



PEARL

**Progression of Hearing Loss in Neurofibromatosis Type 2 According to Genetic Severity**

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**Progression of hearing loss in Neurofibromatosis type 2  
according to genetic severity**

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3 ***Progression of hearing loss in Neurofibromatosis type 2 according***  
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6 ***to genetic severity***  
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10 ***Hearing Loss in Neurofibromatosis type 2***  
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## **Abstract**

### **Objectives**

This study set out to describe the progression of hearing loss in patients with Neurofibromatosis type 2 (NF2), treated in a quaternary multidisciplinary clinic. It also aimed to compare hearing loss across patients grouped according to a known genetic severity score to explore its utility for prognostication.

### **Methods**

We conducted a retrospective cohort study of 147 patients with confirmed NF2 diagnosis for a mean observational period of 10 years. Pure tone audiometry (PTA), optimum discriminations scores (ODS), and genotype data were collected. Patients were classified according to hearing class (American Academy of Otolaryngology), their candidacy for auditory implantation (UK National NF2 consensus) and grouped by genetic severity as :1. Tissue mosaic, 2A. Mild Classic, 2B. Moderate Classic and 3. Severe. Survival analysis investigated the effect of genetic severity on the age of loss of serviceable hearing.

### **Results**

Genetic severity was a significant predictor of hearing outcomes such as ODS, hearing classification and maximum annual PTA deterioration. Whilst the overall median age of loss of serviceable hearing was 78 years, there was significant variation according to the genetic severity (median for severe patients was 32 years compared to a median of 80 for tissue mosaic patients).

### **Conclusion**

This is the first description of long term hearing outcomes in a clinical setting across a large heterogeneous cohort of patients with NF2. The results highlight the potential importance and

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3 benefit of considering the genetic severity score of patients when undertaking treatment decisions,  
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5 as well as planning future natural history studies.  
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13 ***Level of evidence: 2C***  
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18 ***Keywords:***  
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21 Neurofibromatosis 2, genetic severity, natural history, hearing loss, acoustic neuroma, vestibular  
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23 schwannoma  
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## Introduction

Neurofibromatosis type 2 (NF2) is a rare autosomal dominant disorder with a prevalence of 1 in 60,000<sup>1</sup>, which is characterised by the development of multiple benign tumours of the central and peripheral nervous system, polyneuropathy, as well as cutaneous and ocular abnormalities. Bilateral vestibular schwannomas (VS) are the hallmark of NF2 occurring in over 95% of NF2 patients and gradual VS growth or interventions for their treatment can lead to significant hearing loss, which is often bilateral and profound<sup>2</sup>. Since hearing loss significantly impacts on the quality of life for patients with NF2<sup>3-5</sup> hearing preservation is a key aim when considering patient management decisions. Despite this, increasing tumour burden may necessitate treatment interventions at the cost of hearing<sup>2</sup>. In patients with NF2 whose vestibular schwannomas are conservatively managed, hearing loss is usually gradual although sudden sensorineural hearing loss has also been observed<sup>6-9</sup>. Coupled to hearing loss, frequent concomitant poor vision further exacerbates communication issues and highlights the need for a multidisciplinary approach for optimal patient management<sup>10,11</sup>.

Improved understanding of the course of hearing loss in patients with NF2 would enhance prognostication and consequently help to inform management decisions as well as contribute to patient education. There are only a limited number of studies dedicated to the progress of hearing loss in NF2<sup>7,12-14</sup> or the underlying mechanism<sup>15-17</sup> and despite the abundance of natural history studies delineating hearing loss secondary to sporadic VS<sup>9,18-21</sup>, the VS growth rates reported are highly variable and not generalisable to NF2. In addition, the rate of hearing loss in NF2 does not consistently correlate with radiological data measuring VS growth<sup>22</sup>. Studies of conservatively managed tumours in NF2<sup>13</sup> report on more mildly affected cohorts with the mean growth rates of conservatively managed VS being significantly slower when compared to growth rates of VS that are excised<sup>2,23</sup>. Other potential methodological issues in previous longitudinal studies relate to relatively short follow-up times<sup>7</sup> and the eligibility criteria of patients biasing towards certain age ranges<sup>23-25</sup>.

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3 Another confounding factor in natural history studies in NF2 is that there is great variance in the  
4 clinical presentation and disease progression for patients, possibly stemming from the type and  
5 location of the mutation in the *NF2* gene or potential mosaicism<sup>26-29</sup>. These methodological  
6 limitations potentially reduce the practical clinical applicability for patients who desire to be  
7 informed about the probability of and timescale to hearing loss.  
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14 Recently, a genetic severity score was found to reliably predict phenotype for NF2 patients in  
15 several dimensions of morbidity such as hearing, ocular findings, tumour load and burden of  
16 interventions<sup>30</sup>. It would therefore be highly instructive to stratify the risk of hearing loss according  
17 to genetic severity. This study sets out to describe the first large scale observational study of the  
18 progression of hearing loss as experienced for more than a decade by NF2 patients managed in a  
19 multi-disciplinary centre and to examine potential differences arising as a consequence of the  
20 patients' genetic severity<sup>30</sup>. The primary aim was to describe the rate of hearing loss and age at loss  
21 of serviceable hearing for patients with NF2 regardless of treatment intervention, stratifying  
22 according to genetic severity. Such data could then potentially be used to help newly diagnosed  
23 patients and their clinicians further understand the individual's likely rate of hearing loss and  
24 therefore facilitate more informed decisions on treatment options.  
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## **Materials and Methods**

We undertook a retrospective anonymized cohort study by reviewing routinely recorded patient information held in the departmental database to extract demographics, genetic severity and hearing data for all patients managed within the South West of England National NF2 Service. All eligible patients had a confirmed diagnosis of NF2<sup>31-34</sup> and were classified using a genetic severity score<sup>30</sup>. All patients were included regardless of whether they were treatment naive, had undergone surgery, radiotherapy, bevacizumab or a combination of treatment modalities.

The primary outcome measure for hearing was optimum speech discrimination score(ODS) in the better hearing ear. This was determined using Arthur-Boothroyd word lists presented in optimum aided conditions. In patients with <50% ODS, Bamford-Kowal-Bench(BKB) sentence testing scores were also recorded in order to assess their candidacy for auditory implantation<sup>35</sup>. ODS assessments were offered to all patients annually or more frequently since the start of the NF2 national service in 2010, with a few exceptions: patients who lost their serviceable hearing prior to 2010, as well patients who were non-testable due to either learning difficulties, insufficient English language or young age<sup>10</sup>. In addition, pure tone average (PTA) was used as a secondary outcome measure given its widespread availability, especially for patients managed prior to 2010. A PTA was calculated for each ear using the thresholds at 500, 1000, 2000, 4000 Hz<sup>36</sup>. The rate of hearing loss was calculated per ear by dividing the PTA change from baseline to last review by the period of observation. All left ears and right ears were analysed separately as they were considered to be both biologically and statistically independent. Young children with PTA within the normal hearing range ( $\leq 20$  dB)<sup>37</sup> were assumed to have ODS of 100%. All audiological assessments were carried out according to the British Society of Audiology guidelines by fully qualified audiologists in a sound-insulated room.

Patients hearing was classified using two different systems applied to their better hearing ear (table 1): Firstly, we used the American Association of Otolaryngology-Head and Neck Surgery(AAO-



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3 HNS) scheme<sup>38</sup> in order to allow for direct comparison with previous studies, and secondly, we  
4  
5 applied the UK national NF2 consensus grading<sup>35</sup>, which is routinely used in the UK in this setting to  
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7 assess hearing loss and auditory brainstem and cochlear implantation candidacy.  
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10 This study's primary aim was to determine the age of loss of useful hearing in patients with NF2  
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12 in order to provide the most clinically relevant information that may be of use in management  
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14 decisions. Loss of serviceable hearing was defined as AAO-HNS classes C or D or, in the case of some  
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16 patients who lost their hearing prior to 2010, a detailed case note review was undertaken using a  
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18 pragmatic definition of the year in which it was recorded they were no longer able to derive  
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20 significant benefit from hearing aids in terms of speech understanding. Concomitantly with  
21  
22 investigating survival to loss of hearing, we undertook a survival analysis defining the end point as a  
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24 score of <50% ODS, corresponding to Grade 3 or worse on NF2 consensus grading system(AAO-HNS  
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26 class D rather than C & D). This is the threshold where patients would be referred for more detailed  
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28 hearing assessment with sentence score testing and potentially considered for auditory  
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30 implantation.  
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#### 33 34 Statistical analysis:

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37 SPSS 23 was used for all statistical analyses. Genetic severity and hearing classifications were  
38  
39 treated as ordinal variables. We reported standard summary statistics with the statistical  
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41 significance of inferences set to 5%.Associations between variables, and where necessary controlling  
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43 for possible confounders, were investigated using Spearman's correlations, and where appropriate  
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45 partial Spearman's correlations, after visually confirming monotonic relationships of the variables  
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47 using scatterplots.T-tests were used for pairwise comparisons; inspection of outliers in the pairwise  
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49 differences revealed they were not extreme and did not unduly influence the results and they were  
50  
51 therefore kept in the analysis. Trends in the proportion of patients in each hearing classification  
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53 associated with genetic severity were investigated using Mantel-Haenszel linear-by-linear  $\chi^2$  tests of  
54  
55 association. The agreement of the two hearing classification systems was investigated using  
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3 Goodman and Kruskal's  $\gamma$  and we reported the population value G. Kaplan-Meier survival analysis<sup>39</sup>  
4 was conducted to examine if genetic severity had a significant impact to the age of loss of  
5 serviceable hearing and to produce survival probabilities and hazard rates. A similar percentage of  
6 censored cases were present in the four different genetic severity groups and the pattern of  
7 censoring was similar.  
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## 13 **Results**

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16 One hundred and forty seven patients met the inclusion criteria after excluding one patient with  
17 congenital hearing loss. The mean observational period was 10 years(SD=8) and the mean age of  
18 patients at their latest follow-up was 43.5 years(SD=19.3). The dates of diagnoses of NF2 ranged  
19 from 1969 to 2016. The breakdown of the study's patient population by genetic severity score is  
20 recorded in table 2 along with their age and the total period of observation. As expected, patients  
21 were followed-up at a significantly younger age when they had a severe phenotype compared with  
22 tissue mosaic( $p=5.3 \times 10^{-22}$ ) but there was no overall difference in the duration of follow-up amongst  
23 the different genetic severity groups( $p=.17$ ).  
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36 There were 137 patients for whom we had ODS recorded at the latest review and we compared  
37 their relative hearing by focusing on their better hearing ear and stratifying across different genetic  
38 severity groups. Whilst the mean maximum ODS was 72.08% (95%CI=65.49, 78.67) across all  
39 patients, there was significant variability depending on the genotype of the patients( $p=.01$ ). In  
40 particular, table 3 shows that the mean maximum ODS for patients in the tissue mosaic group was  
41 85.84%(95%CI=78.91, 92.76), whereas severe-genotype patients had an average maximum ODS that  
42 was significantly lower and with a greater variation (Mean=55.94%,95%CI=32.23, 79.65%).  
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52 Pure Tone Average results(PTA) were available for 70 right and 69 left ears(Appendix 1). The  
53 mean follow-up period from baseline PTA to last review for the 81 patients for whom we had  
54 audiograms at both points was 82 months(SD=47). There was a statistically significant worsening in  
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3 the mean PTA from baseline to last review of 14.14 dB and 15.07 dB for right( $p=.000008$ ) and  
4 left( $p=.000058$ ) ears respectively. The total magnitude of deterioration in hearing was related to the  
5 total period of observation for both right( $p=.000019$ ) and left ears( $p=.006$ ). Patients who presented  
6 at older age had worse hearing at baseline(right ear: $p=.006$ , left ear: $p=0.000376$ ) but a less severe  
7 phenotype( $p=1.31 \times 10^{-12}$ ). After controlling for age, patients with more severe genotype were found  
8 to have worse pure tone thresholds at presentation(right ear: $p=.009$ , left ear: $p=1.55 \times 10^{-7}$ ).  
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16 We examined the rate of hearing loss of NF2 patients and observed that the maximum rate of  
17 yearly PTA deterioration varied significantly for patients in different genetic severity  
18 categories( $p=.02$ ). Notably from table 4, PTA averages for patients in the severe group could  
19 deteriorate by 15.9dB per year in their most frangible ear; a decline which is more than four times  
20 greater the maximum rate of deterioration of tissue mosaic patients(2.6dB/annum).  
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28 The genetic severity of NF2 patients was found to be a significant predictor of their hearing  
29 classification. In particular, using data from their latest review, we classified 95 patients using the  
30 AAO-HNS class and 143 patients using the UK national NF2 consensus system, and found that there  
31 were significant trends between increasing genetic severity and the proportions of patients in worse  
32 classes of AAO-HNS( $p=.007$ ) as well in worse hearing grades( $p=.001$ )(Figure 1). For example, more  
33 than half (57.1%) of the patients in the severe group were found to be without serviceable  
34 hearing(Class C and D) and only 35% of them were in Class A, compared to 64% of patients in the  
35 tissue mosaic group who were classified as Class A and less than 26% of whom were without  
36 serviceable hearing. Comparably, the genetic severity of patients also dictated their UK NF2 hearing  
37 grade classification well; notably with the percentage of patients in grade 6 rising from 3% in the  
38 tissue mosaic group to 22% in the severe group. Unsurprisingly, the two hearing classifications were  
39 very strongly associated( $G=.998$ ,  $p=1.24 \times 10^{-22}$ ) and described the patients in this study in a similar  
40 fashion although there were thirteen patients who would be classified as having serviceable hearing  
41 using the UK national NF2 consensus but were in Classes C or D using AAO-HNS(Appendix 2).  
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3 In the clinical management of NF2 patients, being able to predict the age of hearing loss would  
4 be of great benefit when making treatment decisions. The age of loss of serviceable hearing was  
5 considered to be the most important end point with regards to hearing impairment. A survival  
6 analysis was performed to determine the age of loss of serviceable hearing (AAO-HNS classes C or D)  
7 in our NF2 cohort and whether it differed between genetic severity groups. Figure 2 illustrates the  
8 survival functions for the patients in each genetic severity group. Genetic severity was a significant  
9 overall predictor of age of loss of useful hearing as determined by a log rank test which revealed that  
10 the survival distributions for the four groups were statistically significantly  
11 different,  $\chi^2(3)=46.25, p=5.03 \times 10^{-10}$ .

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13 We then set out to do pairwise comparisons in order to determine which of the genetic severity  
14 groups differed from each other in terms of age of loss of serviceable hearing and found that there  
15 was a statistically significant difference in the survival distributions between all group-pairs except  
16 when comparing the survival of 2A and 2B, an effect clearly illustrated in figure 1. The mean survival  
17 times and medians (the age at which 50% of patients in a group still maintained serviceable hearing  
18 in at least one ear) were recorded in table 5. From table 5 it is apparent that there are marked  
19 differences in the ages of loss of serviceable hearing for NF2 patients of varying genotype.  
20 Remarkably, in routine clinical practice we observed that whilst 50% of patients in the tissue mosaic  
21 group preserve their hearing until 80 years of age, this threshold rapidly drops to 44-46 years for  
22 mild and moderate classic patients and to only 32 years for patients in the severe group. We further  
23 validated the above data using the UK national NF2 consensus grade determination of auditory  
24 implant candidacy and found that the results replicated the aforementioned findings.

## 50 **Discussion**

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53 This is the first study to have long-term follow up from a heterogeneous cohort of patients  
54 managed within a specialised multidisciplinary NF2 service and provides a 'real world' overview of  
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3 hearing loss including loss due to necessary treatment intervention (not just conservatively/non-  
4 operatively managed patients). The aim was to provide data that would apprise patients and their  
5 clinicians of their likely progression to loss of hearing so as to better inform treatment decisions  
6 relating to the management of their VS as well as to advise future specialised service configurations  
7 and healthcare planning. A known genetic severity score was used to stratify patients to provide  
8 more accurate individualised information<sup>30</sup>.  
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16 Our findings clearly demonstrate the importance of accounting for the genetic severity of patients in  
17 delineating the course of hearing loss in NF2. The type of *NF2* mutation underlies phenotypic  
18 severity of disease such as VS tumour doubling times, which can in turn affect time to loss of useful  
19 hearing<sup>25</sup>. The use of a genetic severity score provides a more in depth understanding of the  
20 variation in the progression of hearing loss amongst a heterogeneous cohort. Notably, we observed  
21 that overall, across all genetic severity groups, 50% of patients with NF2 appear to retain useful  
22 hearing up to the age of 78; this finding however is not very informative for patients who are severe,  
23 half of whom may lose serviceable hearing before 32 years, almost 50 years before milder tissue  
24 mosaic patients. Our results demonstrate significant differences in age of loss of useful hearing  
25 depending on genetic severity; the implications of this are that a patient with a new diagnosis of VS  
26 with a mild genetic severity may be reassured that it is likely they will preserve serviceable hearing  
27 for an extended period of time. In contrast, a patient with vestibular schwannomas and a severe  
28 mutation may be counselled towards earlier intervention that might secure hearing rehabilitation in  
29 the long term. This may include early SRS with or without subsequent cochlear implantation<sup>40</sup>, early  
30 VS resection with cochlear nerve preservation and cochlear implant insertion<sup>41</sup>, or excision with  
31 auditory brainstem implant insertion (including sleeper).  
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51 The genetic severity correlated well with ODS, AAO-HNS class and UK NF2 consensus hearing grades  
52 as well as annual PTA deterioration of the most frangible ear. As our results stem from a  
53 heterogeneous cohort they are not directly comparable to other reported cohorts however the  
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3 overall deterioration in PTA reported herein is within the range reported for conservatively managed  
4 patients in NF2<sup>13</sup>. Whilst the deterioration of the most frangible ear is variable depending on genetic  
5 severity, the rates reported for milder cohorts who are likely to be more conservatively managed,  
6 are also in agreement with previous findings (0-9.6dB/year). The increased rate of PTA deterioration  
7 in severe patients likely relates to increased clinical severity and disease burden specifically  
8 vestibular schwannoma (and other CPA) and their growth behaviour or the treatments required for  
9 these and other NF2 tumours.  
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12 Genetic severity score is known to correlate with disease burden and the need for treatment  
13 intervention (both of which contribute to hearing loss)<sup>30</sup>. Genetic severity score alone was therefore  
14 used to stratify patients disease severity. A further reason for this is that genetic severity can be  
15 determined at diagnosis (including pre-symptomatic) and is therefore more useful for aiding future  
16 prognostication.  
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19 Whilst there was a clear difference in the ages of loss useful hearing between group 1 and 2, and  
20 between 2 and 3, group 2A and 2B patients are the most similar. This might be because our 2A  
21 cohort had relatively few mild missense mutations, which may have resulted in an inability to  
22 demonstrate a significant difference the median ages to loss of useful hearing between 2A and 2B.  
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25 An important limitation of the current observational retrospective cohort study arises from recall  
26 bias or inaccuracies in using historical data for determining age at loss of useful hearing in those  
27 patients in whom it occurred prior to 2010. Moreover, whilst more widely available, PTA is not as  
28 useful in assessing hearing in NF2 as ODS<sup>10</sup> and dB rate of loss of hearing may not be helpful to  
29 patients. Furthermore, changes in treatment in recent years such the introduction of bevacizumab  
30 which may better preserve hearing compared with other modalities<sup>2</sup>, may mean that historical data  
31 may not be accurate when applied to newly diagnosed patients being offered currently available  
32 treatment regimes. It should be noted that all patients were included in this study regardless of  
33 whether they had undergone treatment intervention Whilst there is clear benefit in a natural  
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3 history study of only treatment naïve patients, this would result in exclusion of patients with more  
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5 severe disease who inevitably require treatment as a young adult. Previous studies have therefore  
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7 been limited to milder cohorts. Our aim was to include all NF2 patients in our large clinic regardless  
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9 of whether their hearing loss was due to treatment naïve tumours or secondary to treatment  
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11 interventions that were deemed necessary for tumour control (e.g. decompression of  
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13 brainstem). We acknowledge that there are variations in management philosophy for units treating  
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15 patients with NF2 which may limit the direct usability of the median age to loss of  
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17 hearing. However, importantly the study does highlight the benefit of using a genetic severity  
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19 scoring system to help inform and counsel all patients not only mild ones. Centres with significantly  
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21 different management strategies could undertake a similar review of their cohort to determine time  
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23 to loss of hearing for each genetic severity as achieved by their own individual management  
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25 practices to give more accurate unit specific data. Publication of similar studies such as ours using  
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27 the genetic scoring system would allow for more direct comparison of time to loss of hearing and  
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29 how this may vary according to management philosophy.  
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33 Overall, the main strength of the current work is that it provides a starting point for the use of  
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35 genetic severity scoring as a clinical tool to help predict likely rates of hearing loss and enhance  
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37 individualised patient counselling. Further work should consider extending this work prospectively  
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39 using primarily ODS to determine end points of hearing survival analyses. In addition this could form  
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41 part of the development of a predictive model following further investigation of other potential  
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43 predictors of hearing loss such as tumour size and growth rate.  
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## 48 **Conclusion**

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53 This is the first description of long-term hearing outcomes in a clinical setting across a large  
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55 heterogeneous cohort of patients with NF2 managed using all treatment modalities within a  
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3 specialised quaternary MDT. Stratifying patients according to genetic severity allows for more  
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5 informed prognostication of the likely timescale for hearing deterioration. This information may be  
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7 useful to both patients and clinicians when making complex treatment decisions.  
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## Tables

**Table 1: Classification of patients' hearing according to the American Association of Otolaryngology-Head and Neck Surgery (AAO-HNS) scheme and the UK national NF2 consensus grading,**

American Association of Otolaryngology-Head and Neck Surgery		Ear serviceability	UK national NF2 consensus for auditory brainstem and cochlear implantation	
Class	Definition		Grade	Definition
A	†ODS: 71 -100%	Serviceable hearing	1	ODS: 70 -100%
	‡PTA: ≤30 dB		2	ODS: 50 – 69 %
B	ODS: 50 -100%		3	ODS: 0-49%
	PTA: 31-50 dB			§BKB: 50-100%
C	ODS: 50 -100%	Non serviceable hearing	4	ODS: 0-49%
	PTA > 50 dB			BKB: 0-49%
D	ODS: 0-49%		5	Auditory implant
			6	Dead ears

†ODS: Optimum Discrimination Score, ‡PTA: Pure Tone Average, §BKB: Bamford-Kowal-Bench

Table 2: Cohort descriptives by genetic severity

Genetic Severity	Patients		Age at latest follow-up (years)		Total observation period (years)	
	N	%	Mean	SD	Mean	SD
<b>1. Tissue Mosaic</b>	66	44.9%	57.58	14.42	10	9
<b>2A. Mild Classic</b>	30	20.4%	36.38	12.81	10	9
<b>2B. Moderate Classic</b>	32	21.8%	33.39	15.99	9	7
<b>3. Severe</b>	19	12.9%	23.84	12.45	7	7
<b>Total</b>	147	100.0%	43.51	19.29	10	8

**Table 3: Optimum speech discrimination score in the better hearing ear (%)**

Genetic Severity	Optimum speech discrimination score	
	better hearing ear (%)	
	Mean	SD
<b>1. Tissue Mosaic</b>	85.84	27.27
<b>2A. Mild Classic</b>	57.96	44.56
<b>2B. Moderate Classic</b>	65.47	42.20
<b>3. Severe</b>	55.94	46.12
<b>Total</b>	72.08	39.01

**Table 4: Maximum Pure Tone Average (PTA) (dB/year) rate by genetic severity**

Genetic Severity	Maximum PTA rate	
	(dB/year)	
	Mean	SD
<b>1. Tissue Mosaic</b>	2.87	5.28
<b>2A. Mild Classic</b>	4.65	4.95
<b>2B. Moderate Classic</b>	8.23	12.20
<b>3. Severe</b>	13.54	29.40
<b>Total</b>	6.04	13.74

Table 5: Mean and Median ages of survival to loss of serviceable hearing (AAO-HNS Class C or D) by genetic severity

Genetic severity	Mean	Std. Error	95% Confidence Interval limits		Median	Std. Error	95% Confidence Interval limits	
			Lower	Upper			Lower	Upper
<b>1. Tissue Mosaic</b>	75.76	2.10	71.65	79.87	80.00	1.73	76.60	83.40
<b>2A. Mild Classic</b>	44.25	3.38	37.61	50.88	44.00	4.05	36.07	51.93
<b>2B. Moderate Classic</b>	54.99	7.95	39.40	70.58	46.00	4.55	37.08	54.92
<b>3. Severe</b>	33.20	5.67	22.08	44.32	32.00	6.75	18.77	45.23
<b>Overall</b>	66.58	2.95	60.81	72.35	78.00	5.80	66.63	89.37

## ***Figure legends***

Figure 1: Apportionment of patients in each genetic severity group by each hearing classification: AAO-HNS: American Association of Otolaryngology-Head and Neck Surgery, UK hearing grades: UK national NF2 consensus for auditory brainstem and cochlear implantation.

Figure 2: Plot of the Kaplan-Meier survival function curves for each genetic severity group against age

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5 **Appendix 1: Pure Tone Average (PTA) at baseline and last review for 82 patients for right (PTA-R) ears and left (PTA-**  
6 **L) ears**  
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11 **Appendix 2: Crosstabulation of classifications of patients with NF2 according to two systems: American Academy of**  
12 **Otolaryngology - Head and Neck surgery and UK national NF2 consensus t Hearing Grade**  
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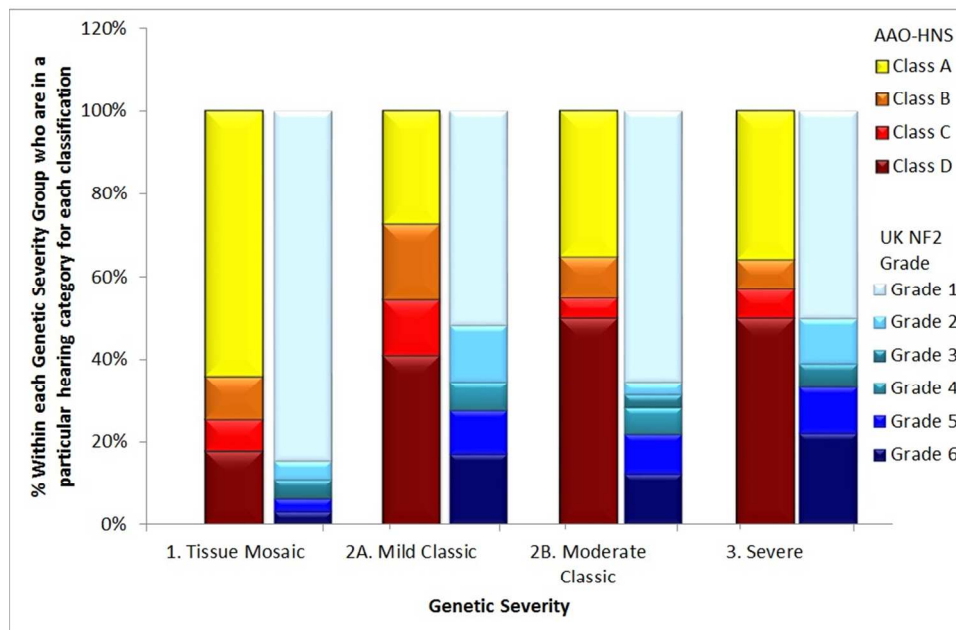


Figure 1: Apportionment of patients in each genetic severity group by each hearing classification: AAO-HNS: American Association of Otolaryngology-Head and Neck Surgery, UK hearing grades: UK national NF2 consensus for auditory brainstem and cochlear implantation.

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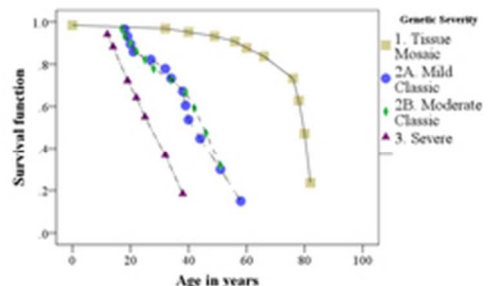


Figure 2: Plot of the Kaplan-Meier survival function curves for each genetic severity group against age  
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