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PRINCIPAL INVESTIGATOR: **Maura Cosetti, MD**

CONTRACTING ORGANIZATION: **New York University School of Medicine**

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6. AUTHOR(S)
Maura Cosetti

E-Mail: mkcosetti@yahoo.com, Maura.cosetti@nyumc.org

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

New York University School of Medicine
Department of Otolaryngology
550 First Ave, Suite 7Q
New York, NY 10016

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
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14. ABSTRACT

Neurofibromatosis Type 2 (NF2), a genetic disorder with highly penetrant autosomal dominant transmission, is characterized by the predictable development of bilateral vestibular schwannomas (VS), and other benign intracranial and spinal tumors. Tumor progression, as well as therapeutic intervention, may lead to significant cranial, spinal and peripheral nerve dysfunction, resulting in global impairment across of variety of domains. Few NF2-specific, validated metrics are currently available. The objective of this research was to develop, refine and validate a multi-dimensional metric for assessment of QoL in patients with NF2. A reliable, externally valid NF2-specific 63-item QoL module was created and tested in an NF2 population (n=118.) Results were analyzed and compared with data from the normative population data as well as cancer.

Overall, QoL in NF2 patients was lower than that of the general population ($p < 0.01$) and similar to that of patients with cancer. Patients whose treatment included radiation therapy had worse overall QoL than patients who did not undergo radiation. Domains related to facial function, hearing and balance were significantly correlated with QoL: patients with more facial weakness, hearing loss and imbalance reported lower QoL. Domains most predictive of overall QoL were psychosocial, future uncertainty and pain. When compared to cancer patients (including sub-groups with head and neck and brain cancer,) responses of NF2 patients demonstrated significantly higher levels of psychosocial stressors, including disease-related anxiety, personal and financial stress and lack of social support. These results demonstrate a significant role for psychosocial and pain domains in NF2 QoL and suggest that these areas may not be adequately addressed by current treatment protocols. Utilization of expertise in areas of mental health, pain management and financial counseling could make an important impact on QoL in this population.

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INTRODUCTION

Neurofibromatosis Type 2 (NF2), a genetic disorder with highly penetrant autosomal dominant transmission, is characterized by the predictable development of bilateral vestibular schwannomas (VS), intracranial and spinal schwannomas, meningiomas, gliomas and ependymomas, cataracts and multiple skin tumors. Tumor progression, as well as therapeutic intervention, may lead to significant cranial, spinal and peripheral nerve dysfunction, resulting in global impairment across of variety of domains. Currently, ideal management of NF2 disease is challenging, complex and controversial. International consensus recommendations and expert panels have described the importance of quality of life (QoL) measurements in clinical decision making and research trials. At present, however, there are few studies examining the QoL in patients with neurofibromatosis and NF2-specific, validated metrics for this population are not widely available. The aim of the current study is to develop, refine and validate a multi-dimensional metric for assessment of QoL in patients with NF2.

BODY

Research accomplishments as well as challenges encountered in methodology are described in detail below and are based on the previously outlined Statement of Work (SOW).

Task 1A-C

Task 1 of the SOW involved the development of a NF2-specific QoL module. Task 1A-C involved generation of an exhaustive list of NF2-specific QoL issues and assessment of content validity using the following methods:

(i) literature review of existing QoL metrics
(ii) structured interviews with members of multidisciplinary NYU Neurofibromatosis Center
(iii) structured patient interviews with NF2 patients
(iv) Operationalization of content into a set of questionnaire items using the EORTC item bank and generation of novel items.
(v) Pre-testing of provisional module to small group of 10 patients not included in phase 1 or 2 with structured, post-survey debriefing.

The unique complexity of the intra-cranial and extra-axial tumor burden in the NF2 population leads to a diverse constellation of symptoms and impairments across a wide variety of functional domains. Therefore, a systematic literature review was performed targeting QoL metrics applied to patient populations with brain, skull base, intracranial, spinal, ocular, or head and neck disease. Additionally, given the eventual development of profound sensorineural hearing loss in this population, research examining QoL metrics in populations with deafness as well as those receiving auditory brainstem implants were included. Lastly, studies investigating QoL in patients with genetic diseases affecting reproduction and family planning were also reviewed.

Literature search was performed using PUBMED and MEDLINE. Relevant articles were reviewed for additional references and then systematically categorized by affected organ system, ie brain, skull base, intracranial, spinal, ocular, and head and neck disease (Appendix A.) A preliminary list of QoL domains applicable to patients with NF2 was generated and used in the structured interview portion of the module development.

Structured interviews were performed with patients with NF2 (Appendix B) and members of multidisciplinary NYU Neurofibromatosis Center (Appendix C). Interviews followed the guidelines outlined in the EORTC Guidelines for Module Development and included both open-ended and semi-structured questions. Interviews lasted 30 minutes – 1 hour. Notes were taken throughout the interviews and were clarified with the interviewee at the end of the session, if necessary.

Structured interviews of patients are detailed in Appendix B and consisted of 3 parts: general, relevance of domains and breadth of coverage. Patients were asked to identify and rank 5 domains which they valued particularly highly and those in which they experienced significant challenges. Neutral probes were used to obtain more specific details about each experience. Open-ended questions were used to query the patients regarding breadth of identified QoL domains as well as additional issues missing or incompletely addressed in the provided list.

Structured interviews of health care providers are detailed in Appendix C and similarly consisted of 3 parts: relevance of domains, relative importance within each domain and breadth of coverage. Providers were asked to rate each domains on a 4-point Likert scale from (1) "not at all relevant" to (4) "very relevant." For instances in which the individual responded with a (1) "not at all relevant," additional follow-up questions were asked to clarify the basis of the response. To identify which issues affect NF2 patients most profoundly, providers were asked to identify and rank the top 5 domains they felt had the greatest impact on QoL in NF2. For assessment of the relative importance of each issue (and ultimately pare down the QoL questionnaire), providers were asked to indicate whether each item should be included on the final questionnaire. Lastly, providers were asked to identify additional issues that were missing or incompletely addressed in the list.

Once completed, responses were analyzed for deletion or addition of issues. Domains were considered for deletion if they 1) were not included in the top 5 of any patient responses to challenges or positive experiences; 2) were not included in the top 5 of any provider response; or 3) had a low mean relevance score (mean < 2) in provider evaluation. New areas were considered for addition if 1) they were mentioned by at least 2 patients or providers or 2) mentioned by 1 patient or provider with significant plausible motivation.

Based on structured interviews of patients and providers outlined above, all domains were found to be relevant and no additional domains were added. Two items universally found to be irrelevant by both were removed from the final survey (bladder control and coughing.) Patients and providers had similar responses with respect to domains with the highest importance, difficulty and relevance including facial function, hearing, balance/ambulation (mean relevance score 4.0) For breadth of coverage, 2 patients noted difficulty related to writing or typing due to peripheral neurofibromas. Additionally, 8 patients suggested that internet based survey (rather than a paper format) would be an easier format to complete given their level of functioning. Among provider responses, hearing, balance/ambulation and facial weakness had the highest rank order and mean relevance score (4.0). Areas with low relevance score (2-3) include sexual activity and future uncertainty. No area received a relevance score of 1.

The provisional module was pre-tested to a small group of patients. All patients were de-briefed following pre-testing using a structured interview (Appendix D.) Individual patient comments to both the interviews and debriefing are included in Appendix E. Overall, individual comments were a powerful insight into the QoL of patients with NF2 and demonstrate the incredible resilience of individuals with this disease. Key trends were apparent in the patient's interview responses, specifically issues related to the psychosocial effects, future uncertainty and physical pain experienced by NF2 patients. Interestingly, psychosocial issues appeared to transcend physical limitations as patients who were genetically mosaic for NF2 reported their QoL was affected by significant anxiety related to future uncertainty.

Task 2A-C

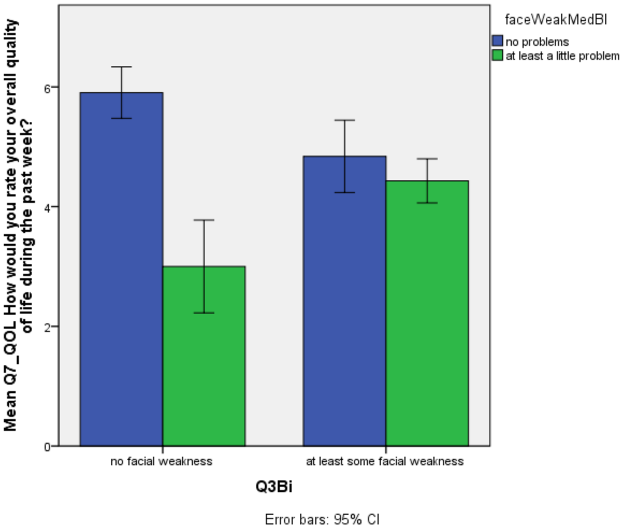
Task 2A-C of the SOW involved the validity assessment and administration of the NF2-specific QoL module, including:

(vi) Completion of the final module (Appendix F)
(vii) IRB approval from New York University (IRB approval #S13-00055)
(viii) identification of the NF2 population through the NYU Neurofibromatosis center and the Children's Tumor Foundation and the NF2 Crew and module administration to N=118 patients with NF2

(ix) Results analysis to assess the relationship between NF2-specific and global heath QoL measures with demographic and treatment variables (Appendix G)

Demographics of the study population and results of the QoL survey are summarized in Appendix G while comparisons to additional groups will be covered in the upcoming section related to Task 3. Patients in the study population ranged in age from 9 years to over 50 years old and the majority were diagnosed more than 5 years prior (n= 87, 73.7%.) Approximately ¾ of the study population reported some facial weakness with 10% indicating complete unilateral or bilateral facial paralysis. Twenty-nine study participants (25%) had either an auditory brainstem implant (ABI) or a cochlear implant (CI). Fourteen patients (11%) reported use of a feeding tube for nutrition. Regarding treatment modality, 31% of patients indicated they had received radiation therapy (including gamma knife) as part of all of their treatment. Most patients (91.5%) had undergone surgery and 33% of patients had participated in an experimental drug trial. Overall QoL did not vary by patient age, time of NF2 diagnosis, presence of an ABI/CI or use of a feeding tube (Spearman non-parametric correlation, $p > 0.05$).

Presence of facial weakness was negatively correlated with QoL with more facial weakness predicting a lower QoL (rho = -.24, $p<.01$). A multinomial logit model with QOL as the dependent variable was used to assess the impact of facial paresis/paralysis on QoL scores in the domains vision, psychosocial, oral intake and speaking. No significant interactions were found between facial weakness and the psychosocial, oral intake or speaking domains. Further assessment of facial paralysis/paresis and the QoL facial weakness domain suggested that there was a greater disparity in QOL relating to appearance/physical attractiveness in patients with no facial weakness (n=29) than in those who reported at least a little facial weakness (n=83). Survey validity was reinforced by significant interaction between patient reports of facial weakness and the facial weakness domain (χ^2=11.4, $p<.05$).



Regarding treatment modality, patients whose treatment included radiation therapy had a lower overall QoL than patients whose treatment did not include radiotherapy; in comparison, similar effects on overall QoL were not seen in patients whose treatment included surgery or experimental medications. To assess for interactions between QoL domains and treatment modality, the interaction between each modality and each domain was examined in a multinomial logit model with QOL as the dependent variable. There were no significant interactions between radiation or the experimental drug treatment and any of the domains. Significant interactions were found between surgery and the facial weakness domain ($\chi2$=4.8, $p<.05$), the vision domain ($\chi2$=10.6, $p<.01$) and the oral intake domain ($\chi2$=8.6, $p<.01$). For these domains there was a stronger association with QOL for the respondents who did not have surgery (n=19) and those who did have surgery (n=99).

Similar analysis using a multinomial logit model was undertaken with the balance domain and treatment modality with QOL as the dependent variable. Regarding radiation therapy, there was no detectable difference between those who did and did not have radiation treatment in the correlation of questions in the balance domain and QOL. For patients who had not undergone surgery (n=19), there was a strong correlation between lack of unilateral muscle weakness ($\chi2$=7.3, $p<.01$), bilateral lower extremity weakness ($\chi2$=8.9, $p<.01$), coordination ($\chi 2=5.8$, $p<.05$) and loss of mobility ($\chi 2=8.9$, $p<.01$) and higher overall QoL. In patients who had not received experimental drug treatment (n=81), trouble doing strenuous activities ($\chi 2=7.8$, $p<.01$) and unsteadiness ($\chi 2=5.5$, $p<.05$) significantly predicted overall QoL.

Presence of an ABI or CI was not consistently correlated with overall QoL. Ability to use the telephone significantly predicted QoL in patients without an ABI/CI (rho=.42, $p<.01$), however among patients with implants, there was no clear correlation between the implant and QoL.

The effect of each domain on overall QoL was assessed using the Bonferronni correction for multiple comparisons. Table 6 in Appendix G lists the domains in order of decreasing impact of QoL. The domains that were most predictive of overall QoL were, respectively, psychsocial, pain and future uncertainty. All domains with the exception of cognition were independently predictive of overall QoL.

Task 3

Task 3 involved creating benchmarks of NF2 data across populations by comparing QoL results of study participants with established normative reference values for the:

(i) general population
(ii) cancer patients
(iii) patients with Head and Neck Cancer
(iv) patients with brain cancer

Using normative reference values obtained from the international EORTC database, overall QoL as well as individual domains were compared between NF2 patients and the 4 populations above. Results are summarized in table format in Appendix H. Overall QoL of NF2 patients was significantly different from the general population ($p < 0.004$), but did not differ from cancer patients or the subgroup of patients with brain cancer (Table 1).

Multiple notable differences on specific QoL domains were seen between NF2 patients and cancer patients. All responses of NF2 patients differed significantly from the general population. On items related to concentration and anxiety, responses of patients with NF2 differed significantly from both groups of cancer patients. Patients with NF2 indicated significantly more difficulty concentrating and a higher level of financial anxiety than cancer patients in general and patients with brain cancer ($p < 0.001$). In addition, NF2 patients reported more pain than patients with brain cancer, although their rates mimicked that of all cancer patients. Rates of memory difficulty were similar between patients with NF2 and brain cancer and differed from all cancer patients.

Additional differences in the psychosocial domain were seen when responses of patients with head and neck cancer were compared with the study population (Appendix H, Table 3). Specifically, NF2 patinets were more likely to have difficulty having social contact with their friends and family and were more likely to have trouble going out in public ($p < 0.001$). Regarding items targeting physical limitations, head and neck cancer patients were more likely to be hoarse and have difficulty swallowing.

Task 4.

Task 4 involved investigation of the relationship between QoL results and objective measures of function as assessed by retrospective chart review. Retrospective chart review of NYU NF2 patients was undertaken to and most recent objective measures of function assessed. Upon review, however, it was apparent few measures were available; additionally, due to distant time frame of those that were available, correlating them with re-administered QoL survey did not appear methodologically sound. Only a small number of patients had relevant recent data and they did not constitute a large enough population for data analysis.

Task 5.

Task 5 involved initiation of prospective, longitudinal cohort study on QoL measures in response to treatment and therapeutic interventions. This has been initiated and QoL data (using a similar, although shorter survey) is included for all patients enrolled in clinical trials through the NF Center at New York University.

Additionally, incorporation of NF2 specific QoL metrics is progressing in all aspects of NF care at NYU. The baseline QoL data will allow for re-assessment of QoL following therapeutic or rehabilitative intervention, such as surgical resection, radiation therapy or auditory brainstem implant. Greater understanding of QoL will

KEY RESEARCH ACCOMPLISHMENTS

The aim of this study was to develop, refine and validate a multi-dimensional metric for assessment of QoL in patients with NF2. All specific aims from the initial project narrative were accomplished and addressed in detail in previous sections.

Specific Aims

1. To apply principles of EORTC module development to create a NF2-specific QoL module with reliable content validity
2. To assess the external validity of the NF2-specific QoL module in an large NF2 population.
3. To compare and benchmark the global health QoL results between NF2 patients and reference values for the 1) normative population data, 2) patients with Head and Neck Cancer and 3) patients with brain cancer.
4. To investigate the relationship between QoL results and objective measures of function in NF2 patients.
5. To begin collection of prospective, longitudinal data on a cohort of NF2 patients with the goal of monitoring responsiveness in QoL measures to therapeutic interventions, primarily microsurgical tumor excision, over time.

Additional accomplishments

6. Identification of the unique impact that psychosocial issues have on the QoL of patients with NF2
7. Identification of the impact of pain and pain management on the QoL of the NF2 population

REPORTBALE OUTCOMES

- Validated NF2-specific QoL metric applicable for clinical and research use
- Standardized, benchmarked data on QoL in a large NF2 population and creation of a NF2-specific QoL database with potential for ongoing research
- Improved clinical care of patients with NF2
    - This research has provided needed insight into the unique impact of psychosocial issues on the QoL of patients with NF2. Although prior research by Neary et al (2006) using structured patient interviews of NF2 patients had identified psychosocial issues as a key component of QoL, they suggest that the key issue was loss of employment due to hearing impairment. This research suggests that disease-related anxiety that may actually underlie QoL issues in this population. Issues of anxiety and future uncertainty were significantly higher in the NF2 population that in other cancer populations, despite the fact that NF2 is a histogically benign disease.

      This research suggests that multi-disciplinary NF teams should consider greater utilization of mental health providers to provide both counseling, and when necessary, treatment of this currently under-recognized aspect of NF2 care. Results of the above study indicate that improvement in overall anxiety may greatly improve quality of life.
    - Results of this study suggest that pain is a large factor in the QoL of NF2 patients. This is crucial information for multi-disciplinary NF care teams to highlight the need for consultation and ultization of pain management expertise in the complex treatment of these patients. As with multi-disciplinary cancer treatment, pain management should be uniformly incorporated into the care of these

  individuals. Attentiveness and treatment of the acute and chronic pain issues of this population has the potential to greatly improve overall quality of life.
  - Results from this study suggest that patients with NF have high levels of future uncertainty, especially as related to financial considerations. When compared to other cancer patients, concern among NF2 patients was uniquely high. It is possible that NF patients could benefit from routine financial counseling to address any disease-specific concerns that may be impacting their QoL.
- Abstract to be submitted to the American Academy of Otolaryngology-Head and Neck Surgery Annual Meeting in Orlando, FL 2014
- Planned Manuscript submission to Otolaryngology-Head and Neck Surgery

CONCLUSION

This study outlined the development, refinement and validation of a multi-dimensional metric for assessment of QoL in patients with NF2. Results in a large NF2 population (n=118) reinforce prior research indicating the importance of hearing loss, imbalance and facial dysfunction, however also uncovered additional areas significantly correlated with QoL in this population. Overall, domains most closely associated with global QoL in this study were related to psychosocial stressors, future uncertainty and chronic pain. While current efforts at auditory rehabilitation with ABI and CI are indisputably important, this study suggests that areas of anxiety and pain may be undertreated in this population. Incorporation of mental health and pain management expertise in the NF multi-disciplinary treatment team may significantly improve QoL in NF2 patients.

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Appendix A: Structured Interview with NF2 patients

Patient Name:____

We are asking your help to devise a questionnaire which will be used to better understand the experiences of patients with Neurofibromatosis Type 2.

I. General

A. *I would like to ask you a few questions about your health and daily life. Can you tell me about the experiences you have had as a result of NF2?*

B. (Neutral probes to follow their response): *Can you tell me more about that? Can you give me an example? In what way?*

II. Relevance of domains

Below is a list of experiences that patients with NF2 may have. You may have had positive and/or negative experiences with each of these. These issues may not be equally important to you and you may consider some areas to be more important than others.

A. *Can you please identify and rank the 5 areas that you value the most highly or are most important to you?*

Domains	**Rank Order**
Hearing	
Balance/Ambulation	
Facial weakness	
Vision	
Speaking	
Psychosocial	
Oral intake	
Cognition	
Pain	
Sexual activity	
Future uncertainty	

B. *Can you please identify and rank the 5 areas that cause you the most difficulty?*

Domains	**Rank Order**
Hearing	
Balance/Ambulation	
Facial weakness	
Vision	
Speaking	
Psychosocial	
Oral intake	
Cognition	
Pain	
Sexual activity	
Future uncertainty	

C. *For each area, please describe the experiences you have had in more detail.*

D. *For areas you did not rank in either A or B above, have you had any experiences in this area that you would like to share?*

III. Breadth of coverage

A. Can you think of anything else which you have experienced or had to cope with that we have not discussed?

B. For each issue mentioned in A, can you tell me more about that?

C. Any additional comments?

Appendix B: Structured interview with NF2 Providers

Provider Name:____

The following is an attempt to get your input on issues affecting the quality of life in patients with Neurofibromatosis Type 2.

I. Relevance of domains

A. *Please answer with the extent to which each of these domains is relevant to patients with NF2. "Relevance" refers to the frequency with which a specific symptom/issue occurs and the degree to which you believe this issue affects their quality of life. (The more frequently a complaint occurs and greater the implications for quality of life, the more "relevant" it will be.)*

Domains	Not relevant	A little relevant	Quite relevant	Very relevant
Hearing	1	2	3	4
Balance/Ambulation	1	2	3	4
Facial weakness	1	2	3	4
Vision	1	2	3	4
Speaking	1	2	3	4
Psychosocial	1	2	3	4
Oral intake	1	2	3	4
Cognition	1	2	3	4
Pain	1	2	3	4
Sexual activity	1	2	3	4
Future uncertainty	1	2	3	4

B. *For each issue in which a "1" or a "2" was circled, please expand upon why this is not or only partially relevant for patients with NF2?*

C. *In an attempt to identify which issues affect NF2 patients most profoundly, please identify the top 5 domains that you feel are most important to assess. Please rank these from 1-5.*

Domains	Rank Order of Relevance
Hearing	
Balance/Ambulation	
Facial weakness	
Vision	
Speaking	
Psychosocial	
Oral intake	
Cognition	
Pain	
Sexual activity	
Future uncertainty	

II. Relative importance within each domain (sub-set identification)

Although NF2 affects a many domains, we can only include a sub-set of items. Please give your opinion regarding whether the items under each domain should be included in the final questionnaire. All items will begin with "In the past week…"

Hearing

Item (Begins with "In the past week…")	Yes	No	Unsure
Have hearing problems stopped you from performing your usual activities?			
Have hearing problems stopped you from performing your professional duties?			
Have you had difficulty communicating with others because of hearing loss?			
Have you been able to use the telephone?			
Have tinnitus or "ringing" or noises in the ear stopped you from performing your usual activities?			

For patients with ABIs or Cochlear implants: Has the implant improved your ability to communicate with others?			
For patients with either ABIs or CIs: Has the implant improved your ability to perform your usual activities?			
For patients with either ABIs or CIs: Has the implant improved your ability to perform your professional activities?			

Balance/Ambulation

Item (Begins with "In the past week…")	**Yes**	**No**	**Unsure**
Have balance problems stopped you from performing your usual activities?			
Did you have any trouble doing strenuous activities, like carrying a heavy shopping bad or suitcase?			
Did you have any trouble taking a long walk?			
Did you have any trouble taking a short walk?			
Did you need to stay in bed or a chair during the day?			
Did you need help with eating, dressing, washing yourself or using the toilet?			
Did you have weakness on one side of your body?			
Did you have weakness of both legs?			
Did you have trouble with your coordination?			
Did you feel off balance?			
Did you feel unsteady on your feet?			
Did you feel drowsy in the daytime?			
Have you worried about loss of mobility because of NF2?			
Have you worried about becoming dependent on others because of your illness?			

Facial weakness

Item (Begins with "In the past week…")	**Yes**	**No**	**Unsure**
Has facial weakness or paralysis stopped you from performing your usual activities?			
Has facial weakness or paralysis caused you difficulty with eating?			
Has your appearance bothered you?			
Have you felt physically less attractive as a result of NF2 or the treatment for NF2?			

Vision

Item (Begins with "In the past week…")	**Yes**	**No**	**Unsure**
Did you have double or blurred vision?			
Did you have difficulty reading because of your vision?			
Did you have difficulty pouring (ie tea or coffee?)			
Did problems with your sight stop you from performing your usual activities?			

Oral intake

Item (Begins with "In the past week…")	**Yes**	**No**	**Unsure**
Have you had trouble eating?			
Have you had trouble eating in front of your family?			
Have you had trouble eating in front of other people?			
Have you had trouble enjoying your meals?			
Have you had problems swallowing food?			
Have you had problems with your sense of smell?			
Have you had problems with your sense of taste?			
Have you gained weight?			
Have you lost weight?			

Cognition

Item (Begins with "In the past week…")	**Yes**	**No**	**Unsure**
Has tinnitus or "ringing" or noises in the ear affected your concentration?			
Did you have seizures?			
Did you have trouble finding the right words to express yourself?			
Have you had difficulty concentrating on things?			
Have you had difficulty remembering things?			

Pain

Item (Begins with "In the past week…")	**Yes**	**No**	**Unsure**

Did you have headaches?			
Have you used pain medication?			
Have you felt hopeful your pain will get better?			
Has pain interfered with your daily activities?			

Speaking

Item (Begins with "In the past week…")	**Yes**	**No**	**Unsure**
Did you have difficulty speaking?			
Have you been hoarse?			
Have you coughed?			
Has you had trouble talking to other people?			

Psychosocial

Item (Begins with "In the past week…")	**Yes**	**No**	**Unsure**
Have you felt calm and peaceful?			
Have you felt happy?			
Have you had trouble having social contact with your family?			
Have you had trouble having social contact with friends?			
Have you had trouble going out in public?			
Have you worried about becoming dependent on others because of your illness?			
Has your physical condition or medical treatment caused you financial difficulties?			

Future uncertainty

Item (Begins with "In the past week…")	**Yes**	**No**	**Unsure**
Did you feel uncertain about your future?			
Did your outlook on the future improve?			
Have you felt positive about your health?			

Sexual activity

Item (Begins with "In the past week…")	**Yes**	**No**	**Unsure**
Have you felt more interest in sex?			
Have you felt more sexual enjoyment?			

Other

Item (Begins with "In the past week…")	**Yes**	**No**	**Unsure**
Did you have difficulty controlling your bladder?			

III. Breadth of coverage

A. *Can you identify any issues that may be relevant to patients with NF2 and are not included above? Please expand on the details of each issue, including the frequency and severity with the NF2 population.*

B. *Any additional comments on the relevance or breadth of coverage?*

Appendix C: Structured debriefing of NF2 patients after pre-testing of the provisional module

Patient Name:____

Thank you for your help in devising a questionnaire about patient experiences with NF2. I want to make sure that we asked the right questions in the right way and that we cover the issues most important to patients with NF2.

For items in which the patient indicated they ***HAVE*** *difficulty (3 "quite a bit" or 4 "very much" on the Likert scale):*

IV. I see you have this problem, is that correct?

V. Do you think this problem is related to NF2?

VI. Can you tell me more about your experience with this?

VII. Did you have any difficulty responding to this question?

VIII. Did you find this question

  a. annoying?

  b. Confusing?

  c. Upsetting?

IX. How would you have asked this question?

For items in which the patient indicated they ***DO NOT HAVE*** *difficulty (1 "not at all" or 2 "a little" on the Likert scale):*

1. I see you have not had this problem during the previous week? Is that correct?
2. Have you experienced this problem before?
3. If yes, do you think it was related to NF2?
    a. Can you tell me more about this problem?
    b. Did you have difficulty responding to this question?
4. Did you find this question
    a. Annoying?
    b. Confusing?
    c. Upsetting?
5. How would you have asked this question?

With respect to the entire questionnaire:

1. Were their questions you found intrusive?
2. Can you think of anything else that you have had to cope with that was not included on the questionnaire?

Appendix D. Individual patient responses illustrating the complexity of psychosocial effects of NF2 and the resilience of patients with this disease.

"NF2 is such a nasty disease in that, it feels like your own body is betraying you. It doesn't really matter what you do or how well you care for yourself. It's self defeating almost in that I have no control overhow it progresses. It controls how I think, the activities I can do, and just when you get optimistic that you are getting better, you are forced on your knees again."

"After [I was diagnosed with] NF2, my life changed to an unpredictable one. I never can predict what will happen. I'm afraid to start a relationship and dare not to approach the a person I might like… my confidence will drop to zero. Every time when friends discuss my disease, I really want to cry, it really triggers my emotion. Sometimes I even think about why I have been chosen by this disease. Besides that,I have excellent I have family and friends support. I can't complain because I still can walk, have vision, not totally deaf, can speak, and not dependent to any one. I am lucky."

"Find a cure. Also please give patients more support. A therapist shouldbe a must. NF2 is not just physical pain. It's more emotional and psychological pain. That pain is hard to explain. Thinking about future how I am going to survive, what may happen to me still scars the crap out of me. We all have unique stories to tell but end of the day NF2 does make you appreciate life."

"since my [spine] surgery, I have had no bad issues, but I am concerned that I will lose my hearing and ability to function in the future."

"The uncertainty is the worst part in one way. If we knew how our Nf2 would progress we'd be mentally more prepared, therefor happier. I have passed Nf2 on to my 22 year old children and this is sometimes almost too much to handle. Seeing your child having brain surgery, and another one unable to walk alone, is not what you thought would happen when you looked at your newborn and dreamed for them. I am the fifth generation with Nf2, all down the female line, and it gets worse in each generation. We need a cure!!!"

"I am waiting on blood test results, but have been told it is a possibilitythat I have the mosaic version, explaining the lack of symptoms so far at my age. Doesn't stop me worrying and feeling uncertain about what the future holds for me."

"I'm a mosaic case diagnosed 3 years ago at age 53. I currently seem to have very mild symptoms compared to other NF2 sufferers. I feel like I'm constantly waiting for the other shoe to drop."

"When talking about the quality of life, with nf2 and life management, Ifeel you can only keep going.. Every day it could be something different. For me I was normal for 30 yrs. then 1 by 1 you start to lose functions or gain pains. It is a constant change in life and there is nothing you can do to stop it. You wake up happy that you only have half of your hearing and not deaf yet, your happy you can still use yourarm at all. Your happy that you can walk although your balance keeps pushing you on your side. With NF your life stinks because you lose what you on s had but have to keep going forward cause you don't know what you might lose next."

"Depression, anger at my disease, frustration and fear are my biggest problems."

"Due to my hearing impairment, I lost my job a year ago, and was forced to go on disability retirement. This event has caused more damage to my self than the primary /secondary effects of Neurofibromatosis. "

"My 2 biggest issues are receptive communication (due to deafness) & memory loss/choosing the wrong words. I can be very frustrating & scary."

"I have an ABI and it helps me lip read, but also helps me to not listen to my tinnitus. I also in addition to general tinnitus I have gaze tinnitus so it screams when my eyes move."

"I love my ABI- its wonderful!

"ABI gives my environmental sounds, and support some lip reading."

"I just received a CI in my left ear which is performing much better than expected. I have an ABI in my right ear. My tinnitus was completely debilitating and I was ready to jump out the window. I had no ability to concentrate at all. It was horrible. The CI has eliminate almost all of that as I said except during the night when I am not wearing my CI."

"I am very fortunate to had a wonderful support system!--I shudder to think what I would do without my husband and Mom who are the wind beneath my wings. Sounds cliché but is heartfelt. I have also had lots of support from friends AND from the community at large. I am very grateful for all that many people have done for me. Not sure what the future holds. "

"I use a walker and cant drive because of weak side so trying to plow through snow with a walker doesn't really work. This also makes you feel more depressed as it's very difficult to do anything, even getting groceries which makes you more dependent on others."

"Right now body is in pain, but I had surgery [recently] to take out bumps on my body to take the pain away. Overall, doing my best"

"I want my pain to go away."

"I have severe nerve pain and seizures so I am on a lot of drugs. My vision is bad and I only have limited hearing in one ear. I cannot drive because of this so I have no contacts outside of my immediate family. "

"One of the most annoying things about NF 2 is learning to live with pain to some degree everyday. At any point of any day, I experience pain of different degrees in different areas, but we must just live with itin order to continue to function as members of society. It's always "amusing" when people ask how I'm feeling because my general answer is fine, mainly because I've lost track of what has hurt at what point and grown accustomed to living with this everyday pain."

"The vision highly affects quality of life!!! To me the deafness is but a minor nuisance at times but the vision with some complications there is just no getting around it! I really wish and hope that the medical community takes more interest in researching vision impairments as the result of NF2 as well as methods to correct and improve them. The acial disfigurement is really bothersome but one can choose to accept and deal with it. My reading has also gone way down because it is either too difficult to focus on the words or too exhausting."

Appendix E. NF2 Quality of Life Survey

Introduction

This survey is designed for individuals with Neurofibromatosis Type 2. We are interested in learning about the health and feelings of people with NF2. There are no "right" or "wrong" answers. All answers will remain anonymous. We appreciate your help and participation. We plan to use this information to help us understand more about the lives and feelings of people with NF2 and help us improve treatment of this disease.

Medical information:

1. **What is your current age**?

<20 years	20-39 years	30-39 years	40-49 years	>50 years

2. **When were you diagnosed with Neurofibromatosis Type 2 (NF2)?**

<6 months ago	1-2 years ago	2-5 years ago	>5 years ago

3. **Do you have facial weakness on one or both sides?**

None	A little Bit	Quite a bit	Complete facial paralysis

4. **Do you have an auditory brainstem implant (ABI) or cochlear implant?** Yes No

5. **Have you used a feeding tube?** Yes No

Overall QOL

Please indicate the number between 1 and 7 that best applies to you:

6. **How would you rate your overall health during the past week?**

1 Very poor	2	3	4	5	6	7 excellent

7. **How would you rate your overall quality of life during the past week?**

1 Very poor	2	3	4	5	6	7 excellent

Hearing

During the past week:	**Not at all**	**A little Bit**	**Quite a bit**	**Very much**
8. Have hearing problems stopped you from performing your usual activities?	1	2	3	4
9. Have hearing problems stopped you from performing your professional duties?	1	2	3	4
10. Have you had difficulty communicating with others because of hearing loss?	1	2	3	4
11. Have you been able to use the telephone?	1	2	3	4
12. Has tinnitus or "ringing" or noises in the ear stopped you from performing your usual activities?	1	2	3	4
13. *For patients with ABIs or Cochlear implants*: Has the implant improved your ability to communicate with others?	1	2	3	4
14. *For patients with either ABIs or CIs:* Has the implant improved your ability to perform your usual activities?	1	2	3	4
15. *For patients with either ABIs or CIs:* Has the implant improved your ability to perform your professional activities?	1	2	3	4

Balance/Ambulation

During the past week:	**Not at all**	**A little Bit**	**Quite a bit**	**Very much**
16. Have balance problems stopped you from performing your usual activities?	1	2	3	4
17. Did you have any trouble doing strenuous activities, like carrying a heavy shopping bad or suitcase?	1	2	3	4

18. Did you have any trouble taking a long walk?	1	2	3	4
19. Did you have any trouble taking a short walk?	1	2	3	4
20. Did you need to stay in bed or a chair during the day?	1	2	3	4
21. Did you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
22. Did you have weakness on one side of your body?	1	2	3	4
23. Did you have weakness of both legs?	1	2	3	4
24. Did you have trouble with your coordination?	1	2	3	4
25. Did you feel off balance?	1	2	3	4
26. Did you feel unsteady on your feet?	1	2	3	4
27. Did you feel drowsy in the daytime?	1	2	3	4
28. Have you worried about loss of mobility because of NF2?	1	2	3	4

Future uncertainty

During the past week:	**Not at all**	**A little Bit**	**Quite a bit**	**Very much**
29. Have you worried about becoming dependent on others because of your illness?	1	2	3	4
30. Did you feel uncertain about your future?	1	2	3	4
31. Did your outlook on the future improve?	1	2	3	4
32. Have you felt positive about your health?	1	2	3	4

Facial weakness

During the past week:	**Not at all**	**A little Bit**	**Quite a bit**	**Very much**
33. Has facial weakness or paralysis stopped you from performing your usual activities?	1	2	3	4
34. Has facial weakness or paralysis caused you difficulty with eating?	1	2	3	4
35. Has your appearance bothered you?	1	2	3	4
36. Have you felt physically less attractive as a result of NF2 or the treatment for NF2?	1	2	3	4

Vision

During the past week:	**Not at all**	**A little Bit**	**Quite a bit**	**Very much**
37. Did you have double or blurred vision?	1	2	3	4
38. Did you have difficulty reading because of your vision?	1	2	3	4
39. Did you have difficulty pouring (ie tea or coffee?)	1	2	3	4
40. Were your activities limited in any way because of your vision?	1	2	3	4

Psychosocial

During the past week:	**Not at all**	**A little Bit**	**Quite a bit**	**Very much**
41. Have you felt calm and peaceful?	1	2	3	4
42. Have you felt happy?	1	2	3	4
43. Have you had trouble having social contact with your family?	1	2	3	4
44. Have you had trouble having social contact with friends?	1	2	3	4
45. Have you had trouble going out in public?	1	2	3	4
46. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

Oral intake

During the past week:	**Not at all**	**A little Bit**	**Quite a bit**	**Very much**
47. Have you had trouble eating?	1	2	3	4
48. Have you had trouble eating in front of your family?	1	2	3	4
49. Have you had trouble eating in front of other people?	1	2	3	4
50. Have you had trouble enjoying your meals?	1	2	3	4
51. Have you had problems swallowing food?	1	2	3	4
52. Have you had problems with your sense of smell?	1	2	3	4
53. Have you had problems with your sense of taste?	1	2	3	4

Cognition

During the past week:	**Not at all**	**A little Bit**	**Quite a bit**	**Very much**
54. Has tinnitus or "ringing" or noises in the ear affected your concentration?	1	2	3	4
55. Did you have seizures?	1	2	3	4
56. Did you have trouble finding the right words to express yourself?	1	2	3	4
57. Have you had difficulty concentrating on things?	1	2	3	4
58. Have you had difficulty remembering things?	1	2	3	4

Sexual activity

During the past week:	**Not at all**	**A little Bit**	**Quite a bit**	**Very much**
59. Have you felt less interest in sex?	1	2	3	4
60. Have you felt less sexual enjoyment?	1	2	3	4

Pain

During the past week:	**Not at all**	**A little Bit**	**Quite a bit**	**Very much**
61. Did you have headaches?	1	2	3	4
62. Have you used pain medication?	1	2	3	4
63. Have you felt hopeful your pain will get better?	1	2	3	4
64. Has pain interfered with your daily activities?	1	2	3	4

Speaking

During the past week:	**Not at all**	**A little Bit**	**Quite a bit**	**Very much**
65. Did you have difficulty speaking?	1	2	3	4
66. Have you been hoarse?	1	2	3	4
67. Have you had trouble talking to other people?	1	2	3	4

Thank you very much for participating in this survey. We greatly appreciative your help in trying to better understand Neurofibromatosis Type 2.

Appendix F. Results of QoL survey in NF2 population (N=118)

Table 1. Current Age of study participants (N=118)

	Frequency	Percent
<20 years	9	7.6
20-29 years	24	20.3
30-39 years	27	22.9
40-49 years	21	17.8
>50 years	35	29.7
Total	116	98.3
Missing	2	1.7
Total	118	100.0

Table 2. Age at diagnosis of Neurofibromatosis Type 2 (NF2)?

	Frequency	Percent
<6 months ago	4	3.4
1-2 years ago	5	4.2
2-5 years ago >	19	16.1
5 years ago	87	73.7
Total	115	97.5
Missing	3	2.5
Total	118	100.0

Table 3. Responses to question: Do you have facial weakness on one or both sides?

	Frequency	Percent
None	29	24.6
A little Bit	43	36.4
Quite a bit	30	25.4
Complete facial paralysis	12	10.2
Total	114	96.6
Missing	4	3.4
Total	118	100.0

Table 4. Presence of an auditory brainstem implant or cochlear implant?

	Frequency	Percent
No	84	71.2
Yes	29	24.6
Total	113	95.8
Missing	5	4.2
Total	118	100.0

Table 5. Treatment modality

	Frequency	Percent
Radiation	37	31.3
Surgery	103	91.5
Experimental drug	39	33

treatment		
Missing	6	5
Total	118	100

Table 6. Relationship between each domains and overall QoL (in decreasing order of significance)

Domain	**Spearman's rho correlation coefficient**	**Significance (2-tailed)** * ***Bonferroni correction p < 0.004***
psychosocial	-0.639	p = 0
	N	115
pain	-0.486	p = 0
	N	115
Future Uncertainty	-0.479	p = 0
	N	116
Balance	-0.452	P = 0
	N	116
Facial weakness	-0.444	P=0
	N	117
Hearing	-0.372	p-0
	N	117
Oral intake	-0.336	P=0
	N	117
vision	-0.298	p < 0.001
	N	117
Sexual activity	0.289	P < 0.002
	N	117
speaking	0.247	0.008
	N	115
Cognition	-0.162	0.084
	N	115

Appendix G. Benchmark of NF2 study participants across populations.

Table 1. Comparison of overall QoL across populations

			very poor						**excellent**	
			1	**2**	**3**	**4**	**5**	**6**	**7**	**p-value**
29) Overall health	*In general, how would you rate your overall health during the past week?*	General population	1%	3%	9%	15%	21%	29%	22%	0.004
		All cancer patients: all stages	4%	5%	12%	24%	24%	20%	10%	0.051
		Brain cancer	2%	3%	13%	25%	28%	18%	11%	0.038
		NF2	*0%*	*4%*	*19%*	*19%*	*19%*	*27%*	*12%*	
30) Overall quality of life	*How would you rate your overall quality of life during the past week?*	General population	1%	3%	7%	15%	22%	31%	21%	0.000
		All cancer patients: all stages	4%	6%	12%	21%	23%	21%	13%	0.300
		Brain cancer	3%	5%	12%	25%	27%	17%	11%	0.156
		NF2	*1%*	*5%*	*20%*	*21%*	*21%*	*20%*	*13%*	

Table 2. Comparison of specific items across cancer populations

			Not at all	**A little Bit**	**Quite a bit**	**Very much**	
			1	**2**	**3**	**4**	**p-value**
1) Strenuous activities	*During the past week, did you have any trouble doing strenuous activities, like carrying a heavy shopping bad or suitcase?*	General population	56%	23%	14%	7%	0.000
		All cancer patients: all stages	33%	32%	21%	15%	0.195
		NF2	*37%*	*22%*	*22%*	*19%*	
2) Long walk	*During the past week, did you have any trouble taking a long walk?*	General population	72%	15%	8%	5%	0.000
		All cancer patients: all stages	39%	28%	18%	15%	0.048
		NF2	*39%*	*20%*	*17%*	*23%*	
3) Short walk	*During the past week, did you have any trouble taking a short walk?*	General population	87%	8%	3%	1%	0.000
		All cancer patients: all stages	72%	18%	7%	4%	0.000
		NF2	*51%*	*26%*	*11%*	*11%*	
4) Bed or	*During the*	General population	90%	7%	2%	1%	0.000

chair	*past week, did you need to stay in bed or a chair during the day?*	All cancer patients: all stages	57%	25%	13%	5%	0.541
		NF2	*55%*	*22%*	*17%*	*6%*	
5) Self care	*During the past week, did you need help with eating, dressing, washing yourself or using the toilet?*	General population	98%	2%	1%	0%	0.000
		All cancer patients: all stages	90%	6%	2%	1%	0.269
		NF2	*89%*	*7%*	*1%*	*3%*	
9) Pain	*During the past week, has pain interfered with your daily activities?*	General population	55%	25%	15%	5%	0.003
		All cancer patients: all stages	43%	32%	17%	8%	0.567
		Brain cancer	63%	27%	8%	2%	0.000
		NF2	*37%*	*37%*	*19%*	*7%*	
20) Concentration	*During the past week, have you had difficulty concentrating on things?*	General population	75%	18%	5%	2%	0.000
		All cancer patients: all stages	66%	22%	9%	3%	0.000
		Brain cancer	47%	32%	14%	8%	0.001
		NF2	*29%*	*49%*	*15%*	*7%*	
25) Memory trouble	*During the past week, have you had difficulty remembering things?*	General population	62%	28%	8%	2%	0.000
		All cancer patients: all stages	59%	30%	8%	3%	0.000
		Brain cancer	43%	37%	14%	5%	0.089
		NF2	*32%*	*42%*	*21%*	*5%*	
28) Financial difficulties	*During the past week, has your physical condition or medical treatment caused you financial difficulties?*	General population	83%	9%	5%	3%	0.000
		All cancer patients: all stages	69%	17%	8%	5%	0.000
		Brain cancer	61%	22%	14%	4%	0.000
		NF2	*37%*	*33%*	*12%*	*17%*	

Table 3. Comparison of specific items between the NF2 study population and head and neck cancer population

				Not at all 1	A little Bit 2	Quite a bit 3	Very much 4	p-value
7) Problems swallowing solid food	*During the past week, have you had problems swallowing food?*	HNSW		40%	28%	15%	17%	0.000
			NF2	*61%*	*29%*	*7%*	*3%*	
13) Sense of smell	*During the past week, have you had problems with your sense of smell?*	HNSE		70%	15%	6%	10%	0.023
			NF2	*79%*	*15%*	*5%*	*1%*	
14) Sense of taste	*During the past week, have you had problems with your sense of taste?*	HNSE		63%	21%	9%	7%	0.302
			NF2	*69%*	*17%*	*11%*	*4%*	
16) Been hoarse	*During the past week, have you been hoarse?*	HNSP		41%	29%	16%	14%	0.000
			NF2	*64%*	*27%*	*5%*	*4%*	
18) Appearance bothered you	*During the past week, has your appearance bothered you?*	HNSC		67%	23%	7%	4%	0.000
			NF2	*43%*	*26%*	*18%*	*13%*	
19) Trouble eating	*During the past week, have you had trouble eating?*	HNSO		45%	30%	14%	11%	0.013
			NF2	*58%*	*30%*	*8%*	*4%*	
20) Eating in front of family	*During the past week, have you had trouble eating in front of your family?*	HNSO		73%	19%	4%	3%	0.065
			NF2	*83%*	*10%*	*5%*	*2%*	
21) Eating in front of other people	*During the past week, have you had trouble eating in front of other people?*	HNSO		66%	21%	7%	6%	0.736
			NF2	*65%*	*18%*	*10%*	*7%*	
22) Trouble enjoying meals	*During the past week, have you had trouble enjoying your meals?*	HNSO		55%	27%	11%	8%	0.399
			NF2	*61%*	*26%*	*7%*	*5%*	
23) Trouble talking to people	*During the past week, have you had trouble talking to other people?*	HNSP		57%	25%	11%	7%	0.073
			NF2	*47%*	*36%*	*12%*	*5%*	
25) Social	*During the past week,*	HNSC		73%	21%	4%	1%	0.000

contact with family	*have you had trouble having social contact with your family?*		*NF2*	*53%*	*31%*	*8%*	*8%*	
26) Social contact with friends	*During the past week, have you had trouble having social contact with your friends?*	HNSC		70%	23%	6%	2%	0.000
			NF2	*35%*	*38%*	*14%*	*13%*	
27) Trouble going out in public	*During the past week, have you had trouble going out in public?*	HNSC		71%	19%	6%	3%	0.000
			NF2	*50%*	*27%*	*12%*	*10%*	
29) Less interest in sex	*During the past week, have you felt less interest in sex?*	HNSX		46%	24%	16%	14%	0.478
			NF2	*41%*	*29%*	*13%*	*16%*	
30) Less sexual enjoyment	*During the past week, have you felt less sexual enjoyment?*	HNSX		50%	22%	14%	14%	0.330
			NF2	*54%*	*19%*	*18%*	*9%*	