TheNetworkEdge
The NF Network presents a quarterly research review
by science writer, Vanessa Merker, BS

The Network Edge Volume 12: Summer, 2016

***The Network Edge* brings you regular updates on the latest neurofibromatosis (NF) research and clinical advances from recent scientific publications. *The Network Edge* is organized into "bite sized" sections by specific subtopic, so you can focus on the information that interests you most.**

The Network Edge features…

- **The Bottom Line**: Each section starts with a **summary sentence** highlighting the "take home" points.

- **Federally-Funded Research**: All research identified as being either fully or partly funded by the Congressionally Directed Medical Research Neurofibromatosis Research Program (CDMRP NFRP) or the National Institutes of Health (NIH) is **tagged** CDMRP or NIH after the author name.

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Highlights from Volume 12 of *The Network Edge*:

- **NF1 Learning Disabilities:** Lovastatin may help improve memory in children and adults with NF1.
- **NF1 and Cancer:** People with NF1 under 30 are the most likely to develop brain tumors or MPNST; women with NF1, especially those under 45, have an increased risk of breast cancer.
- **NF1 Brain Tumors:** Children with NF1 and low grade gliomas have good short-term and long-term survival after treatment; controversy continues over MRI screening for optic pathway gliomas.
- **NF2 Vestibular Schwannomas:** Treatment with bevacizumab can improve hearing in some patients with NF2; a new mouse model offers a good opportunity to test new drugs.
- **Schwannomatosis Update:** Schwannomas may appear cancerous on PET scans even when they are not; advances in MRI techniques may improve our ability to understand this phenomenon.
- **Quality of Life**: A preliminary study of Acceptance and Commitment Therapy (ACT) shows promising results helping adolescents with NF1 and chronic pain.

The Network Edge: Volume 12 – Contents

NEUROFIBROMATOSIS 1

1. Learning Disabilities and Social Difficulties

a. Clinical Trial of Lovastatin to Improve Cognition in People with NF1

The Bottom Line: Lovastatin, an FDA-approved drug used to treat high cholesterol, may help improve memory in children and adults with NF1. An ongoing clinical trial should help clarify if lovastatin can improve attention and visual perception as well.

Learning disabilities are common in children with NF1, affecting approximately 30% to 65% of the afflicted population. Children with NF1 may have difficulty with visual and spatial processing, executive function, working memory, or attention. Executive function is a group of skills related to controlling your thoughts and actions so you can achieve a goal. These skills include working memory, which is the ability to hold information in your head while you perform a task.

Using mouse models of NF1, researchers have worked to unravel the molecular pathway by which NF1 causes learning deficits. A key player in this pathway is a family of proteins called Ras, which are too active in people with NF1. Lovastatin, a drug that is already FDA-approved to treat high cholesterol, reduces the activity of one kind of Ras protein. For this reason, researchers began testing lovastatin in mouse models of NF1. In studies by **Li et al.** FREE, NIH (United States), lovastatin successfully reduced the activity of Ras and improved spatial learning and attention in the mice.

To determine whether lovastatin would be safe to give to children with NF1, **Acosta et al**. (United States) conducted a small pilot study, called a Phase 1 trial wherein they gave lovastatin to 24 children ages 10-17 for three months. They found that lovastatin caused very few side effects, and could be used at the same dose that is already given to children with high cholesterol. In addition, the researchers looked at how lovastatin affected children's performance on cognitive tests. Over the three months, children taking lovastatin improved in verbal and nonverbal memory tests. These results are only preliminary, though, because this study did not look at a control group of kids with NF1 not taking lovastatin. Without a control group, we can't know if children in the trial performed better on cognitive tests because the lovastatin actually helped them, or because they simply got better at taking the tests as they had more practice.

For this reason, **Bearden et al.** FREE, NIH (United States) conducted a randomized, double-blind placebo-controlled trial of lovastastin to look for more robust evidence of a beneficial effect of lovastatin on cognition. Forty-four individuals with NF1, ages 10-50, were enrolled in the trial, and half were randomly assigned to receive lovastatin, while half received an inactive pill (called a placebo). Randomly putting people into one group or the other helps ensure that overall, the people in each group are similar. By giving one group a placebo and not letting the doctors nor the patients know who is receiving the placebo, researchers reduce the chances for bias in the study.

In this clinical trial, participants took lovastatin once a day for 14 weeks. People taking lovastatin improved more than people taking placebo in two areas: working memory and verbal memory. However, there were no significant differences in nonverbal memory, visual-spatial ability, or attention between the two groups.

Of note, participants in the **Bearden et al.** FREE, NIH study did not necessarily have any learning disability at the time they started the study. It is possible that there was no significant improvement in visual perception or attention because only people who are struggling with those areas would be helped. For this reason, an even larger clinical trial was funded by the CDMRP Neurofibromatosis Clinical Trial Consortium. The STARS trial investigated the effect of lovastatin on children ages 8-15 with NF1 and problems in visual-spatial learning and/or attention. This clinical trial recently finished, and researchers are analyzing the data now. Once results are published, we'll be sure to cover the outcome in a future issue of *The Network Edge*!

b. Understanding Social Function in Children with NF1

The Bottom Line: Children with NF1 can experience social difficulties regardless of their intelligence or other cognitive abilities. These social difficulties might be due to issues understanding what other people are thinking and feeling.

Research has shown that children with NF1 have a higher than expected rate of Autism Spectrum Disorder (ASD) symptoms, particularly in social areas like the ability to make close friends. Two recent articles looked at social difficulties in children with NF1 with the goal of figuring out what causes these difficulties, and whether social difficulties are related to a child's intelligence or to symptoms of ADHD.

Allen et al (United States) looked at social functioning and recognition of facial expressions in 23 children with NF1 and 23 controls (age-matched peers without NF1 or developmental disorders). On average, children with NF1 had a lower estimated IQ and lower social functioning (as reported by themselves and by their parents). To test facial expression recognition, kids were shown pictures of faces and were asked to determine if the person pictured was happy, sad, angry, or scared. On average, children with NF1 had more trouble deciphering subtle emotions, but they did just as well as their peers when the emotion was very intense. Within the group of children with NF1, there was no relationship between a child's performance on the facial expression test and that child's intelligence or cognitive functioning.

Payne et al. (Australia) looked at theory of mind in 26 children with NF1 and 36 children without NF1. Theory of mind is the ability to put yourself in another person's mind – to understand a person's thoughts and desires, and predict how they will behave. Children usually begin to develop theory of mind at age three or four. Payne et al. tested theory of mind in children ages 4-12 by asking them to put pictures in the correct order to tell a story. While children with NF1 had no difficulty understanding concepts like cause and effect, they made more errors than children without NF1 on stories that required an understanding of theory of mind. Children with NF1 who performed worse on the test did not score lower on an intelligence test, nor experience more symptoms of ADHD (Attention Deficit Hyperactivity Disorder). The researchers suggest that difficulties understanding theory of mind might be one reason children with NF1 are more likely to experience social difficulties than other children.

2. NF1 and Cancer Risk

The Bottom Line: Individuals with NF1 under 30 are the most likely to develop brain tumors or MPNST, and they have the highest risk of cancer compared to individuals without NF1. Women with NF1, especially those under the age of 45, are at an increased risk of developing breast cancer.

Individuals with NF1 are at a higher risk than the general population of developing multiple types of tumors (some of which are benign, and some of which are cancerous). These include neurofibromas, malignant peripheral nerve sheath tumor (MPNST), gliomas, pheochromocytoma, and gastrointestinal stromal tumor (GIST). Many studies have tried to quantify the risk of developing each of these types of tumors, but scientists have been limited by the availability of data sources to locate individuals with NF1 and track their outcomes.

Recently, **Uusitalo et al.** FREE (Finland) published a comprehensive study on the risk of cancer for individuals with NF1. First, the researchers tried to identify all NF1 patients in Finland by looking at the medical records of all 20 academic and national hospitals located there. Then, they used national databases to find every NF1 patient who developed cancer and/or died during the study period of 1987-2011. Finally, they compared the rates of cancer in people with NF1 to the general Finnish population.

A very important point to note about this study is how researchers defined cancer. To find cases of cancer, the researchers used ICD-10 codes – codes that doctors and hospitals use to describe what disease or symptom a patient has. The ICD-10 codes the researchers used to look for brain cancer include both malignant/cancerous brain tumors and benign brain tumors. For this reason, it's important to remember that their estimates of cancer include tumors that some doctors would not describe as cancerous (like optic pathway gliomas and other low-grade gliomas).

The researchers estimated that about 60% of people with NF1 in Finland will develop cancer at some point in their lives, compared to 30% of the general population. This extra risk was most apparent in younger people (age <30 years), and was due largely to MPNSTs and brain tumors. The extra risk of developing cancer decreased with age, and by the age of 70, individuals with NF1 develop new cancers at the same rate as individuals without NF1.

Uusitalo et al. FREE confirmed prior studies showing that individuals with NF1 have a higher risk of developing breast cancer, particularly women ages 30-45. (Information on prior research on NF1 and breast cancer is available in Volumes 9 and 11 of *The Network Edge*). Women with NF1 should talk to their doctors about this risk, in order to decide the appropriate time to start screening for breast cancer with mammograms or breast MRIs.

For interested readers, **Dr. Gareth Evans** FREE (United Kingdom) wrote an editorial summarizing the results of **Uusitalo et al.** compared to previous research on cancer risk in NF1. This editorial is free to access, but it does use technical language that may be difficult to understand.

3. Optic Pathway Gliomas and Other Brain Tumors

The Bottom Line: Children with NF1 and low-grade gliomas have good short-term and long-term survival after treatment; in some areas, their outcomes are even better than children without NF1.

a. Treatment of Low-grade Gliomas with Vincristine and Carboplatin

A recently completed clinical trial looked at chemotherapy treatment for low-grade gliomas (a type of brain tumor that includes most optic pathway gliomas). The trial enrolled children 10 years old or younger with growing tumors, some of whom had NF1 and some of whom did not. All of the children with NF1 and half of the children without NF1 were treated with a combination of two chemotherapies – carboplatin and vincristine (CV).

Ater, Zhou, et al. FREE, NIH (United States) previously reported on the outcomes of children without NF1 who were treated with these drugs, comparing those who got treatment with CV to those who received a different combination of chemotherapy. Now, **Ater, Xia, et al.** NIH (United States) have looked at the results for the 127 children with NF1 and compared them to results from the 137 children without NF1 who received the same treatment (CV).

In this trial, children with NF1 had better outcomes than children without NF1. Five years after treatment with CV, children with NF1 were more likely to be alive (98% of children with NF1 vs. 87% of children not afflicted with NF1) and less likely to have experienced a negative event (31% children with NF1 vs. 61% of children not afflicted with NF1). For this trial, a negative event was defined as significant tumor growth, a tumor coming back after surgery, a new cancerous tumor, or death. Within the group of children with NF1, those under the age of three and children with larger tumors (>3cm^2) were more likely to experience a negative event.

It's important to remember that the groups of children with and without NF1 weren't exactly the same – children with NF1 were more likely to have an optic glioma (as opposed to a tumor in a different part of the brain), and they were much less likely to have had surgery prior to the study. But even after using statistical techniques that take these differences into consideration, children with NF1 were still less likely to experience a negative event than children not afflicted with NF1. These results highlight the fact that individuals with NF1 can respond differently to drugs than people with the same kinds of tumors who are not afflicted with NF1. For this reason, it's important to include individuals with NF1 (and NF2 and schwannomatosis) in clinical trials, so that we can more accurately determine the benefits and risks of new treatments for individuals with all types of NF.

b. Long-term Outcomes for Children with Low-grade Gliomas

The short-term and medium-term prognosis for children with low-grade gliomas is usually very good – most children are alive two, five, and even 10 years later. But we know less about what happens to children in the long term, because it can be difficult to keep track of people for more than 10 years; patients change doctors or move to new places, and the original researchers don't know what happened to them. **Krishnatry et al.** (Canada) were able to get around some of the difficulties of studying long-term outcomes by using unique data from Ontario, Canada. Virtually all children in Ontario with brain

tumors are treated at five specialized hospitals, and these hospitals established a special database in 1985 to collect detailed clinical information on all of their patients with tumors.

Krishnatry et al. looked for all of the individuals in the database who were diagnosed with a low-grade glioma when they were less than 18 years of age; they identified 1,202 individuals who were diagnosed between 1985 and 2012 and collected all the information available on what happened to these individuals after they were diagnosed. For one of the five hospitals (Hospital for Sick Kids in Toronto), they were also able to determine which of the individuals with low-grade glioma had NF1.

The researchers estimated that 90% of children with low-grade glioma were still alive 20 years after treatment, and 88% were still alive 30 years after treatment. Age and sex did not significantly affect outcomes, except for the subgroup of children with optic pathway glioma (OPG). Children who had an OPG diagnosed before they were three years old were less likely to survive 20 years later than children who were diagnosed after age three. Children who received radiotherapy also had decreased long-term survival, because in those cases, low-grade tumors were more likely to transform into high-grade (more aggressive) tumors, and they were also more likely to develop a new cancer.

Looking specifically at low-grade glioma patients from the Hospital for Sick Kids in Toronto, there were 125 children with NF1, and 116 of those kids had an OPG. The researchers estimated that 95% of children with NF1 and an OPG survived 20 years after diagnosis. Based on data researchers had access to, only four children with NF1 died between 1985 and 2012. Two children died from causes unrelated to their brain tumors, and two children who had received radiation died because their tumors transformed into high-grade malignancies.

This data on children with low-grade glioma shows us that most children, including those with NF1, will live many years after being diagnosed with a brain tumor. It also shows that treatment with radiation can cause problems many years later. This long-term risk is something patients and their doctors must carefully balance with other, immediate factors when they decide what treatment is best for them.

c. Pregnancy-related Risk Factors of Brain Tumors in Children with NF1

The NF1 Patient Registry Initiative (NPRI) is an internet database run by researchers at the Washington University in Saint Louis Neurofibromatosis Center. Adults with NF1 or parents of children with NF1 provide information about their health/their child's health, so that researchers can better understand the spectrum of medical and social issues associated with NF1. **Johnson et al.** [NIH] (United States) have used the NPRI to investigate the association between things that happen when a child with NF1 is in utero (when the mother is pregnant), and the chance that the child will develop a brain tumor.

To accomplish this, researchers looked at 606 children (age <18) in the NPRI who had been enrolled before July 2015 and whose parents had entered information about their births. One hundred and eighty-four of these children had a brain tumor, out of which 65 specified that the brain tumor was an OPG. When the researchers compared children who had brain tumors to those who didn't, they found there was no association between having a brain tumor and most of the pregnancy-related factors they studied. These factors included the child being born prematurely, being a twin/triplet, or being conceived with the help of assisted reproductive technology (such as in-vitro fertilization). Parent factors that were not related to brain tumor development included smoking, having NF1, being age 35

or older at the time of birth, or taking vitamins during pregnancy (mothers only). The one association that researchers did find was between higher birth weight and an increased risk of having an OPG. This association is not unique to NF1, however, as multiple studies in the general population have also shown an association between higher birth weight and the development of pediatric brain tumors.

For readers who are interested in learning more about the NPRI, you can visit their website at https://nf1registry.wustl.edu/ The NPRI also regularly publishes a newsletter available online that highlights stories of registry participants and research on NF1.

d. MRI Screening for Optic Pathway Gliomas: Continued Controversy

The Bottom Line: Experts agree that children with NF1 should regularly get comprehensive eye exams to check for visual problems that might be a sign of an optic pathway glioma. However, there is disagreement regarding children with NF1 routinely receiving brain MRIs to check if they have an OPG.

Optic pathway gliomas (OPGs) are a common tumor in children with NF1, affecting approximately 15-20% of the population. OPGs are most common in children under six years. Many OPGs cause no symptoms, but in some cases, they can cause vision loss, proptosis (when the eyeball is pushed forward), or precocious puberty (when signs of puberty like growth spurts or developing pubic hair occur prior to age eight or nine). In cases of symptomatic or growing OPG, the most common treatment is chemotherapy, rather than surgery or radiation.

Because OPG is relatively common in children with NF1, doctors wanted to know if and how they should screen for these tumors. Screening is the process of looking for a tumor or disease even in people without symptoms. In 1997, The National Neurofibromatosis Foundation (now known as The Children's Tumor Foundation) formed an NF1 Optic Pathway Glioma Task Force to address this question. The experts on the task force recommended children have comprehensive annual eye exams, and brain MRIs only when a child had an abnormal finding on their eye exam. Since that time, some research has supported the recommendation, but some has not, leading some doctors to recommend both eye exams and brain MRIs on a regular basis.

Recently, two studies with large numbers of patients came out that attempt to answer the question, "Should we use brain MRIs to screen asymptomatic children with NF1 for optic pathway gliomas?" Both research groups reviewed all the children with NF1 treated at their respective hospitals and looked at how many children had an OPG and how many needed treatment for it.

Prada et al (United States) reviewed all the children with NF1 seen at the Cincinnati Children's Hospital Medical Center between 1990 and 2010. At this hospital, children with NF1 were screened with a brain MRI at the age of 15 months, or at the time they first visited the NF Clinic. Across the sample of 826 children ages one to nine who received a screening MRI, 18% (149 children) were found to have an OPG. Twenty-two children with OPG were treated with chemotherapy – that's 15% of the 149 children with OPG, but only 2.7% of the entire group of children with NF1.

Blanchard et al. (France) reviewed all the children with NF1 seen at the six major pediatric NF clinics in France between 2001 and mid-2007. At these hospitals, all newly-diagnosed children under age six received a screening MRI, and in some cases, they received a second brain MRI two years later.

Across 303 children screened with a brain MRI, 45 children (14.7%) had an OPG. However, eight of these children had symptoms at baseline, and so for the purposes of evaluating screening MRIs, they shouldn't really be considered (because screening is for people without symptoms, and these eight children had a clinical reason to get a brain MRI). Considering only the 36 children who had an asymptomatic OPG discovered on screening MRI, 11 (31%) had worsening clinical symptoms over time, and three of these 11 received treatment with chemotherapy.

So what should we make of these numbers? On the whole, the two groups saw similar percentages of children with OPGs, but they differed in their interpretation of the results. **Prada et al** noted that children who already had visual problems at the start of chemotherapy were more likely to experience worsening vision compared to children without vision problems at the start. This led the authors to suggest that MRI screening would be useful to catch OPGs before they start causing visual symptoms, and thus hopefully lead to a better outcome in cases where chemotherapy is needed. However, **Blanchard et al**. argued that it didn't matter if doctors caught OPGs before they caused visual symptoms, because treatment would not begin until after visual symptoms presented anyway. In this way, MRI screening for OPGs might identify more tumors, but it would not change clinical management.

Beyond the topic of whether MRI screening changes treatment decisions, we should also consider the psychological benefits and harms of screening. Children who undergo an MRI screening and have no OPG are highly unlikely to develop one later on (Across both studies, only two children out of the 1,038 with normal brain MRIs later developed a symptomatic OPG). So parents of children with negative MRIs can rest assured that their children are unlikely to develop an OPG. But in the cases of children who undergo MRI screening and have an OPG, the tumor will not likely have symptoms or need treatment. This can cause parents a lot of extra anxiety, and the child would have to undergo even more MRIs (which for young kids often involves being sedated).

For interested readers, **Millichap** [FREE,] published a very short, free commentary summarizing the findings of Prada et al. and others. In this comment, he suggests that the NF1 OPG Task Force should meet again to discuss the issue of MRI screening for OPGs. Given the continued controversy on this topic, expert guidance and a well-designed, prospective study (one that goes forward in time, instead of looking back on old records like the studies completed by **Prada et al**. and **Blanchard et al.**) are certainly needed.

4. Malignant Peripheral Nerve Sheath Tumors (MPNST)

The Bottom Line: The prognosis for individuals with MPNSTs who have NF1 is worse than the prognosis for people without NF1; this is mostly due to the fact that individuals with NF1 are more likely to have large tumors that are deep in the body and therefore cannot be completely surgically removed.

a. MPNST Prognosis in People with and without NF1

Individuals with NF1 have an 8-13% chance of developing a malignant peripheral nerve sheath tumor (MPNST) in their lifetime. (To put that another way, in a group of 100 people with NF1, we would expect somewhere between 8 and 13 people to get an MPNST at some point during their lives.) But

people without NF1 can also get MPNSTs. Recently, two papers have been published comparing the outcomes of MPNST treatment in large samples of people with and without NF1.

Watson et al. [NIH] (United States) looked at a database of individuals with MPNSTs who were seen at the University of Texas MD Anderson Cancer Center from 1990-2014. They found 289 individuals with detailed clinical information; of these, 148 (51%) had NF1 and 141 (49%) did not. **Valentin et al**. (France) looked at individuals with MPNSTs who were seen at a network of French cancer centers from 1990-2013. They found 340 individuals: 131 (39%) had NF1 and 209 (61%) had sporadic tumors.

All studies presented similar findings. Individuals with NF1 had larger tumors on average and were more likely to have deep tumors (underneath the last layer of skin). Individuals with NF1 who had surgery were more likely to have an incomplete resection (this is when cancer cells present at the edges of the piece of tissue surgeons removed during surgery). **Valentin et al**. looked at how advanced the MPNST was and found that people with NF1 were more likely to have tumors that spread into nearby tissues like blood vessels and bone.

Watson et al. and **Valentin et al.** found that because of these differences between the two groups, individuals with NF1 were more likely to have their MPNST return after surgery and were more likely to die earlier. For example, **Valentin et al**. found that 50% of people with NF1 who got surgery were still alive five years after being diagnosed with an MPNST; in contrast, 65% of people without NF1 who got surgery were still alive five years after being diagnosed.

These results mean that while individuals with NF1 generally have a worse prognosis when they get an MPNST, it is mostly due to identifiable clinical characteristics that we can hopefully improve on. With quicker and more accurate detection of MPNSTs, perhaps doctors will be able to catch tumors when they are smaller and haven't had time to spread to nearby tissue. This would hopefully lead to more tumors being completely resected, which would lead to better outcomes for people with MPNST.

b. Differentiating Benign Neurofibroma from MPNST

While some tumors are easy to identify under the microscope, other tumors can have confusing features. For example, sometimes atypical neurofibromas and cellular schwannomas (both of which are non-cancerous) can look like MPNSTs. **Rohrich et al** (Germany) looked at 171 different peripheral nerve sheath tumors (the type of tumor that includes neurofibromas, schwannomas, and MPNSTs) to determine whether DNA methylation profiling could help pathologists distinguish the different types of tumors. Methylation is the process of adding molecules to DNA to turn certain genes on or off. The researchers found that a particular loss of methylation was seen only in MPNSTs, and never in schwannomas or neurofibromas. This gives pathologists new information to help them diagnose tumors and avoid cases where a benign tumor is mistakenly thought to be cancerous.

NEUROFIBROMATOSIS 2

5. Bevacizumab for the Treatment of NF2 Vestibular Schwannomas

The Bottom Line: Treatment with bevacizumab can improve hearing and reduce the size of vestibular schwannomas in some patients with NF2.

a. Clinical Trial to Improve Hearing in People with NF2 and Progressive Hearing Loss

The hallmark symptom of NF2 is bilateral vestibular schwannomas – tumors that occur on the hearing and balance nerves located inside both ears. Vestibular schwannomas can cause hearing loss, tinnitus (ringing in the ears), and balance problems. Currently, there are no FDA approved drugs to treat these symptoms. In recent years, doctors have tried using bevacizumab (also known as Avastin) to treat people with NF2 with hearing loss or growing vestibular schwannomas. In 2009, researchers from Massachusetts General Hospital published encouraging results showing that some NF2 patients had improved hearing and/or smaller tumors after being treated with bevacizumab. Since then, individuals with NF2 around the world have been treated with bevacizumab in an attempt to improve hearing and/or shrink vestibular schwannomas. Some patients report that they are much better after taking bevacizumab, but unfortunately, others do not.

In order to provide better scientific evidence as to whether bevacizumab really helps improve hearing in patients with NF2, clinicians decided to conduct a clinical trial. A clinical trial provides stronger evidence than earlier research because everyone is treated in the same way, and the outcomes are specified in advance. When planning a trial, researchers can use statistics to figure out how many patients need to be in the trial in order for us to be confident that the results we find are actually true.

Blakeley et al.[NIH] have now published the results of the first clinical trial of bevacizumab in individuals with NF2. The trial enrolled 14 NF2 patients who were experiencing hearing loss. Each patient was treated with bevacizumab for one year, except in the case of a medical complication or in the case that the patient chose to discontinue participation sooner. After one year, patients stopped taking bevacizumab for six months, so that doctors could determine whether any benefits from treatment could be maintained during that time.

The main goal of the study was to examine what happened to an individual's hearing in the ear that was losing hearing before treatment with bevacizumab. The researchers found that five of the 14 patients (36%) had a sustained improvement in hearing. A sustained improvement meant that hearing was significantly better on two hearing tests in a row, conducted three months apart. Three more patients (21%) had better hearing on one hearing test, and none experienced worse hearing during the year of treatment with bevacizumab. After stopping bevacizumab, three of the five patients with sustained hearing improvement continued to have improved hearing for six months.

The second outcome for this clinical trial was change in tumor size. Every patient in the trial had bilateral vestibular schwannomas – one tumor in the right ear and one tumor in the left ear. Since 14 individuals participated in the trial, that means there were 28 vestibular schwannomas to measure. Five of the 28 tumors (18%) shrank by more than 20% in size, and 13 of 28 tumors (34%) shrank between 5%

and 20% in size. None of the tumors grew by more than 20% in size while patients were taking bevacizumab.

Interestingly, there was no relationship between how much a patient's tumor shrank and how much hearing improved. Some individuals had better hearing but had tumors that stayed about the same size. This highlights that the size of a vestibular schwannoma is not the only thing that impacts whether or not an individual with NF2 will lose hearing. More research is needed to figure out exactly why individuals with NF2 lose hearing so that we can determine better ways to treat and prevent hearing loss.

**Disclosure – The author of this newsletter is also a co-author on the study by Blakeley et al.*

b. The Best Dose of Bevacizumab?

Liu et al. FREE (China) described a patient at their hospital who was treated with a lower dose of bevacizumab than what was used in the **Blakeley et al**. NIH clinical trial. Despite receiving a lower dose of the drug, the patient's vestibular schwannomas decreased in size. While the patient's formal audiology testing did not show any improvement, the patient reported that he felt better able to communicate.

This case highlights the fact that we are still figuring out the best dose of bevacizumab to administer to patients. Doctors and patients want to find the dose that offers the best balance between improving hearing and shrinking tumors on the one hand, and decreasing side effects like kidney damage and high blood pressure on the other. This is one of the reasons a second clinical trial of bevacizumab is currently underway. Compared to the **Blakeley et al.** trial, this trial utilizes a higher dose of bevacizumab for the first few months, and a lower dose of bevacizumab after that. More information about this ongoing trial of bevacizumab can be found at https://clinicaltrials.gov/ct2/show/NCT01767792

6. Mouse Models of NF2

The Bottom Line: Researchers have developed a new mouse model of vestibular schwannomas that can be used to determine whether new drugs can shrink the tumors or improve hearing.

Mouse models can be a useful tool to find new drugs that might work in treating NF. By looking at which drugs work in mice, researchers have a better idea of which drugs are worth testing in clinical trials for people. The most useful mouse models are those that closely mimic human disease. The mouse tumors should look as close as possible to human tumors under the microscope, and the mice should develop the same symptoms as humans.

Bonne et al (United States, France) have developed a new mouse model to study vestibular schwannomas (also known as acoustic neuromas). The researchers surgically implant schwannoma cells directly into the area around the mouse's 8th cranial nerve – the nerve that controls hearing and balance. These cells grow into tumors that fill up the inner auditory canal and cerebellopontine angle of the brain – the same location in the brain where people develop vestibular schwannomas. Researchers can then give the mice MRIs to track the tumor's size and determine whether new drug treatments can

shrink the tumor or slow its growth. The mice also lose their hearing as the tumors grow. This means that researchers can test whether a drug improves hearing or prevents hearing loss in the mouse. While the way researchers measure hearing in mice isn't the same way researchers measure hearing in NF2 clinical trials, this represents a good opportunity to start examining the effect of new treatments of hearing.

7. Schwannomatosis

The Bottom Line: Schwannomas may appear cancerous on PET scans even when they aren't; advances in MRI techniques may be able to improve our ability to understand schwannomas.

a. Medical Imaging Techniques in Schwannomatosis

Doctors use PET scans (positron emission tomography) to attempt to identify malignant (cancerous) tumors in the body. During a PET scan, a small amount of radioactive dye is injected into a patient before imaging. Tumors that are metabolically active take up more of the dye and then light up on the scan. In many types of cancers, PET scans make it easy to see where tumors are located, because cancerous tumors are very metabolically active.

However, in people with NF1, we know that some neurofibromas can look very bright on PET scans even though they are not cancerous. **Lieber et al**. (United States) report on a case that shows the same thing might be true for schwannomas in people with schwannomatosis. A woman with schwannomatosis was given a whole-body PET scan, because she had multiple large, painful tumors. Four tumors looked very bright on the PET scan, which would normally lead doctors to believe that the tumors were cancerous. However, when doctors actually biopsied those four tumors, they found that all of them were normal, benign schwannomas. This information is important for all clinicians to consider when they are interpreting PET scans of patients with schwannomatosis.

Because schwannomas can falsely appear cancerous on PET scans, special kinds of MRI scans may be more useful in monitoring people with schwannomatosis. **Ahlawat et al.** (United States) reviewed whole-body MRIs of 13 individuals with schwannomatosis at Johns Hopkins Medical Institute. They described the characteristics of 149 tumors in these 13 people, in order to provide a comprehensive listing of what schwannomas look like on different kinds of MRI images. This information lays the groundwork for determining what MRI characteristics may predict malignant transformation in schwannomatosis-related schwannomas.

Interestingly, **Ahlawat et al.** also found that three patients had thick nerve roots on MRI, even though they didn't have any tumors nearby. The authors suggest that perhaps this nerve thickening is related to the neuropathic pain many people with schwannomatosis experience. This is an interesting hypothesis that will have to be tested in a future study.

b. Unilateral Vestibular Schwannomas Occurring in Schwannomatosis

Unlike NF1 and NF2, schwannomatosis can be caused by mutations in multiple genes. Individuals with schwannomatosis may have mutations in SMARCB1, LZTR1, or other genes that

researchers have yet to pinpoint. Researchers are looking to see if the kind of mutation an individual has can predict what type of symptoms he or she will develop – a genotype/phenotype correlation. Recent research has suggested that individuals with SMARCB1 mutations may be more likely to have meningiomas, and that individuals with LZTR1 mutations may be more likely to have a unilateral vestibular schwannoma (a tumor on only one side).

Mehta et al. [NIH] (United States) described the case of a schwannomatosis patient without either an LZTR1 or a SMARCB1 mutation who developed a unilateral vestibular schwannoma. This case is important for two reasons: First, it underscores that even though vestibular schwannomas are predominantly a feature of NF2, a single vestibular schwannoma can occur in schwannomatosis patients; second, it shows that a vestibular schwannoma may appear in a patient who does not have an identifiable mutation in the two known genes that cause schwannomatosis.

QUALITY OF LIFE AND NF

8. Finding Interventions to Improve Quality of Life

The Bottom Line: Evidence-based psychosocial programs are needed to improve quality of life for people with NF. A preliminary study of Acceptance and Commitment Therapy (ACT) shows promising results in helping adolescents with NF1 and chronic pain.

In the past few years, the NF community has increasingly recognized the importance of psychological and social treatments in improving quality of life for people with NF. Multiple groups are working to adapt existing, well-researched programs to suit the unique challenges faced by individuals with NF. **Martin et al.** [NIH] (United States) have just published results of a pilot study testing one kind of psychosocial skills program, Acceptance and Commitment Therapy (ACT), for adolescents/young adults ages 12 to 21 with NF1 and chronic pain (To simplify, we'll refer to this group as adolescents for the rest of the article.).

ACT tries to help participants focus on their values and goals instead of the pain they are in, so that they can still complete activities that matter to them. Adolescents completed three two-hour workshops on ACT, spread out over two days. The workshops covered topics like mindfulness techniques, imagery to help accept and deal with pain, and methods to outline goals and ways to commit to goals. There was also a separate ACT workshop for parents of the adolescents, which focused on helping parents cope with their child's pain and better support their child when he or she is in pain. After the sessions, adolescents and their parents were given a workbook with exercises to individually review their progress and encourage them to continue working on their goals.

Ten adolescents with NF1 and chronic pain finished the ACT workshops and filled out surveys three months later to determine the effectiveness of the workshop. Adolescents reported improvements in regard to the intensity of pain and how much it interfered with their life, and 6 of 10 patients were taking less pain medication. There was no significant change in how much anxiety the pain caused, or adolescents' ability to perform daily activities. Six of the 10 adolescents said they used ACT techniques at least once a week. Overall, the results were promising, but this study was very small,

and more evidence is needed before researchers can confidently say that ACT will help adolescents with NF1.

For this reason, a larger follow-up study on ACT is currently enrolling patients. This study is enrolling individuals with NF1 ages 16-34 who have one or more plexiform neurofibroma and chronic pain. More details about this study can be found at https://clinicaltrials.gov/ct2/show/NCT02471339.

A second trial related to quality of life is also currently enrolling patients. This study involves a mind-body resiliency program for people with NF that was first reviewed by **Vranceanu et al** (United States). The current trial is for adolescents aged 12-17 with NF1 or NF2; it is a group program delivered on the computer using the free videoconferencing software Skype. More information about this study can be found at https://clinicaltrials.gov/ct2/show/NCT02387177.

9. Investigating Factors That Impact Quality of Life

The Bottom Line: Individuals with NF have very different experiences of the disease, even when they have similar clinical symptoms. A focus on helping people adapt to their physical appearance and function and deal with uncertainty about the future of their NF may be a good approach to improving quality of life.

a. Health-related Quality of Life for People with NF2

The NF2 Natural History Study was a large, international study of individuals recently diagnosed with NF2 conducted in the early 2000s. Recently, researchers went back to the data collected in this study to look at the quality of life surveys that participants completed.

Merker et al. CDMRP (United States) looked at 81 individuals with NF2 from the United States, Great Britain, and Australia. On average, adults with NF2 rated their physical and mental quality of life as slightly lower than people in the general population. Two exceptions were the areas of pain and energy/fatigue, in which adults with NF2 scored the same as the general population. Individuals with a larger vestibular schwannoma experienced more difficulty carrying out their work or other daily activities because of physical health, pain, and mental health.

As part of the NF2 Natural History Study, doctors measured each individual's hearing and facial function (how the nerves and muscles of the face are working). Surprisingly, there was no relationship between hearing or facial function and quality of life; this might be due to the fact that in this particular survey the researchers didn't ask enough questions specific to the kind of problems individuals with NF2 might experience. Or it might be that the way a doctor rates hearing and facial function is not as important as how individuals adapt to their hearing loss or facial paralysis. If this is true, then psychological and social support could help people improve their quality of life, even if their symptoms don't improve.

**Disclosure – The author of this newsletter is also the primary author of Merker et al.*

b. Appearance Concerns for Adolescents and Young Adults with NF1

As children with NF1 age, they can develop more neurofibromas, making their disease more visible to others; however, it is uncertain if and when these neurofibromas will appear. In interviews with adolescents with NF1 and their parents, **Barke et al.** found that having visible tumors and feeling anxious about developing more tumors were important factors in adolescents' emotional wellbeing. To find out more about this topic, **Barke et a**l. (United Kingdom) surveyed 73 adolescents and young adults (age 14-24) with NF1, and 55 parents of adolescents with NF1.

The researchers found that while some adolescents/young adults had very low self-esteem in regard to physical appearance, most were happy and experienced mostly positive social interactions. On average, adolescents who reported that their NF1 was very noticeable had the same self-esteem in their appearance, same happiness level, and same comfort in social situations as those who reported that their NF1 was not very noticeable. In contrast, parents who said their child had more noticeable NF also said their child experienced more stigma and was therefore less comfortable in social situations.

There are multiple reasons that parents and adolescents might see differently on this issue. Parents and their children might not agree on how noticeable the child's NF is. Parents might perceive others stigmatizing their child in a way that the adolescents miss. Or parents might be so worried about their child having NF, that they are projecting their fears about stigma and social acceptance onto their child's experiences.

Interestingly, the survey also included an open-ended question asking about adolescents' main concern regarding NF1. Sixty-four adolescents answered the question, and of these, 18 (28%) were most worried about a specific medical issue (like an optic pathway glioma or plexiform neurofibroma), 16 (25%) were most worried about what they would look like in the future, and 15 (23%) were most concerned about passing on NF1 to their future children. The remaining 15 adolescents were most concerned with their current appearance, learning difficulties, social problems, or other people not knowing about NF1.

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213 S. Wheaton Avenue, Wheaton, IL 60187
Phone 630-510-1115 **www.nfnetwork.org** **admin@nfnetwork.org**