TheNetworkEdge
The NF Network presents A quarterly research review
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The Network Edge **brings you quarterly updates on the latest neurofibromatosis (NF) research and clinical trial advances from recent scientific publications. The newsletter is organized into "bite-sized" pieces by specific subtopic, so you can focus in on the information that interests you most.**

The Network Edge Also Features…

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Highlights from Volume 9 of *The Network Edge*:

- **A new mouse model of NF1 dystrophic scoliosis:** A new mouse model will allow closer study and drug testing.
- **Malignant peripheral nerve sheath tumors:** New drug targets show promise; studies examine a "personalized medicine" approach to finding the right drug treatments.
- **Increased age-specific breast cancer risk in NF1**: A British population study suggests women with NF1 may be at greatest increased risk of breast cancer in their 30's.
- **NF1 learning disabilities**: A new candidate drug target is identified; studies examine impact of NF1 mutation type.
- **Recognizing early life cognitive differences in NF1:** Differences in brain function in children with NF1 may be seen in the first months of life, before they are recognized by parents.
- **Quality of life in NF2**: Complications of NF can prevent people from engaging with the world. New studies examine how challenges may be identified and addressed.
- **NF2 Drug Treatments:** Bevacizumab remains most promising; studies suggest tapering down the dose to reduce side effects while maintaining the drug's tumor-treating effects.

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1. NF1 Clinical Management

a. NF1 Bony Abnormalities

The Bottom Line: A new genetically-engineered mouse model will allow closer study of NF1-related dystrophic scoliosis.

Bony abnormalities are commonly diagnosed in NF1, with an estimated third to a half of people with NF1 cases having some evidence of abnormalities in skeletal structures including the long bones, spine, skull or ribcage.

A New Mouse Model of NF1-Related Dystrophic Scoliosis

Scoliosis in the spine is a common bony abnormality in NF1, and when diagnosed as dystrophic scoliosis this can be particularly impactful with a rapid onset and progression. **Rhodes *et al*** *(China, United States)* [CDMRP, NIH, FREE] describe the characterization of new mouse models that they genetically engineered to have NF1-related dystrophic scoliosis. These mice lacked one copy of the *Nf1* gene throughout the body, and *both* copies of the *Nf1* gene in either mesenchymal stem cells (the early cell type that will give rise to bony structures at large) or osteoblasts (the specific cell type that generates new bone during development or during bone healing or remodeling). Once the mice were fully grown, findings from the mice were compared to data from a person with NF1 and dystrophic scoliosis. The study found that the biodynamics of mice and humans are different; for example, the curvature in the spine of the genetic mouse model was not as great as the curvature seen in the human spine. Nevertheless, overall the genetically engineered mice appear to reflect features of the human bony abnormalities of NF1, and they make a novel and potentially useful model for studying scoliosis as well as the drugs that might help to prevent or treat its impact.

b. NF1 Malignant Peripheral Nerve Sheath Tumors

The Bottom Line: Candidate drug targets STAT-3 and HIF-1alpha may be useful for developing NF1 MPNST treatment; a "personalized" mouse model is used to test drugs to identify the best for treating for an individual's MPNST.

Malignant peripheral nerve sheath tumors (MPNSTs) develop in about 10% of NF1 benign plexiform tumors. These cancerous tumors are difficult to treat and, unfortunately, often have a poor outcome. There are no effective drugs to halt MPNST growth, but understanding the complex biology of these tumors and identifying effective drug therapies for them is a very active area of NF1 research.

Identifying New Drug Targets for MPNST Treatment

One of the great challenges of figuring out how to treat MPNSTs is that multiple signaling pathways are overactive in these tumors and may need to be simultaneously dampened by drugs in order to find an effective treatment. **Rad *et al.*** *(United Kingdom)* take on this challenge in a study that uses four different MPNST cell lines, each with unique characteristics. Cell lines are a continually growing population of cells, and these four cell lines had been developed from four original human tumors.

The group conducted a complex series of experiments to block the activity of various cell signals in the MPNST cells, either by using drugs or by directly inhibiting the synthesis/production of these signals within the cell through RNA blockade. Not all of these treatments were effective in all of the cell lines, supporting the idea that not all cell signals are dominant to the same extent in all MPNST tumors.

In a search for signals common across the four MPNST cell lines that might be blocked to successfully halt tumor cell growth, the group identified the signals STAT3 and HIF-1alpha as key players in tumor growth and metastasis. When STAT3 and HIF-1alpha are blocked, the cancerous activity of all four MPNST cell lines is reduced. The group proposes that targeting these signaling pathways could be a good approach that might benefit a large sector of NF1 patients with MPNSTs.

Bringing Personalized Medicine to NF1 MPNST Treatment

Personalized medicine has become a "buzz word" in medical research that refers to a treatment regime that is specific not just to a patient's specific disease but to his or her individual case. This could be highly applicable to NF1, since - as exemplified by the last report above - the same tumor types can have different molecular "profiles" in different people.

Castellsagué *et al.* FREE *(Spain)* take on this area by developing a mouse model that essentially offers a personalized tool for screening drugs against a specific person's MPNST tumors. The group implanted a person's MPNST into a mouse so that the tumor would grow in the mouse and be used to test drug efficacy. The tumors seemed to stay genetically stable (i.e. mouse tumors retained the characteristics of the original human tumors) after transplant. The tumors in the mice responded to drug treatments targeting specific molecular pathways that were identified from analysis and molecular profile of the tumor cells.

This type of approach can be used to better understand an individual person's tumor before drug treatments are given, to help determine what drugs might be most effective based on the types of signaling abnormalities seen.

c. NF1 and the Eye: Optic Pathway Gliomas and Other Features

The Bottom Line: Many different approaches are used to assess children with NF1 for the occurrence of OPGs; early ongoing assessment is recommended.

Assessing How Children with NF1 Are Monitored for OPGs

An evolving topic in NF1 clinical management is how best to examine and monitor children for the appearance of optic pathway gliomas (OPG), tumors that most commonly appear in the early years of life, and will affect around 15% of children with NF1. These tumors are often identified because of the visual changes they induce. However, when they occur in very young children, changes in vision may not be reported. Other signs of OPG that can be monitored include recognizable changes in the eye and precocious puberty (due to the tumor's effect on endocrine hormone production by the brain).

Though less than half of all OPGs will eventually require treatment, it is important to monitor all children with NF1 for these tumors so that, if needed, intervention can be provided as soon as possible to maximize the chances of success and maintain vision. Chemotherapy and surgery are most commonly used in favor of radiotherapy, which can lead to secondary malignant tumors.

To investigate the question of how OPGs can best be monitored, **Caen *et al.*** *(Belgium)* used a three-step process. First, they reviewed screening approaches that have been published. Second, they sent out questionnaires to thirty-three clinics in Europe and two clinics in the United States that treat NF patients, asking these clinics what OPG screening protocols are used. Third, at a European clinical meeting, the researchers distributed a questionnaire of seven questions on this topic to two-hundred-and-thirty-five participating ophthalmologists.

Together the information gathered gave the authors a broad capture of how OPG screening is executed today. The group learned there is a lot of diversity in how screening is deployed. However, based on the feedback received, the group overall recommend ophthalmological screenings every six months until the age of six, then a yearly exam. The exam should include assessment of the visual acuity

and papillary reflexes, and a fundoscopy. Magnetic resonance imaging (MRI) should be used only if something looks clinically suspicious.

d. Breast Cancer Risk in NF1

The Bottom Line: Further evidence shows women with NF1 have an increased risk of breast cancer; women with NF1 may have a higher risk of breast cancer at earlier ages than women in the general population; a case study proposes a breast cancer link between *NF1* mutation and *BRCA1* mutation on Chromosome 17; the challenge of diagnosing breast cancer in NF1 when there are other NF1-related tumors in the locale of the breast is examined.

Over the past few years additional evidence has emerged that women with NF1 are at significantly increased risk of developing breast cancer compared to women without NF1. Some recent international publications present further findings.

Age and Breast Cancer Risk in NF1

Eye-opening results come from **Seminog and Goldacre** *(United Kingdom)*, who compared the rates of new diagnosis of breast cancer in the United Kingdom in the general population to the rates of new diagnoses of breast cancer in women with NF1. They used medical records to identify women with NF1 who had a new breast cancer diagnosis between the years 1999-2011. In the age bracket of thirty to thirty-nine, women with NF1 have a six-and-a-half time greater risk of developing breast cancer compared to women in the general population in the same age bracket. In the age bracket of forty to forty-nine, the risk of breast cancer for women with NF1 is still elevated at four-and-a-half times greater than the rates among women in the general population in the same bracket.

The authors cautioned that this study looked at a finite population of women in the United Kingdom, but nevertheless it confirms that there is an increased risk for breast cancer in women with NF1. It also goes further to suggest that women with NF1 who will go on to develop breast cancer are more likely to do so at a younger age than women in the general population.

BRCA1 Mutations – A Role in NF1-Associated Breast Cancer?

A young woman with both NF1 and early-onset breast cancer is the subject of a case report by **Jeon *et al.*** FREE *(Korea)*. The subject had been diagnosed with breast cancer in her early twenties and was undergoing treatment. She was found to have nonsense mutations in both the *NF1* gene and the *BRCA1* gene (*BRCA1* mutations are associated with an increased risk in breast cancer in the general population).

The subject's mother was also diagnosed with NF1 and early-onset breast cancer and died at age forty-one. The group was unable to complete a genetic study of the mother, as she was deceased. There was no other family history of NF1. Though the young woman's grandmother had also been diagnosed with breast cancer, she was deceased and could not be tested for a *BRCA1* mutation.

The *BRCA1* and *NF1* genes are located in close proximity on Chromosome 17. As yet, no evidence exists to show a possible link between both genes mutating. However, this report did highlight the fact that when breast cancer risk is increased in NF1 it may be due to a co-existing *BRCA1* mutation.

Differentiating Between Breast Cancer and Neurofibromas in NF1

The physical features of NF1 may present a challenge for effective diagnosis of breast cancer in women with NF1, as highlighted by **DaSilva AV *et al.*** *(Brazil)* FREE. In a case study of a fifty-four-year-old woman with NF1, the group describes how it was very difficult to confirm breast tumors either by palpation or by mammogram due to the presence of a very large number of dermal neurofibromas.

Ultimately a breast tumor was detected by needle biopsy in this woman, and she underwent a successful mastectomy and course of chemotherapy.

This report highlights one challenge of diagnosing breast cancer in NF1 can simply be conducting breast checks in the presence of other tumor tissue. The authors encourage extensive monitoring for early signs of breast cancer in women with NF1, above and beyond that given to the general population. Ultrasound and magnetic resonance imaging (MRI) are both recommended, effective approaches.

2. NF1 Learning & Development: Social Challenges in NF1

The Bottom Line: Studies examine types of NF1 gene mutation and their link to the severity of impact of NF1, starting with learning ability; hyperpolarization-activated cyclic nucleotide-gated current is deficient when NF1 gene activity is reduced in mice restored by the drug lamotrigine – potential as a new drug target for NF1-related learning disabilities. Fears of uncertainty, and pain; in young people with NF1, loneliness is more prevalent than in children without NF1, due to factors such as bullying and limited social networks; children with NF1 have reduced participation in organized physical activities compared to children without NF1, but finding a way to change this behavior may be more difficult than it appears; testing children with NF1 in the earliest months and years of life may detect early developmental challenges as yet unseen by parents.

In the past few years, research has significantly broadened understanding of the full clinical impact of NF, and particularly its ability to affect different people in unique ways. One area of focus is the impact of NF on a person's overall quality of life (known as QoL for short). QoL may include the ability to interact socially or participate in physical activities. Understanding how QoL might be affected by NF is important; NF can undoubtedly impact everyday life.

a. Type of NF1 Gene Mutation May Dictate Impact on Learning, Other Aspects of NF1

NF1 may be inherited from a parent, and if it is it will be identifiable by the presence of a mutation in the *NF1* gene in the blood as well as in the eggs of females and sperm of males, and this will mean that every cell in the person's body will have an *NF1* gene mutation from the time of birth. This is called a germline mutation (It is important to note that germline mutations can sometimes also occur spontaneously in non-inherited cases of NF1). **Anastasaki *et al.*** [NIH] *(United States)* wanted to look at whether having a germline NF1 mutation might have a greater impact on the extent of a person's learning disabilities. To test this they used cells taken from people with NF1 germline mutations and mice that were genetically engineered to have different types of mutations. The group examined dopamine signaling in the brain (an indicator of learning function) and tested mice in learning assessments. Overall this research showed that cells or mice with the equivalent of germline mutations - in which there is a greater stunting of *NF1* gene activity - perform worse on these learning assessments than do those with *NF1* gene mutations that allow a greater level of NF1 gene activity to prevail. This research highlights the fact that there may be different clinical cases of NF1 where the *NF1* gene is active at different levels and this may offer one explanation of or at least be a contributor to the broad spectrum of how NF1 affects different people.

b. Potential New Drug Target for Treatment of NF1-Related Learning Disabilities

Omrani *et al.* *(The Netherlands, United States)* target in on a cell signaling mechanism called hyperpolarization-activated cyclic nucleotide-gated (HCN) current and demonstrate that when NF1 gene signaling is reduced, HCN activity is also reduced and may contribute to learning difficulties in NF1. Using two different mouse models with deficiency in HCN activity, the group showed that normal signaling could be restored to HCN using a drug called lamotrigine. This presents a new understanding of, and potential new drug target for, learning disabilities in NF1.

c. Understanding Loneliness in NF1

The possibility of increased loneliness in teenagers and young people with NF1 was examined by **Ejerskov, Lasgaard *et al.*** *(Denmark)* in an effort to qualify whether it might be confirmed as a risk for individuals with NF1. Sixty people with NF1, aged fourteen to twenty (average age seventeen), and twenty-three of their siblings without NF1 in a similar age spread completed a self-reported questionnaire that asked about experiences of loneliness and depression, about shyness and self-esteem, about their social support, and about any experiences of bullying and whether participants experienced difficulties making friends.

Eighteen percent of those with NF1 reported feelings of loneliness, while none of the sibling group (without NF1) reported having these. The young people who reported experiencing loneliness also reported having depression, shyness, bullying experiences, a self-perceived conception of illness burden and a low level of social support from friends.

Overall this study highlighted that there is a greater risk of loneliness in those with NF1 than in those of the same age without NF1. It also suggested there may be predictive indicators of this, and that interventions, e.g. to reduce bullying or improve social networks, could reduce risk of loneliness in young people with NF1.

d. Interventional Tactics to Increase Physical Activities of Young People With NF1

Recent research reports have indicated that children with NF1 may have impaired muscle development and that this can impact their ability to participate in physical activities. This is worrisome, as these interactions are an important part of childhood development.

Johnson *et al.* *(United States)* examined activity and participation levels in young people with NF1 by collecting data from thirty-four young people with NF1 aged between five and eighteen. People who might have otherwise participated were excluded if they had learning disabilities or a long bone dysplasia caused by NF1, since both of these features could directly reduce the ability to participate in physical activity.

Half of the study group was given a physical training program (ten weeks of twice-weekly exercise at home with an instructor). They were asked to continue this program on their own for the remainder of the year without an instructor, and to keep an exercise log. They received monthly check-in phone calls to see how they were doing with this program. The other half of the study group was given no physical training. At the start of this study, at 12 weeks, and then again at one year, the participants went through standard assessments measuring their activity and participation. Information was collected directly from the children as well as their parents.

Overall the ability to participate in physical activity, as well as the happiness derived from this participation, were lower in the entire NF1 group studied, compared to a parallel group without NF1. Rather than engaging in formal activities like team sports, the NF1 group was more likely to engage in "informal" activities in the home: playing with pets, making crafts, walking with family, etc. Those with

NF1 who were least engaged in formal activities tended to have the greatest level of psycho-social problems. The authors speculated that psycho-social problems might affect self esteem and in turn inhibit participation in team activities.

The researchers also looked at the impact of offering exercise therapy to the children with NF1. This did improve upper body function but actually made participating children unhappy. The majority of exercise program participants dropped out early on. Only a small number followed along and completed the full year of training. The researchers speculated that participation might be improved by including a social aspect in the training, and by keeping therapist-led activities throughout the study period.

Overall, this research offers some understanding of the impact of physical limitations on the lives of children with NF1.

e. Recognizing NF1 Developmental Differences in the Early Years of Life

To "map out" the path of the early developmental years of children with NF1, **Lorenzo *et al.*** CDMRP *(Australia)* followed thirty-nine children without NF1 and thirty-nine children with NF1 over a number of years. The group tested the children using scales of development and intelligence, vocabulary and behavior, and tested them at twenty-one, thirty and forty months of age. The children with NF1 consisted of a mixture of inherited and non-inherited cases.

The reports of the parents did not indicate any difference in behavior between the NF1 and non-NF1 groups; however, the testing revealed consistent differences between the two groups, namely a slowing down of early developmental events in children with NF1. These differences are so subtle that they are not necessarily apparent to the parents. These early changes might indicate future general intelligence and performance of the child.

These findings highlight the value of very early life cognitive and behavioral testing of babies and toddlers with NF1, in order to identify any developmental impairment that may be unrecognized by parents so that interventions and therapy may be offered as necessary.

In another report, using a technique called resting state functional magnetic resonance imaging (fMRI), which images signaling in the brain while the subject is at rest (not asleep, just at rest), **Loitfelder *et al.*** *(Austria, Germany, The Netherlands)* examined a group of eight young people with NF1 and thirty young people without NF1, both groups averaging about twelve years of age. The NF1 group showed specific signaling differences in areas of the brain associated with cognitive and social functioning. These findings correlated with questionnaire testing results and with reports from parents on their child's cognitive, social and behavioral functioning. Compared to the study reported above where differences were identified that were unseen by parents, this study suggests that as children grow up their differences become progressively more apparent to the parent.

3. What's New in NF1 Biology?

The Bottom Line: *Grb10* emerges as a new molecular player – and potential drug target – for NF1 tumor growth; low-dose MEK inhibitor shows promise for holding NF1 tumor growth at bay; a mouse model aids understanding of adrenal cortex tumors in NF1.

a. A New Contributing Cause of NF1 Tumor Formation?

It is known that a number of molecular changes occur within cells to cause growth of NF1 tumors, on top of the mutation of the *NF1* gene itself. It is important to understand these molecular changes so that drug strategies can be developed to target, treat and prevent NF1 tumor growth.

Through a study of genetically-engineered mice, **Mroue *et al.*** NIH, FREE *(United States)* have identified mutations in a gene called *Grb10* ("Growth factor receptor bound protein 1") as a contributor. Grb10 seems to interact with all kinds of signaling pathways within the cell that are known to be affected in NF1 tumors, but the specific function of *Grb10* is not well understood. *Grb10* gene activity is reduced in cells that have no *Nf1* gene activity, and when *Grb10* activity is restored, these cells are less able to make tumors, even though *Nf1* gene activity is still impaired. This suggested a link between *Nf1* activity and *Grb10* activity. The group showed that when *Nf1* gene expression is reduced in mice, *Grb10* activity is reduced. Through a series of complex experiments using genetically engineered mice, the group showed that *Grb10* is a negative regulator of Ras signaling (Ras being a central element of the signaling pathways of the *Nf1* gene) and that *Grb10* may contribute significantly and directly to *Nf1* gene-mediated tumor growth in these mice and, therefore, potentially in human NF1 tumors.

Grb10 is an imprinted gene. For most genes an individual inherits two working copies - one from each parent. An individual can inherit NF1 if either parent passes on a mutated copy of the *NF1* gene. But with imprinted genes, an individual inherits only one working copy of the gene, and one copy is silenced. This happens to *Grb10* and can impact the function of that gene throughout life. The identification of *Grb10* as a potential key player in NF1 tumor formation and growth should be worthy of future exploration to understand its biological role and potential as a new drug target.

b. Promising Findings for an MEK Inhibitor Suggest Lasting Impact at Low Doses in NF1 Tumors

Testing candidate drugs in mice with genetically engineered NF1 tumors is a very important stage of research called preclinical drug testing, which can help to identify drugs that appear to be the most promising for potentially advancing to clinical testing. It is extremely important that these preclinical mouse models are as representative of the human NF1 condition as they can possibly be. A report from **Jousma *et al.*** NIH *(United States)* utilizes a sophisticated mouse model called *Nf1* $^{flox/flox}$*; Dhh–Cre*. This mouse is genetically engineered so that it will develop NF1 tumors with the appearance and growth rate comparable to their human equivalents, as verified by close analysis and even MRI imaging. These mice were treated with a drug called PD-0325901 that inhibits a signal called MEK, known to be overactive in NF1 tumors and a key player in the growth of these tumors. When the mice received this drug before the timeframe tumors would normally develop, their tumors grew far slower than in mice that received no drug. When the drug treatment was stopped, the tumors did keep growing but continued to be smaller than those that growing in the mice that received no drug. The drug was effective at low doses. These promising findings suggest this drug may be given at low doses over a long period of time and continue to have an effect even once drug treatment is discontinued.

c. A Look at Adrenal Tumors in NF1

Several cases of tumors in the cortex of the adrenal gland have been reported in people with NF1. The adrenal gland is a structure in the body that secretes a variety of hormones, including those linked to stress. However, the biology of this area has not been explored.

Kobus *et al.* FREE *(Austria,Germany, The Netherlands)* look at this issue using mice where *Nf1* gene activity was fully depleted in the developing limbs, head and adrenal gland cortex, but where the *Nf1* gene was still active as usual in the adrenal medulla and in the brain. The mice have a larger than normal adrenal gland. Closer examination shows structural abnormalities in certain regions of the gland due to absence of *Nf1* gene activity, which affects adrenal function. In the female mice the adrenal hormones corticosterone and aldosterone were overproduced.

The genetic underpinnings of these changes were explored in the mice and a number of underlying molecular signaling abnormalities identified, these signals being commonly aberrant in NF1

nerve tumors (e.g. signals ERK 1/2; cAMP; etc.) The research team also examined adrenal tissue from a woman with NF1 who also had overgrowth of the adrenal gland and overproduction of cortisol. A number of the same molecular changes seen in the mouse were also identified in the human tissue.

This study is important because it confirms a direct link between a clinical diagnosis of NF1 and the occurrence of adrenal abnormalities leading to raised hormone levels. This study raises awareness that this may happen in NF1, and the biological findings pave the way to developing treatments for this manifestation of NF1 when it is identified.

4. NF2 Clinical Management

The Bottom Line: The quality of life for people with NF2 is mainly reduced by psychosocial challenges.

a. Measuring Quality of Life in NF2

Monitoring the overall QoL for people with NF2 is absolutely critical because the key challenge they face - hearing loss or deafness - will have a profound impact on the way they communicate with others. **Cosetti *et al.*** CDMRP *(United States)* developed an electronic questionnaire to look at QoL in people with NF2., which was completed by one-hundred-and-eighteen people, through the online tool SurveyMonkey. The questionnaire contained sixty-one questions about a broad range of topics. These included (but were not limited to) hearing, balance, facial function, uncertainty about the future, sexual activity, pain, and vocal communication. Responses from this NF2 group were compared to responses to a similar survey of a group of people diagnosed with head/neck or brain cancer, since this group would also be expected to have a reduced QoL.

The NF2 group reported a lower QoL than the group affected by some form of cancer. They reported key factors affecting QoL were the occurrence of facial weakness, hearing loss, and imbalance. However, interestingly the most predictive factors for an overall poorer QoL were psychosocial challenges, future uncertainty, and pain. This survey therefore provides some new insight into the impact of NF2 on QoL.

The researchers pointed out that the survey requires a significant time commitment to complete, but it does ultimately provide data that could be used by other clinics.

5. NF2 Clinical Trials Update

The Bottom Line: Studies review biological intervention strategies for NF2; reducing dose of Bevacizumab over time reduces risk of side effects while maintaining drug efficacy in three adults with NF2.

a. A Review of NF2 Therapeutic Approaches

McCabe and Evans FREE *(United Kingdom)* present a review and update of therapeutic approaches for NF2 tumors. They include radiotherapy and drug therapies, highlighting the fact that the most promising treatment to date is Bevacizumab (Avastin). However, this drug's principle effects are limited to stabilizing tumor growth and restoring partial hearing; and the drug does have side effects such as cumulative kidney toxicity. Researchers also note that attempts to develop biological interventions that aim to replace the function of Merlin protein (which is normally made by the *NF2* gene and is missing or reduced in people with NF2) have not yet been greatly successful. They look forward to the opportunity to combine drug therapies and to develop drugs that don't just treat

established tumors but can be used to prevent their growth and address NF2 broadly rather than just specific tumors. This is an interesting and comprehensive FREE review.

b. *Tapering Bevacizumab Dose With Sustained Effect in NF2 Treatment*

Bevacizumab has shown to impact growth of NF2 tumors and is now more widely used as a treatment. However, NF2 tumors will need long-term treatment, since they may continue to grow. Side effects of using the drug over the long-term include proteinuria and hypertension. These can be problematic and can result in discontinuation of therapy even when the drug is effective in keeping the tumors at bay.

Farschtschi *et al.* *(Germany)* explore the possibility of tapering the Bevacizumab dose down for use in NF2 in an effort to maintain the drug benefits but avoid the side effects. They report on three individuals with NF2 – two men and a woman - who received Bevacizumab for around five to six years and whose doses were halved from 5mg/kg to 2.5mg/kg either every two or every three weeks. Measures of speech, tumor volume and hearing ability appeared consistent over many months. These findings offer promise for those with NF2 benefiting from Bevacizumab.

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