TheNetworkEdge

The NF Network presents a quarterly research review
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***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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- *The Network Edge* Archive: At the end of this volume of *The Network Edge*, there is a table showing topics covered by past volumes. This should help if you wish to search for further information in *The Network Edge* archive.

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Highlights from Volume 14 of *The Network Edge*:

- **NF1 Clinical Trials:** In an early stage clinical trial, selumetinib shrank plexiform neurofibromas in 71% of children, with anecdotal improvements in appearance, pain and motor function.
- **NF1 Clinical Trials**: Lovastatin does not significantly improve visual/spatial processing or attention in children with NF1.
- **NF1 Brain Tumors:** Larger optic pathway gliomas are more likely to cause vision problems; research in mice suggests that estrogen might lead to more vision problems in females.
- **NF2 Clinical Management:** Bevacizumab can shrink fluid-filled cysts in spinal ependymomas, leading to clinical improvements in some patients.
- **Schwannomatosis Update:** An international patient registry seeks to increase research opportunities and collaborations for schwannomatosis.
- **Quality of Life**: Two new surveys specifically designed to measure quality of life in children, adolescents and adults with NF1 are being developed.

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1. NF1 Clinical Trials

a. Clinical Trial of Selumetinib for Plexiform Neurofibromas in Children with NF1

The Bottom Line: In an early stage clinical trial, selumetinib significantly shrank plexiform neurofibromas in 71% of children, with anecdotal improvements in appearance, pain and motor function. Follow-up clinical trials will seek to confirm this benefit, and test if selumetnib can treat other NF1-related tumors.

Phase 1 clinical trials are the first step in testing a new drug. These studies usually involve a small number of people, and the main purpose is to identify what dose of a drug works best. At this stage of drug development, clinicians and researchers are focused on making sure the new drug is safe, and secondarily, looking to see if the drug works (for instance, if it shrinks tumors or decreases pain).

Dombi et al. FREE, NIH (United States) report the exciting results of a Phase 1 clinical trial of selumetinib for the treatment of plexiform neurofibromas in children with NF1. This study enrolled 24 children, ages 3 to 18 years old. The children were treated for an average of 2.5 years, with 19 of the 24 kids still receiving treatment at the time the data for this article was collected (in January 2016).

First, the researchers found that selumetinib was relatively safe to use. The most common side effects were rashes (which could usually be controlled with creams or other medicines), gastrointestinal problems (such as stomach pain, diarrhea, or nausea) and a mostly asymptomatic increase in an enzyme in the blood called creatinine kinase. All of the more severe side effects got better after children starting taking a lower dose of medicine or stopped taking the medicine.

Amazingly, every person in the trial had their tumor shrink by at least 5% in size for at least a brief amount of time. 17/24 kids (71%) had their tumors shrink by at least 20% in size, with 15/17 tumors still that small at the time of the article was written. None of the 24 kids have had their tumor increase in size by 20% or more, which is exciting because at least 9 kids had fast-growing tumors when they started the study. The researchers did notice that some children's tumors have been slowly regrowing, usually if the child had to reduce their dose of the medicine or stop taking it temporarily because of side effects. It will be important in future studies to make sure that long-term treatment with selumetinib is safe, and to figure out what the best timing of giving the medicine will be.

Beyond having their tumors shrink, many kids in the clinical trial were feeling better and doing better physically. This part of the study wasn't planned ahead of time, so the doctors looked back at all their clinical notes to describe what happened. They found that 8/13 (62%) of kids with pain had less pain or had to take less pain medication; 5/9 (56%) kids with limitations in motor function improved; and 5/18 (28%) of kids with disfiguring tumors had noticeable improvements in appearance. Now that we know selumetinib may have an effect on these areas, researchers can plan to collect this data in a standardized way, right from the beginning of new trials.

Of note, selumetinib is not approved by the U.S. Food and Drug Administration for use in any disease. This means that the FDA has not yet reviewed the evidence about the drug's safety and efficacy, and that doctors can't prescribe this drug yet. The drug company that makes selumetinib is working with the investigators of this study and the National Cancer Institute to continue this study as a larger phase 2 clinical trial. This trial will be what called a "registration trial", which means that the trial

confirms that selumetinib is safe and effective, the data will be submitted to the FDA for review. More information about this trial is available at https://clinicaltrials.gov/ct2/show/NCT01362803

Selumetinib is also currently being tested (or will be tested soon) in other clinical trials to see if it can also help adults with NF1 and to see if it can help with other kinds of NF1-related tumors, such as dermal neurofibromas and optic pathway gliomas. If you have any questions about these clinical trials, you can find them on https://clinicaltrials.gov or contact your doctor for more information.

b. Clinical Trial of Lovastatin to Improve Cognition in Children with NF1

The Bottom Line: Lovastatin does not significantly improve visual and spatial processing or attention in children with NF1.

Using mouse models of NF1, researchers have worked to unravel the molecular pathway by which NF1 causes problems with learning. 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.

As we reported in Volume 12 of the Network Edge, **Li et al.** FREE, NIH (United States) found that lovastatin reduced the activity of Ras and improved spatial learning and attention in mice. Then **Acosta et al**. (United States) conducted a small pilot study of lovastatin in humans. They gave lovastatin to 24 kids with NF1, and after 3 months, children improved in tests of verbal and nonverbal memory. While these results were promising, there was no control group of kids not taking lovastatin to compare the results to. It's possible that even kids not taking any medicine would improve on cognitive tests, because of natural fluctuations in their ability over time, or because they would get better at taking the tests as they had more practice.

For this reason, two rigorously designed clinical trials were conducted to see if lovastatin really can improve cognition in people with NF1. Both trials had a control group who got a placebo, which is an inactive pill that looks the same as the real drug. Both trials were randomized, which means that people were randomly picked to get lovastatin or a placebo – as if you were a flipping a coin to decide. Randomly putting people into one group or the other helps make sure that overall, the people in each group are as similar as possible. This helps make sure that there are no other factors, like years of schooling, that might make one group do better on the cognitive tests than the other group.

Finally, both trials were double-blind, which means that neither the kids nor the study doctors knew who was getting lovastatin and who was getting the placebo. This reduces the chances for inadvertent bias in the trial. For instance, if someone knew they were getting lovastatin, they might be more motivated to try hard on the cognitive tests than someone who knew they were getting the placebo. This would make it seem like lovastatin improved the first person's scores, when really it was just that they were more motivated.

In Volume 12 of the Network Edge, we reported the results of the first of these two clinical trials, by **Bearden et al.** FREE, NIH (United States). This trial had 44 people with NF1 ages 10-50 years old, half of whom 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, people taking lovastatin did not have significantly better nonverbal memory, visual-spatial ability, or attention.

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-spatial ability and attention because only people who are struggling with those areas would be helped by the drug. For this reason, an even larger clinical trial was funded by the CDMRP Neurofibromatosis Clinical Trial Consortium. This trial, called the STARS trial, specifically investigated the effect of lovastatin on children ages 8-15 with NF1 who demonstrated problems in visual-spatial learning and/or attention.

Unfortunately, **Payne et al**. CDMRP (United States, Australia) report that STARS trial also showed no effect of lovastatin on visual-spatial learning or attention. This trial had 146 children with NF1, about half of whom took lovastatin once a day for 16 weeks. While these results may be disappointing to members of the NF community, now researchers can refocus their resources into what will hopefully be more effective avenues for treating learning disabilities in NF.

2. Breast Cancer Risk in NF1

The Bottom Line: Women with NF1, especially those ages 30-50, are at an increased risk of breast cancer compared to women without NF1.

In Volume 12 of the Network Edge, we reported on research from **Uusitalo, Rantanen et al.** FREE (Finland), who studied the risk of cancer in people with NF1 in Finland. First, the researchers tried to identify all NF1 patients in Finland by looking at the medical records of all 20 academic and national hospitals in Finland. Then, they used national databases to find out every NF1 patient who developed cancer and/or died during the study period. Finally, they compared the rates of cancer in people with NF1 to the general Finnish population. They found that people with NF1 have a higher risk of breast cancer than people without NF1.

Now **Uusitalo, Kallionpää et al.** FREE (Finland) have expanded their research to look more closely at the people who developed breast cancer. Of the 1404 NF1 patients identified in Finland, 31 women and 1 man developed breast cancer during the time period of the study (from 1987 to 2013). The researchers estimated that about 18% of women with NF1 in Finland will develop breast cancer at some point in their life, compared to 9.7% of people without NF1. This extra risk of was most apparent in women ages 30-50 (at older ages, the risk of women with and without NF is more similar).

The researchers were able to get tumor samples for 26 of the women with NF1, and they compared them to tumor samples from women of the same ages without NF1. They found that women with NF1 were more likely to have estrogen-receptor negative and progesterone-receptor negative breast cancers then women without NF1. Breast cancers with these characteristics are not likely to respond to hormonal therapy. Women with NF1 were also more likely to have HER2 amplified breast cancer, which can indicate a faster growing tumor.

Women with NF1 who are concerned about their risk of breast cancer should talk to their doctors, in order to decide if and when screening mammograms or breast MRIs may be appropriate. As a starting point for discussion, it may be helpful to note the most recent guidelines from the National Comprehensive Cancer Network. They recommended that women with NF1 consider starting annual

mammograms at the age of 30, with the option of doing breast MRIs instead of mammograms between ages 30 to 50.

3. Optic Pathway Gliomas and other Brain Tumors

The Bottom Line: Larger OPGs have an increased risk of causing vision problems; research in mice suggests that females might have more vision problems from OPGs because of estrogen. While many unique research resources facilitate research into NF1 low grade glioma, collaboration with patients will be key to developing new tools.

a. Predicting Vision Loss from NF1 Optic Gliomas

Optic pathway gliomas (OPGs) are a common tumor in children with NF1, affecting approximately 15-20% of kids. The majority of OPGs do not cause any visual symptoms, and many tumors do not grow much over time. Having a measure that can help predict which kids are more or less likely to develop vision problems would help doctors pick who should get treatment for their OPG and who should just be carefully monitored. Work from Dr. Robert Avery and colleagues is leading the way to discovering what kinds of visual and MRI measurements might predict vision loss in kids with NF1 and OPGs.

Avery, Liu et al. (United States) FREE, NIH previously showed that children with impaired vision from OPGs had a thinner layer of nerve fibers in their retina (the inner part of the back of your eye). Then, **Avery, Cnann et al.** (United States) FREE, NIH followed kids with OPGs over time, and found that if the child's vision got worse, their nerve fibers also got thinner. Together, these two studies indicated that the thickness of nerve fibers in the retina is a good indicator of vision loss in kids with NF1-related OPGs. Now, **Avery, Mansour, et al.** (United States) have shown that kids with larger OPGs, particularly in tumors affecting the optic chiasm, also had thinner nerve fibers. This suggests that kids with larger sized OPGs may be at higher risk of developing visual problems.

As **Listernick** (United States) commented in an editorial related to the **Avery, Mansour, et al.** article, finding factors that can predict who will and will not experience vision loss from OPGs is important for deciding who to treat. As research advances, we will hopefully be able to combine measurements of tumor volume and the thickness of nerve fibers in the retina with other clinical information to provide a more precise estimate of each child's risk of having vision problems. That way, the children at highest risk can receive early treatment with chemotherapy, and hopefully have improved visual outcomes because of that.

b. Gender Differences in NF1 Mice with Optic Pathway Gliomas

While the majority of optic pathway gliomas (OPGs) don't need treatment, prior research has shown that girls with NF1-related OPGs are more likely than boys to have vision problems and need treatment. **Toonen et al.** NIH (United States) compared male and female mice with NF1 to try to understand why females seem more likely to have worse vision.

They found that female mice with OPGs had fewer nerve cells and a thinner layer of nerve fibers in the retina (which is a marker of poor vision, as discussed in the review above) than female mice without OPGs. In contrast, male mice with OPGs and without OPGs had similar numbers of nerve cells and nerve fibers in the retina. The researchers showed that this difference between genders was due to

the female sex hormone estrogen. Estrogen affects OPGs by acting on microglia, a kind of cell that supports nerve cells. When female mice were given a drug that works against microglia, they showed less damage to retinal nerve cells and thicker nerve fibers. Future work on the role of estrogen and microglia in OPGs will hopefully lead to better strategies to protect females from vision loss due to OPGs.

c. Research Needs for NF1-associated Low-Grade Gliomas

Ricker et al. FREE (United States) reviewed the current landscape of research tools for NF1-associated low-grade gliomas (a class of brain tumors that includes optic pathway gliomas and pilocytic astrocytomas). The authors note that there are many research resources currently available for NF1 research into low-grade gliomas.

These include two international patient registries, which are large online databases of people with NF. The NF1 Patient Registry Initiative – located at https://nf1registry.wustl.edu/ and managed by researchers at the Washington University in Saint Louis Neurofibromatosis Center – helps collect medical data about people with NF1 to investigate possible associations between disease features. The NF Registry – located at https://nfregistry.patientcrossroads.org/ and managed by the Children's Tumor Foundation – connects researchers to patients and families interested in research. Multiple hospitals have established tumor banks which can store tumor tissue left over after surgery. Researchers have also been able to make multiple kinds of genetically engineered mouse models which develop low grade gliomas.

However, researchers have so far been unsuccessful in getting a sample of a low grade glioma from an NF1 patient to grow continuously in a dish in the lab. There have also been no successful attempts at a taking a sample of a human NF1 low grade glioma and transplanting it into a mouse (which is called a xenograft model). If these resources could be established, it would help researchers understand tumor biology better and test new drugs. According to the authors, increased partnerships between patients and their families on the one hand, and researchers and funding agencies on the other, will be the key to building up these resources in the future.

4. Malignant Peripheral Nerve Sheath Tumors (MPNST)

The Bottom Line: PET/CT scanning is a useful but not perfect way to distinguish plexiform neurofibromas from MPNSTs; advances in the lab point to the possibility of one day combining chemotherapy with photothermal therapy to treat MPNST.

a. Using PET/CT Scans to Identify MPNST

Doctors use PET scans (positron emission tomography) to try to identify malignant (cancerous) tumors in the body. Before a PET scan, a small amount of radioactive dye is injected into a patient's bloodstream. Tumors that are metabolically active take up more of the dye, making them appear brighter on the images. Because cancerous tumors are very metabolically active, PET scans usually make it easy to see if someone has cancer. But plexiform neurofibromas can look very bright too, even though they are not cancerous. This can make it hard for doctors to tell if a plexiform neurofibroma has become an MPNST.

Tovmassian et al. FREE (Australia) reviewed all the research articles that have been published about the use of PET scans in people with NF1 to see if a plexiform neurofibroma has transformed into an MPNST. They found that while, on average, MPNSTs are brighter than plexiform neurofibromas, there is no perfect cutoff value to completely separate the two groups. Some researchers reported that injecting the dye into someone earlier (4 hours before the scan instead of one hour beforehand) makes it easier to tell apart neurofibromas and MPNST. Further study of this idea would be helpful.

b. Adding Photothermal Therapy to MEK Inhibitors to Treat MPNSTs in Mice

Inside our cells, the RAS pathway is a major player in controlling how fast cells grow and divide. In this pathway, RAS proteins act like a car's gas pedal and the NF1 protein acts like the car's brake. When RAS and NF1 are working together, the cell grows at a normal pace. But when the NF1 protein isn't working, there is no brake in the car to control growth, and the cell can become a tumor. One of the ways the RAS proteins signal the cell to keep growing is by activating a protein called RAF, which then activates a protein called MEK.

MEK inhibitors are a class of drugs that work against MEK, to add a brake back into the pathway and turn down the signals to the cell to keep growing. Selumetinib (discussed in the first article of this newsletter) is just one of many MEK inhibitors being studied for use in NF1 and in cancer. Another type of MEK inhibitor is called PD-0325901. This drug was recently studied for use in treating adults with plexiform neurofibromas by the CDMRP-funded NF Clinical Trials Consortium. (The results of that clinical trial have not yet been released though.)

Sweeney et al. FREE (United States) looked to see if combining PD-0325901 with photothermal therapy could effectively treat MPNSTs in mice. Photothermal therapy involves injecting tiny particles into the tumor. When these particles are hit by a certain type of laser light (which can pass through the skin into the tumor inside the body), they heat up and kill the tumor cells around them. This type of treatment is very new and being tested in mice with various kinds of cancer, but is not yet used in humans. **Sweeney et al.** FREE found that combining PD-0325901 with photothermal therapy slowed tumor growth and led to longer survival in mice with MPNSTs more so than using either treatment alone. While this type of combined treatment is still very far away from being used in people with NF1, it still represents an innovative new area of research into MPNST treatment.

5. Bevacizumab for NF2

The Bottom Line: High blood pressure is more frequent in older NF2 patients and those taking higher doses of bevacizumab; bevacizumab can lead to shrinkage of cystic spinal ependymomas and may improve pain in some patients.

Over the past ten years, doctors have used bevacizumab (also known as Avastin) to treat a growing number of people with NF2. Most commonly, this is for hearing loss or growing vestibular schwannomas, but recent reports (detailed below) explore the use of bevacizumab to treat ependymomas and pain. In addition, investigators from the United Kingdom report on the side effects of bevacizumab in a large number of patients treated for growing vestibular schwannomas.

a. Side Effects of Treatment with Bevacizumab

In the US, bevacizumab is not approved by the FDA for use in people with NF2, and so treatment with bevacizumab is considered an "off-label" indication, that may not be covered by insurance. In the UK, however, bevacizumab has become an established treatment for growing vestibular schwannomas, and is available through the UK National Health Service's National Specialized Commissioning for NF2. Patients in the UK are treated according to a national protocol, which suggests a higher starting dose of bevacizumab until tumor growth is controlled (about 6 months) and then a reduced dose afterwards to hopefully maintain the benefits of tumor shrinkage while minimizing side effects.

Morris, Golding et al. (United Kingdom) reviewed the records of 80 NF2 patients receiving bevacizumab in the UK to understand the side effects of bevacizumab treatment, primarily in regards to kidney damage and high blood pressure. This paper looked at medium-term side effects, in that patients had been treated with bevacizumab for 3 months to 5 years. The most common side effects were fatigue, high blood pressure, and infection (usually due to minor skin wounds that had delayed healing because of bevacizumab). 19 patients (24%) experienced moderate or severe high blood pressure, and 14 (17.5%) had kidney problems, as measured by the amount of protein present in their urine. 9/19 people with high blood pressure and 6/14 people with high urine protein levels needed to take a break in treatment because of these side effects.

High blood pressure and high urine protein levels were not correlated – that is, people with one side effect were no more likely to have the other side effect too. However, older people (particularly those over age 30 when they started bevacizumab) were more likely to get high blood pressure then younger people. Interestingly, there were also differences in high blood pressure by dose amount and timing. Some people started treatment with a larger drug doses administered less frequently (7.5 mg/kg every 3 weeks), and some people started treatment at a lower, but more frequent, dose of bevacizumab (5 mg/kg every 2 weeks). Over time, these two dosing regimens deliver the same amount of drug (15 mg/kg total over 6 weeks). However, patients on the higher but less frequent dose were more likely to develop high blood pressure. This points to the need for more research on the optimal dose to minimize the risk of side effects, without compromising the benefit of bevacizumab for NF2 patients. Based on their experience, the researchers suggest strategies such as lower starting doses and frequent breaks from treatment for those individuals who may be on bevacizumab long-term.

b. Effect of Bevacizumab on Spinal Ependymomas

The same group of researchers from the United Kingdom who looked at side effects of bevacizumab in the article above, also looked at the effect of bevacizumab on tumors of the spinal cord, called ependymomas. Everyone in this study was receiving treatment because of a growing schwannoma, and the researchers looked to see if there was a secondary benefit for those same patients' ependymomas.

Morris, Afridi et al. (United Kingdom) reviewed the records of 95 NF2 patients who were treated with bevacizumab and found that 41 (43%) had an ependymoma. 32/41 (78%) of those patients had enough available MRI scans of the spine to adequately assess the change in size of the tumors. The researchers found that when measuring each tumor's longest diameter, it was mostly ependymomas with cysts (pockets of fluid either within or next to the tumor) that decreased in size during

bevacizumab treatment. 16/18 (89%) of ependymomas with cysts shrank at least 20% in size, but only 1 out of 53 (2%) of ependymoma without cysts shrank that much. Even more strikingly, in 4 of the 18 ependymomas with cysts, the cystic areas completely disappeared during treatment.

The 18 ependymomas with cysts were in 12 people. 7 of these 12 people (58%) had clinical improvements while being treated, including two patients who had been using wheelchairs but regained the ability to walk. This study suggests that bevacizumab may benefit patients with cystic ependymomas, as it is theorized that bevacizumab may have an anti-swelling effect on the tumor. Future prospective studies of ependymomas using 3-dimesional volumes (which are even more accurate in measuring change in size than 2-dimensional measures of the longest diameter) and standardized measures of clinical benefit would help provide further evidence that bevacizumab can improve cystic ependymomas.

c. Potential Use of Bevacizumab to Improve Pain

Most people with NF2 who receive bevacizumab are being treated because of their vestibular schwannomas (either for hearing loss or tumor growth), although some receive treatment for growing tumors in other locations, such as spinal schwannomas or ependymomas. Two doctors from Stanford University report on the use of bevacizumab to specifically treat tumor-related pain.

Linda and Recht FREE (United States) have treated 5 people with NF at their hospital (3 people with NF2 and 2 people with NF1). 4 of the 5 people (all 3 with NF2 and 1 person with NF1) said their pain got better within 3 to 8 weeks of starting bevacizumab. Of the 4 people with improvements, 2 were able to stop taking narcotic pain medication, and one switched from taking narcotics every day to just occasionally. However, one patient who hadn't been on any pain medicine before started taking one, making it unclear if bevacizumab or the new pain medicine was responsible for their improvement.

While this case series provides only very limited evidence that bevacizumab may effect pain in people with NF2, it does suggest that future studies of bevacizumab may want to look at pain using structured, validated measures. By tracking people's pain right from the start of treatment using a standard survey, future studies could offer stronger evidence as to whether bevacizumab can significantly improve pain and how long-lasting that change may be.

6. NF2 Diagnosis and Clinical Management

The Bottom Line: Gamma –knife radiosurgery may be useful to slow the growth of vestibular schwannomas or meningiomas; while most people with unilateral vestibular schwannomas have NF2, a small percentage have schwannomatosis.

a. Gamma Knife Radiosurgery for Vestibular Schwannomas and Meningiomas

Gamma Knife radiosurgery is a very focused kind of radiation treatment, where many beams of gamma rays are focused onto a specific point (usually a brain tumor). Like surgery, it is usually delivered all at once in one day of treatment, but it does not actually involve making a surgical incision to open up the brain. Recently, doctors from two health systems have reported on the clinical outcomes of people

with NF2 who received Gamma Knife radiosurgery at their hospitals. Overall, both sets of researchers propose that Gamma Knife radiosurgery may be a useful treatment option for some people with NF2.

Kruyt et al. (Netherlands) looked at all the people with NF2 at their hospital in the Netherlands who received Gamma Knife to treat a vestibular schwannomas between 2002 and 2014. They found 34 patients who had 46 vestibular schwannomas treated. After an average of 5 years of follow-up, 18 tumors (38%) were smaller than at the time of treatment, 23 tumors (49%) were roughly the same size, and 6 tumors (13%) had grown significantly. Larger tumors (those over 6 cubic centimeters in size) were more likely to start growing again after treatment. Patients had at least some useful hearing in 23 of the 46 ears where a tumor was treated. After an average of 3.3 years of follow-up, 10 of these ears (43%) had stable hearing and 12 (52%) had worse hearing (and 1 person did not get hearing tests.)

Birckhead et al. (United States) looked at all the people with NF2 at the Mayo Clinic who received Gamma Knife to treat a meningioma between 1992 and 2013. They found 15 patients who had a total of 62 meningiomas treated (with a range of 1 to 13 meningiomas treated per patient). All of the patients got radiosurgery because their menigioma was growing. After treatment, 34 tumors (55%) decreased in size and 26 tumors (42%) stayed roughly the same size. 4 people had complications from radiation, with one patient dying after having radiation necrosis (an area of dead brain tissue) and brain swelling.

b. Unilateral Vestibular Schwannomas – A Feature of NF2 and Schwannomatosis

While most people with NF2 have bilateral vestibular schwannomas (tumors in both their left and right ears), some people with NF2 have a unilateral vestibular schwannoma (a tumor in only one ear). People with schwannomatosis can also have a unilateral vestibular schwannoma. And both people with NF2 and people with schwannomatosis often have non-vestibular schwannomas (schwannomas near the spine or on nerves in other parts of the body). This makes it challenging to diagnose a patient who has a unilateral vestibular schwannoma and multiple non-vestibular schwannomas. Technically, this person would meet the criteria to be diagnosed with NF2, but there is a chance that they might actually have schwannomatosis.

To figure out what the chances are that someone with these symptoms has NF2 or schwannomatosis, **Smith et al.** (United Kingdom) looked at all the NF2 patients in their national clinical database. They identified 70 people who had a unilateral vestibular schwannoma and two or more non-vestibular schwannomas when they first came to clinic. 20 of these 70 people (28%) eventually developed a vestibular schwannoma in their other ear, meaning they had NF2 (since as far as we know, people with schwannomatosis don't get bilateral vestibular schwannomas). Of the 50 people who never got a vestibular schwannoma in their other ear, 9 (18%) had genetic testing that proved they had NF2. 5 (10%) had genetic testing that showed they had LZTR1-associated schwannomatosis and no one had evidence of SMARCB1-associated schwannomatosis. The remaining 36 people probably have NF2, but it could not be proven, mostly because there weren't tumor samples to do genetic testing on.

This means that overall, if a person comes to clinic with a unilateral vestibular schwannoma and at least two other non-vestibular schwannomas, there is about a 7% chance they actually have schwannomatosis. For this reason, the authors suggest changing the current diagnostic criteria for NF2, to mandate that people with this specific set of symptoms be offered genetic testing for the LZTR1 gene to make sure they don't have schwannomatosis.

7. Schwannomatosis Update

The Bottom Line: A large, international database of people with schwannomatosis seeks to increase research into the disorder; the genetics of schwannomatosis are reviewed.

a. Creation of an International Database of People with Schwannomatosis

Ostrow et al. (United States, United Kingdom, Canada, Germany, Italy) report on the creation of the International Schwannomatosis Registry (ISR), an online database of patients with schwannomatosis from across the world. The ISR hopes to encourage research in schwannomatosis by facilitating scientific collaborations and connecting researchers studying the disease to affected individuals interested in participating in research. So far, 389 individuals from ten hospitals in six countries have agreed to take part in the registry.

When a person joins the registry, that person's doctor enters medical information about them into the online database – information like their gender, approximate age at diagnosis, if they experience pain, and if they've had any tumors removed that could be used for research. This information allows other researchers to see if the person might be eligible for new research studies. In order to protect participants' privacy, their names and contact information are not put into the database. Only the doctor who signs each person up for the registry knows their contact information, and can send them information about new research studies. If your doctor does not participate in the ISR, you can still join the registry by sending your information to the ISR coordinating office, which is located at the Johns Hopkins Comprehensive Neurofibromatosis Center. For information on how to do this, or to read more about the ISR, you can visit http://sid2011.squarespace.com/

*Disclosure – The author of this newsletter is also a co-author of the paper by Ostrow et al.

b. Review of Schwannomatosis Genetics

Unlike NF1 and NF2, schwannomatosis can be caused by mutations in multiple different genes. People with schwannomatosis may have mutations in SMARCB1, LZTR1, or other genes that researchers have yet to pinpoint. **Kehrer-Sawatzki et al**. FREE (Germany) have written a free review of the genetics of schwannomatosis, which will hopefully spread the word about this disorder to wider audience of clinicians and researchers.

The authors estimated the percentage of people with schwannomatosis who have mutations in each type of gene. In patients who have other family members affected by schwannomatosis, about half will have a SMARCB1 mutation, just over a third will have LZTR1 mutations, and the remaining 14% likely have mutations in another gene or genes. Among people who are the only one in their family to have schwannomatosis, 30% will haveLZTR1 mutations, 10% will have SMARCB1 mutations, and the remaining 60% may have mutations in another gene or genes.

Kehrer-Sawatzki et al. also reviewed the clinical features of NF2 and schwannomatosis, and noted the overlap and differences between the two disorders. While unilateral vestibular schwannomas, other cranial nerve schwannomas, and menigiomas can occur in schwannomatosis, they

are more common in NF2. Ependymomas and eye problems such as epiretinal membranes and juvenile cataracts have never been reported in people with schwannomatosis.

8. Measuring Quality of Life and Other Factors

The Bottom Line: Two new questionnaires are being developed to measure quality of life in children, adolescents, and adults with NF1; higher health literacy is associated with greater satisfaction with medical care for NF

Health-related quality of life (HRQOL) is the total picture of an individual's physical, mental, emotional, and social health. Taking into account each of these elements is important because they go beyond mortality to understand how people live with disease. Two new surveys are being or have been designed to specifically measure HRQOL in people with NF1. The first is the Pediatric Quality of Life Inventory (PedsQL) NF1 module for children, adolescents and young adults, and the second is the Impact of NF1 on Quality of Life (INF1-QOL) for adults.

a. Developing the PedsQL Survey for Children, Adolescents and Young Adults with NF1

HRQOL surveys for children can help us understand the effects of treatment and help caregivers understand children's experiences. However, few studies have examined HRQOL in children and young adults with NF1, and so little is known about how children might experience the disease (and treatment) differently from adults. Two recent papers by **Nutakki et al.** (United States) and **Draucker et al**. (United States) build on what we know about HRQOL in youth with NF1 by developing a questionnaire to measure the health and well-being of children, adolescents, and young adults with NF1. This survey is called the Pediatric Quality of Life Inventory (PedsQL) NF1 module, and it seeks to capture HRQOL from both the perspectives of young patients and their families.

To develop this measure the research team conducted interviews with NF1 patients ages 5-25 years old and their parents. Researchers analyzed what patients and parents said, and made sure they had questions on the new survey that corresponded to people's concerns. Then, the questions were tested with a separate group of patients and parents to ensure that they were clear and easy to understand, and the questions were edited if necessary.

The important areas of HRQOL that were identified during interviews fell into the following categories: medical signs and symptoms (spots/freckling, neurofibromas, pain, skin sensations, vision, stomach/gastrointestinal symtpoms, speech, sleeping; physical functioning; cognitive functioning; social functioning (stigma/isolation, communicating with others, dependence/independence); emotional and behavioral functioning (feelings, psychiatric disorders); family impact (worries); and treatment burden. Several specific survey questions were then developed to assess the extent to which patients experience burden due to each of these areas. The survey is now being tested in multiple hospitals across the U.S. with a larger number of people, to make sure that it accurately measures each of these HRQOL areas as intended. Once the results of this larger study are published, we'll be sure to share them in an upcoming issue of the Network Edge!

Interestingly, the authors noted that while this questionnaire will focus on understanding difficulties with NF1, patients and their caregivers interviewed for this study also often talked about

adaptation and resiliency in the face of NF1. This means that the survey does not take into account the (often positive) strategies that youth use to deal with difficulties of living with NF1. This will be an important concept to measure in future studies of psychosocial treatments for NF.

b. A New Measure of Quality of Life in Adults with NF1 – the INF1-QOL Survey

Ferner et al. FREE (United Kingdom) have developed a quality of life questionnaire, called the Impact of NF1 on Quality of Life (INF1-QOL), for adults with NF1. The aim was to create and validate a questionnaire that was easy to understand and complete quickly, but still encompassed the wide range of disease concerns in NF1 patients. In order to decide what questions should go on the survey, the researchers conducted interviews and focus groups with adults with NF1 and consulted a panel of NF1 doctors from multiple medical specialties, including a psychologist. Then, they gave a preliminary version of the survey to 50 people with NF1, and analyzed their responses to make sure the questions were reliable and to determine the final questions to include.

At the end of this process, the INF1-QOL survey consisted of 14 questions covering the following topics: vision, cosmetic appearance, pain (both how bad it is and how much it interferes with life), learning problems, behavior and personality, walking, hand function, speech, bone health, breathing, sleeping, role and outlook on life, and anxiety and depression. The survey was given to another 50 patients who receive care at NF clinics in the United Kingdom, and across

The final INF1-QOL questionnaire was distributed among another 50 NF1 patients who receive their care at the UK NF clinics. The authors found that anxiety and depression and outlook on life had the largest impact on quality of life. 32% of patients reported moderate or severe problems with anxiety and depression, and 42% of patients reported moderate or severe problems from the effects of NF1 on their role and outlook on life (for example, on their career, relationships, and family). Importantly, there was only a medium strength relationship between how clinicians rated the severity of disease and how patients rated their quality of life. This fact points to the importance of directly asking patients about their quality of life, since it might not be exactly what doctors would expect. In the future, the INF1-QOL survey has the potential to help monitor patients during their normal clinical treatment, as well as be used in clinical trials.

c. Health Literacy and Patient Satisfaction with Medical Care

Riklin et al. NIH (United States) report on the first assessment of patient satisfaction in adults with NF. Eighty adults with NF1, NF2, or schwannomatosis were surveyed at their regular NF clinic visit. The goal was to assess whether health literacy, an individual's ability to understand and use health-related information, and psychosocial factors affect a patient's satisfaction with their medical visit and with their doctor's communication. Higher health literacy was the strongest predictor of higher satisfaction with the overall doctor's appointment and with the doctor's communication specifically. In addition, psychosocial factors like more anxiety, depression, and pain were associated with lower satisfaction with the medical visit, and to a lesser degree, the doctor's communication.

Of note, this patient group consisted of mostly follow-up patients seeing their established NF doctor at a single hospital. Due to this, these results may not be fully representative of the entire NF population. Nevertheless, health literacy has been a strong predictor of a patient's satisfaction with

their care in previous studies in people with a range of medical conditions. This points towards the importance of increasing health literacy in patients with NF and tailoring communication during medical visits to match each patient's level of health literacy.

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

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