advanced impairment, one would be interested to investigate if this restraint would also exist regarding innovative therapeutic strategies, such as gene therapy.

The aim of this study is to explore the attitudes of DFNA9 patients towards different therapeutic interventions in a hypothetical scenario methodology.

Methods

Ethics committee approval. The Committee for Medical Ethics of the Antwerp University Hospital approved the study (file number: 19/34/387). All participants gave written informed consent.

Study design. We designed a questionnaire-based study to assess the attitudes towards potential gene therapy clinical trials in possible future study participants and used hypothetical scenario methodology, as previously reported in genetic research. [28]

Population. Patients were recruited through the Dutch and Belgian DFNA9 patient association "De Negende Van…" at the annual patient meeting. We included participants aged 18 years or older: individuals diagnosed with DFNA9 (confirmed by blood sample) in the symptomatic stage; individuals diagnosed with DFNA9 (confirmed by blood sample) in the pre-symptomatic stage; and individuals at-risk for DFNA9 (hearing loss and positive family history) with no genetic testing. Demographic data were collected, such as age, gender and education of the participants as well as data on the onset age of hearing loss and/or dizziness.

A survey consisting of Likert scale responses and several multiple-choice questions were utilized including hypothetical scenarios. We generated hypothetical interventions, e.g. daily oral intake of an active molecule, monthly or yearly injection of an active agent in the inner ear. Different factors that may affect the decision-making of participation in clinical trials, such as placebo-controlled methodology, were examined.

The Likert scale of *willingness to participate* is built up by a series of multiple choice questions limited to the following possible answers: "very unlikely, unlikely, likely, very likely", whereas the Likert scale of i*mportance* limits the answers to only 3 possible answers: very important, important, not important" (figures 2 and 3). Each answer was categorized as indicated in the figures and legends.

Results

A total of 53 participants completed the questionnaire. The majority of patients were symptomatic *COCH* gene pathogenic variant carriers (n=49), of which 46 patients had both hearing and vestibular complaints, whereas only 3 patients had vestibular loss without subjective hearing loss. None had subjective hearing loss with normal vestibular function. Only 1 participant was a pre-symptomatic carrier and only 3 participants were at risk with hearing loss and a positive family history. Table 1 summarizes the demographics of the population.

Table 1: Demographic characteristics per subgroup. SD, standard deviation; GED, general educational diploma.

	Total	**At Risk**	**Presymptomatic**	**Symptomatic**
Number	53	3	1	49
Number of males (%)	18 (34)	2 (66,7)	1 (100)	15 (30,6)
Mean age ± SD (years)	57,7 ± 9,6	70,3 ± 7,1	35	57,34 ± 8,79
Education level				
GED	1	0	0	1
High School	18	1	0	17
Higher Education	15	1	1	13
University Bachelor	8	1	0	7
Unversity Master	8	0	0	8
Doctorate	3	0	0	3

All 49 symptomatic patients described dizziness with an average age of symptom onset at 40,53 ± 10,83 years old. Hearing loss was reported in 46 patients with a mean age of onset of 44,20 ± 5,81 years old, while 3 patients reported no subjective hearing loss.

Different scenarios were presented, as demonstrated in figure 1.

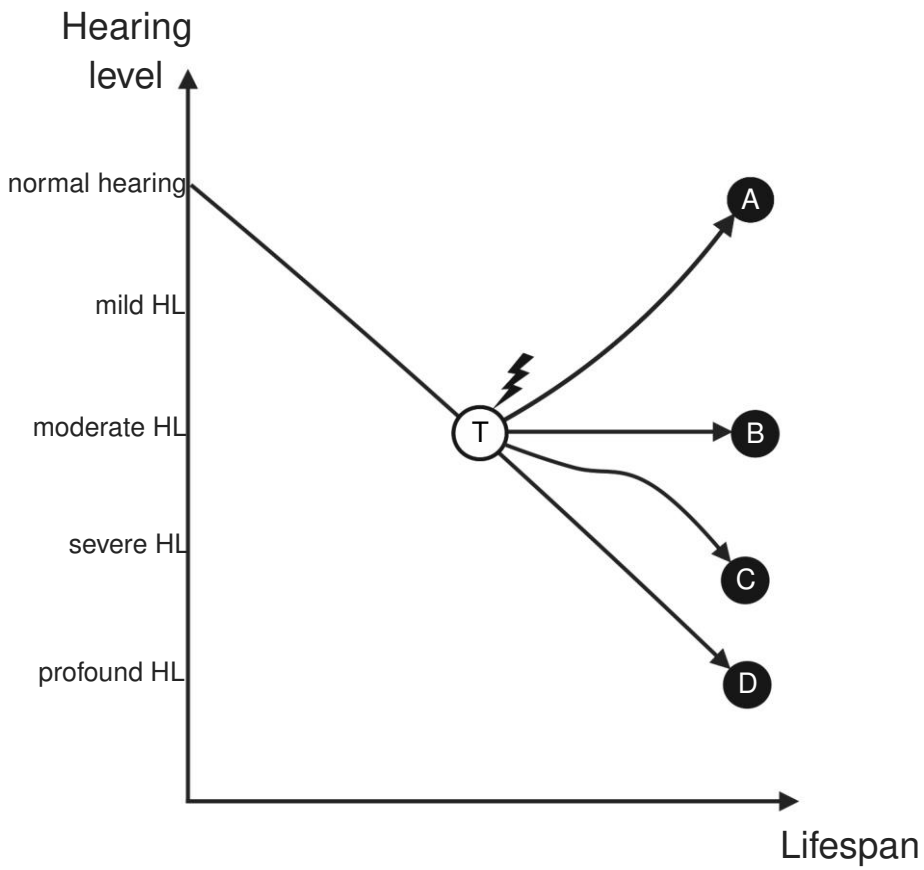


Figure 1. Hypothetical scenarios in case of progressive hearing loss when treated with an innovative therapy (T): A, improvement of hearing level, B, stabilizing hearing level; C, slow down progression of hearing loss; D, natural evolution of progressive hearing loss.

Figure 2 lists the questions about the willingness to participate and the Likert scale for each question. As shown in Figure 2, a positive attitude was observed towards participation in future clinical trials. The likelihood of willingness to participate was lowest when there was a high risk associated to any potential intervention, but the average answer was still relatively positive. In the different potential clinical trial designs, those treatment strategies with less invasive approaches and consisting of less frequent treatment contacts (or handling to achieve satisfactory results) increased the likelihood for enrollment: e.g. “taking a pill daily” and “intravenous infusion yearly” were awarded the highest scores. The more invasive scenario of a single injection in the ear was still likely to be accepted but the

willingness to participate decreased if monthly injections would be necessary. The presence of a placebo arm also lowered the likelihood to participate.

Figure 2. Willingness to participate in potential future clinical trials

A. Objectives of a potential innovative treatment

1. How likely are you to participate in future gene therapy trials?
2. … to cure hearing and vestibular loss in DFNA9
3. … to slow the progressive hearing and vestibular loss
4. … to stop the progressive hearing and vestibular loss
5. … knowing there is no immediate benefit to you but will definitely help future generations?
6. … knowing there is no immediate benefit to you but will possibly help future generations?
7. … knowing that there is no risk to you but limited improvement of your condition
8. … knowing that there is a high risk to you but a high improvement of your condition?

B. Administration of a potential innovative treatment

How likely are you to participate in future gene therapy trials if the treatment is

9. … taking a pill once a day
10. … an IV infusion in the arm once a month requiring a clinic visit
11. … an IV infusion in the arm once a year requiring a clinic visit
12. … an injection in the ear once a month requiring a clinic visit
13. … an injection in the ear once a year requiring a clinic visit
14. … a single injection in the ear requiring a clinic visit
15. … an injection in only one ear
16. … an injection in both ears simultaneously

C. Study design

17. How likely are you to participate in future gene therapy trials if there is a chance you receive a placebo

Likert scale: 0. Very unlikely 1. Unlikely 2. Likely 3. Very likely

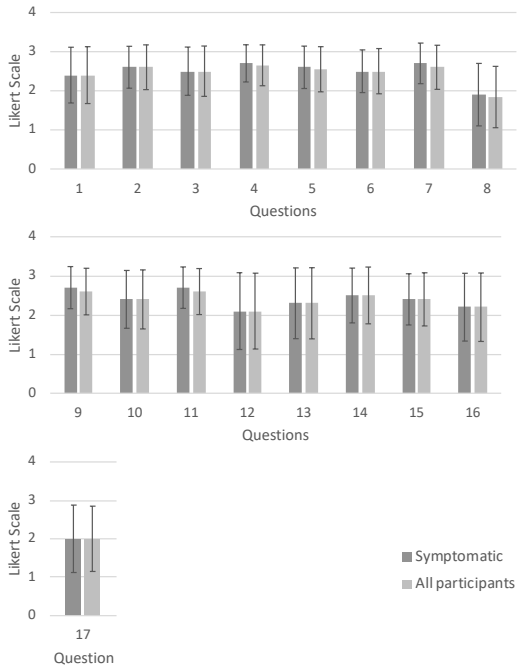


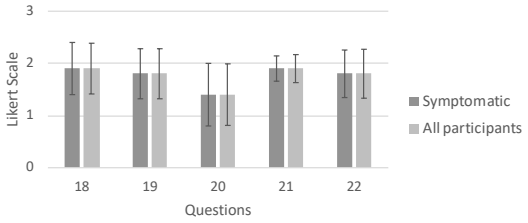
Figure 3 shows the questions about the importance of different factors in the decision-making as used in the Likert scale for each question. As shown in Figure 3, all the different factors were considered important between 'somewhat important' and 'very important'. Helping the children and curing DFNA9 scored the highest and the risk to the patient scored the lowest.

Figure 3. Factors that influence the decision to participate in potential clinical trials

D. How important are the following factors in your decision to participate in clinical trials?

18. Helping my children who are at risk
19. Improving my quality of life
20. Risk to myself
21. Curing DFNA9
22. Helping science

Likert scale: 0. Not important 1. Somewhat important 2. Very important



Discussion

A survey was performed to test various hypothetical scenarios for willingness to participate in future clinical trials involving potential innovative therapies. Overall, most patients would likely consider participation in future innovative inner ear therapy trials, even if it would only slow down the decline of hearing and vestibular function.

Hearing rehabilitation in patients with SNHL includes acoustic HA to amplify sounds for patients with mild-to-moderate SNHL and unilateral CI for cases of severe-to-profound SNHL for whom amplification does no longer lead to meaningful speech perception. Despite the availability of these treatments, hearing-impaired patients are often reluctant to adopt. According to the 2017 EuroTrak data, the hearing loss prevalence in Belgium is 11.5% in adults (11.8% in the Netherlands), while the hearing aid adoption rate is only 30.6% in adults (41.1% in the Netherlands) [29][30]. CI is an effective treatment for severe-to-profound SNHL in adults and children that do not benefit from HA [31][32]. Congenital bilateral severe-to-profound SNHL is identified at a very young age using neonatal hearing screening and the cochlear implantation rate in children is high. In contrast, potential adult CI candidates are more reserved to adopt this treatment strategy, with less than 10% of those with severe-to-profound bilateral SNHL receiving a CI. This low rate is widespread, regardless of geographical location, and is independent of how health services are organized and country-specific economic output [33]. The low adoption rates of HA as well as CI raised the question whether or not *COCH* gene pathogenic variant carriers would present identical behaviour to potential gene therapy trials. DFNA9 is a highly relevant population: the awareness of pre-symptomatic carriers of their medical family history, the impact of DFNA9 on hearing and vestibular impairment in daily life as experienced by their next of kin and the knowledge that they are at risk of carrying the pathogenic variant.

Recently, innovative inner ear therapies, including in vivo gene therapy, have been reported in rodents as well as in human clinical trials in order to (partially) reverse SNHL. [21] In case of AD progressive adult-onset SNHL (such as DFNA9), the aims of future innovative inner ear therapies could be to

reverse the symptomatology and to cure the disease, to stabilize or slow down the evolution of symptoms from an annual deterioration rate of 3 dBHL per year to 1 dBHL per year, comparable to presbyacusis. [11]

Considering the relatively low rates of HA and CI adoption in adults, the aim of this study was to study patients' attitudes on potential gene therapy trials to prevent the hearing decline towards severe-to-profound SNHL, as demonstrated in figure 1. These innovative inner ear therapies may have limited effect on treating the progression of hearing loss by merely slowing down or stabilizing the decline, meanwhile the recipient may expect curing the SNHL. Similar work has been performed in AD progressive neurodegenerative diseases such as Huntington's disease (HD). However, HD has a significantly higher impact on quality of life than bilateral severe-to-profound SNHL, as demonstrated by respective mean EQ-5D scores of 0.30-0.56 versus 0.95. [34-37]

Throughout the survey patients reported that they were likely to very likely to participate in any potential future gene therapy trials to cure their symptoms or stabilize their symptom progression. A less obvious and yet remarkable finding was that patients were still likely to very likely to participate in any potential gene therapy trial, even if the therapy would only slow down their symptom progression (rather than cure or stabilize the symptoms). This information yields important consequences for willingness to enrolment to future innovative treatment strategies.

The lowest survey scores were observed when patients were asked if they would consider a high-risk treatment (e.g. small risk of deafness due to the approach, similar as in conventional ear surgery) in order to reach a high gain, which tells us there is a limit to the risk they are willing to take to cure their symptoms [38]. Additionally, lower scores were observed when asking patients whether they would consider entering in a potential gene therapy clinical trial if it includes a placebo arm. The latter finding will have a significant impact on study design in any future study design on innovative inner ear therapies and raises potential ethical issues in the design of future clinical studies of this kind. The outcome of the present study is not necessarily applicable to other AD disorders leading to severe-to-

profound SNHL, let alone age-related SNHL without an identifiable genetic etiology. One cannot emphasize enough the importance of vestibular impairment in affecting the quality of life to carriers. This may further motivate carriers to show a higher rate of willingness to participate.

Limitations of this study include the relatively small sample size of symptomatic carriers, which are all members of a patient association advocating for innovative treatment to cure DFNA9. Another limitation is the hypothetical scenario methodology being used in a lay population that is unaware of drug development stages. We tried to overcome this by giving a plenary introductory session preceding the completion of the survey explaining basic aspects on development stages of innovative inner ear therapies (first and last author). Moreover, the DFNA9 patients also suffers from BVP which increases disease burden. Despite the limitations mentioned above, the outcome of the survey was relatively positive towards potential gene therapy trials to counter SNHL, which will spark further research expanding into other AD disorders causing adult-onset progressive SNHL and other populations with different potentially treatable etiologies of SNHL.

Conclusion

Overall, most DFNA9 patients would likely consider participation in future innovative inner ear therapy trials, even if it would only slow down the decline of hearing and vestibular function. However, they were less unequivocal on high-risk treatments or on a placebo-controlled study design. These data can be used for recruitment and consent processes of future innovative treatments to treat autosomal dominant nonsyndromic SNHL, but raises questions on the attitudes of patients suffering from otologic disorders other than DFNA9.

References

1. WHO. *Priority Medicines for Europe and the World Update Report*. 2013 26th January 2017]; Available from: http://www.who.int/medicines/areas/priority_medicines/Ch6_21Hearing.pdf.
2. World Health Organization. *Dementia: Fact sheets*. 2016 [cited 2017 March 1st]; Available from: http://www.who.int/mediacentre/factsheets/fs362/en/.
3. D'Haese, P.S.C., et al., *Severe Hearing Loss in the Aging Population Poses a Global Public Health Challenge. How Can We Better Realize the Benefits of Cochlear Implantation to Mitigate This Crisis?* Front Public Health, 2019. **7**: p. 227.
4. Wei, J., et al., *Hearing Impairment, Mild Cognitive Impairment, and Dementia: A Meta-Analysis of Cohort Studies.* Dement Geriatr Cogn Dis Extra, 2017. **7**(3): p. 440-452.
5. Cosetti, M.K. and A.K. Lalwani, *Is cochlear implantation safe and effective in the elderly?* Laryngoscope, 2015. **125**(6): p. 1279-81.
6. Claes, A.J., et al., *Impaired Cognitive Functioning in Cochlear Implant Recipients Over the Age of 55 Years: A Cross-Sectional Study Using the Repeatable Battery for the Assessment of Neuropsychological Status for Hearing-Impaired Individuals (RBANS-H).* Front Neurosci, 2018. **12**: p. 580.
7. Claes, A.J., et al., *Cognitive outcomes after cochlear implantation in older adults: A systematic review.* Cochlear Implants Int, 2018. **19**(5): p. 239-254.
8. De Belder, J., et al., *Does Otovestibular Loss in the Autosomal Dominant Disorder DFNA9 Have an Impact of on Cognition? A Systematic Review.* Front Neurosci, 2017. **11**: p. 735.
9. Chen, D.Y., et al., *Clinical characterization of a novel COCH mutation G87V in a Chinese DFNA9 family.* Int J Pediatr Otorhinolaryngol, 2013. **77**(10): p. 1711-5.
10. Bom, S.J., et al., *Cross-sectional analysis of hearing threshold in relation to age in a large family with cochleovestibular impairment thoroughly genotyped for DFNA9/COCH.* Ann Otol Rhinol Laryngol, 2003. **112**(3): p. 280-6.
11. JanssensdeVarebeke, S., et al., *A systematic review of hearing and vestibular function in carriers of the Pro51Ser mutation in the COCH gene.* Eur Arch Otorhinolaryngol, 2019. **276**(5): p. 1251-1262.
12. Robertson, N.G., et al., *A targeted Coch missense mutation: a knock-in mouse model for DFNA9 late-onset hearing loss and vestibular dysfunction.* Human Molecular Genetics, 2008. **17**(21): p. 3426-3434.
13. Bom, S.J., et al., *Non-syndromal autosomal dominant hearing impairment: ongoing phenotypical characterization of genotypes.* Br J Audiol, 1999. **33**(5): p. 335-48.
14. Bom, S.J.H., et al., *Progressive Cochleovestibular Impairment Caused by a Point Mutation in the COCH Gene at DFNA9.* The Laryngoscope, 1999. **109**(9): p. 1525-1530.
15. Bischoff, A.M., et al., *Vestibular deterioration precedes hearing deterioration in the P51S COCH mutation (DFNA9): an analysis in 74 mutation carriers.* Otol Neurotol, 2005. **26**(5): p. 918-25.
16. Kemperman, M.H., et al., *Audiometric, vestibular, and genetic aspects of a DFNA9 family with a G88E COCH mutation.* Otol Neurotol, 2005. **26**(5): p. 926-33.
17. Lucieer, F., et al., *Full Spectrum of Reported Symptoms of Bilateral Vestibulopathy Needs Further Investigation-A Systematic Review.* Front Neurol, 2018. **9**: p. 352.
18. Calzada, A.P., et al., *Cochlin expression in vestibular endorgans obtained from patients with Meniere's disease.* Cell Tissue Res, 2012. **350**(2): p. 373-84.
19. Van Rompaey, V., et al., *Semicircular Canal Fibrosis as a Biomarker for Lateral Semicircular Canal Function Loss.* Front Neurol, 2016. **7**: p. 43.
20. de Varebeke, S.P., et al., *Focal sclerosis of semicircular canals with severe DFNA9 hearing impairment caused by a P51S COCH-mutation: is there a link?* Otol Neurotol, 2014. **35**(6): p. 1077-86.
21. Praetorius, M., et al., *Adenoviral vectors for improved gene delivery to the inner ear.* Hear Res, 2009. **248**(1-2): p. 31-8.
22. Ren, Y., L.D. Landegger, and K.M. Stankovic, *Gene Therapy for Human Sensorineural Hearing Loss.* Front Cell Neurosci, 2019. **13**: p. 323.

23. Omichi, R., et al., *Gene therapy for hearing loss.* Hum Mol Genet, 2019.
24. Pan, B., et al., *Gene therapy restores auditory and vestibular function in a mouse model of Usher syndrome type 1c.* Nat Biotechnol, 2017. **35**(3): p. 264-272.
25. Emptoz, A., et al., *Local gene therapy durably restores vestibular function in a mouse model of Usher syndrome type 1G.* Proc Natl Acad Sci U S A, 2017. **114**(36): p. 9695-9700.
26. Yoshimura, H., et al., *Targeted Allele Suppression Prevents Progressive Hearing Loss in the Mature Murine Model of Human TMC1 Deafness.* Mol Ther, 2019. **27**(3): p. 681-690.
27. Van Camp, G. and R.J.H. Smith. *Hereditary Hearing Loss Homepage*. [cited 2019 24 September 2019]; Available from: https://hereditaryhearingloss.org.
28. Persky, S., et al., *Assessing hypothetical scenario methodology in genetic susceptibility testing analog studies: a quantitative review.* Genet Med, 2007. **9**(11): p. 727-38.
29. Anovum, *EuroTrak Belgium 2017.* 2017.
30. Anovum, *EuroTrak Netherlands 2016.* 2016.
31. Bond, M., et al., *Systematic reviews of the effectiveness and cost-effectiveness of multi-channel unilateral cochlear implants for adults.* Clin Otolaryngol, 2010. **35**(2): p. 87-96.
32. Vickers, D., L. De Raeve, and J. Graham, *International survey of cochlear implant candidacy.* Cochlear Implants Int, 2016. **17 Suppl 1**: p. 36-41.
33. Sorkin, D.L. and C.A. Buchman, *Cochlear Implant Access in Six Developed Countries.* Otol Neurotol, 2016. **37**(2): p. e161-4.
34. Calvert, M., et al., *Health-related quality of life and supportive care in patients with rare long-term neurological conditions.* Qual Life Res, 2013. **22**(6): p. 1231-8.
35. Hocaoglu, M.B., E.A. Gaffan, and A.K. Ho, *Health-related quality of life in Huntington's disease patients: a comparison of proxy assessment and patient self-rating using the disease-specific Huntington's disease health-related quality of life questionnaire (HDQoL).* J Neurol, 2012. **259**(9): p. 1793-800.
36. Smulders, Y.E., et al., *Cost-Utility of Bilateral Versus Unilateral Cochlear Implantation in Adults: A Randomized Controlled Trial.* Otol Neurotol, 2016. **37**(1): p. 38-45.
37. Ramakers, G.G., et al., *Agreement between health utility instruments in cochlear implantation.* Clin Otolaryngol, 2016. **41**(6): p. 737-743.
38. Van Rompaey, V., et al., *Prospective effectiveness of stapes surgery for otosclerosis in a multicenter audit setting: feasibility of the Common Otology Database as a benchmark database.* Otol Neurotol, 2009. **30**(8): p. 1101-10.