TheNetworkEdge
The NF Network presents a periodic 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.

- A Global NF Picture: To keep you abreast of all NF research advances, *The Network Edge* includes publications from the United States and around the world. **Country of origin** of the research study is indicated after the author name.

- *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 18 of *The Network Edge*:

- **NF1 Clinical Trials:** Selumetinib shrank plexiform neurofibromas in 68% of children and improved pain, motor function, appearance, and quality of life for many participants, leading to FDA approval of Selumetinib for kids with NF1 and symptomatic plexiform neurofibromas.
- **NF1 Clinical Trials**: Selumetinib and everolimus are both promising treatments for low-grade gliomas that did not respond to prior chemotherapy in children and young adults with NF1.
- **NF1 Translational Science**: Minipigs can mimic NF1 symptoms and be used to test new treatments; dietary supplements with L-carnitine improve muscle function in mice with NF1.
- **Cutaneous Neurofibromas**: European adults with NF1 say #1 treatment priority for cutaneous neurofibromas is developing a new cream, pill, or implant to block their continued growth.
- **NF2 Clinical Trials:** Higher doses of bevacizumab are no more effective than standard doses in treating vestibular schwannomas.
- **Schwannomatosis Update:** Damage to small nerve fibers called C-fibers may play a role in causing schwannomatosis pain.

- **Quality of Life**: A small-group, live-video intervention teaching resiliency and coping skills successfully improves the quality of life of teenagers with NF1 and NF2.

The Network Edge: Volume 18 – Contents

1. Update on Selumetinib and the Use of MEK-Inhibitor Drugs

The Bottom Line: Selumetinib significantly shrank symptomatic plexiform neurofibromas in 68% of children with NF1, and improved pain, motor function, appearance, and quality of life for many trial participants. An ongoing clinical trial is testing whether selumetinib also works for adults with plexiform neurofibromas, with promising early results, and additional clinical trials for other MEK inhibitor drugs are also in progress. NF doctors have also issued guidance on how to monitor and treat potential side effects of these medications.

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

In Volume 14 of the Network Edge, we reported the results of a Phase 1 clinical trial of selumetinib for the treatment of plexiform neurofibromas in children with NF1. Now we are excited to share the results of the follow-up, Phase 2 clinical trial performed to confirm whether treatment

could shrink kids' tumors and improve their function. The positive results of this clinical trial led the FDA to approve selumetinib (brand name Koselugo) on April 10, 2020 for children with NF1 ages 2 and older who have symptomatic, plexiform neurofibromas that are not well-suited for surgery.

In this Phase 2 clinical trial, **Gross et al.** FREE*, NIH (United States) treated 50 children, ages 3 to 17, in the hopes of reducing the size and symptoms associated with their plexiform neurofibromas. The children were treated for an average of 2.75 years, with 29 of the 50 kids still receiving treatment at the time the data for this article was collected (at the end of March 2019). Each child took selumetinib as a pill twice a day. 34 of 50 kids (68%) had their tumors shrink by at least 20% in size, with 28 of the 34 tumors staying at this smaller size for at least one year. On average, it took about 8 months for tumors to shrink by 20% and about 15 months for the tumors to reach their smallest size, although this did range widely from a few months to multiple years. The most anyone's tumor shrunk was by 55%.

Beyond having their tumors shrink, many kids in the clinical trial were feeling better and doing better physically. Children were asked to rate the pain associated with their tumor on a 0 to 10 scale (with 0 being no pain and 10 being the worst pain imaginable). 14/19 (74%) of children who said their plexiform neurofibroma was painful at the start of the study had their pain go down 2 points or more, which is considered a meaningful improvement. 38% of all kids on the trial (19/50) and 50% of their parents (25/50) also said that pain was interfering less with kids' daily activities like doing schoolwork or playing. After 1 year of treatment, 72% of children and 86% of parents rated kids' tumor-related problems other than pain as at least minimally improved, and 48% of children and 58% of their parents rated kids' overall quality of life as significantly improved.

Other improvements from selumetinib included changes in appearance, motor function, breathing/airway function, and bladder or bowel function. Out of 44 children with disfiguring tumors at baseline, 24 parents (54%) and 11 kids (25%) thought their appearance had at least minimally improved after 1 year. A number of children with limitations in motor function had significant increases in strength, range of motion, and mobility. And while these issues were less common, some children also had better breathing/airway function and less bladder or bowel incontinence.

Unfortunately, selumetinib didn't work for everyone. Five children (10%) had to stop taking selumetinib because of side effects *(refer to discussion of side effects on p.5)*, and six children (12%) had their tumors grown more than 20% in size despite treatment. Luckily, there are multiple other drugs in clinical trials for NF1-associated plexiform neurofibromas in kids and adults that will hopefully be effective for patients who aren't helped by selumetinib. If you have any questions about these clinical trials, you can find them on https://clinicaltrials.gov or contact your doctor for more information.

Additional clinical trials are also ongoing to see if selumetinib will also be effective for adults with NF1. Promising preliminary results for adults with NF1 were shared in November 2019 at the International Conference on Molecular Targets and Cancer Therapeutics. These early findings from the first 21 adults who were treated for at least 1 year with selumetinib showed that 11 people (52%) had a sustained reduction in tumor volume of at least 20%. We will be eagerly anticipating the final study results and will share them via the Network Edge as soon as they are published!

*Note: This article was published in the New England Journal of Medicine (nejm.org), where you can access 3 articles per month if you register for a free online account.

b. Current Status of Research on Selumetinib and other MEK Inhibitors

Gross, Dombi, and Widemann NIH (United States) detailed the research advances that helped lead to the FDA approval of selumetinib and the current status of clinical trials for selumetinib and similar drugs. In order to run a rigorous clinical trial that would provide strong evidence that a new drug was beneficial for people with plexiform neurofibromas, the NF community had to solve a number of research challenges.

First, the team had to collect natural history data to show that any tumor shrinkage would be caused by a new drug, rather than just the natural course of the disease. This required following a large number of kids with NF1 over time with MRIs to show that without any treatment, tumors rarely decreased in size. Researchers also had to figure out a better way to measure the size of tumors on MRIs. Standard criteria for measuring the size of cancerous tumors was to look at the diameters of one or two cross-sections of the tumor (1D or 2D measurement). But plexiform neurofibromas have irregular shapes and grow more slowly than many cancers, so this was not very accurate and did not change fast enough to measure plexiform neurofibromas in clinical trials. So, researchers developed computerized tools to measure the full volume of a tumor and came to a consensus that a 20% change in volume represented a reliable, significant difference in size. Finally, the FDA requires evidence that a new drug improves how long people live, how they feel, or how they function. This meant the NF community had to work to develop good functional measures (to assess things like muscle function or breathing) and patient-reported outcomes measures (to assess things like pain and quality of life) for people with NF1.

These many years of collaboration, technical advances, and the participation of patients in countless studies all culminated in the selumetinib clinical trial (reported above) and the FDA approval of selumetinib for kids with symptomatic plexiform neurofibromas. Ongoing clinical trials will examine whether selumetinib can help adults with symptomatic or growing plexiform neurofibromas too, and whether it can prevent symptoms from starting in the first place in kids with asymptomatic plexiform neurofibromas.

Clinical trials for drugs like selumetinib are also ongoing. Selumetinib works by inhibiting an enzyme called MEK, which helps stop the over-activation of the RAS-MAPK pathway that we see in people with NF1. An entire class of drugs, called MEK inhibitors, have been developed that act on this pathway in slightly different ways. Even though selumetinib works well for treating plexiform neurofibromas in many kids with NF1, we hope that other MEK-inhibitors may help people who don't respond to selumetinib or that these drugs may be able to shrink tumors with fewer side effects.

MEK inhibitors currently in clinical trials for NF1 plexiform neurofibromas include binimetinib (NCT03231306), mirdametinib (NCT03962543), and trametinib (NCT03741101). If you want to learn more about these clinical trials you can go to https://clinicaltrials.gov and search for the NCT number in parentheses.

c. Clinical Guidelines for Using MEK Inhibitors and Managing their Side Effects

Now that the FDA has approved selumetinib for kids with symptomatic plexiform neurofibromas, it can be prescribed by any clinician across the United States. And with the growing number of clinical trials for MEK inhibitors, use of these medicines is likely to spread quickly. In **Klesse et al.** FREE (United States), the members of the Children's Tumor Foundation Clinical Care Advisory Board wrote general guidance on how clinicians should monitor kids receiving these medicines and how to best manage any side effects.

The most common side effects of MEK-inhibitors include problems with skin, gastrointestinal issues, and fatigue. Skin-related issues can include rashes and nail infections (called paronychia)

which can often be treated with special creams or other treatments. There are also a number of steps people can take to try to avoid skin problems, including staying out of the sun/using good sun protection, keeping skin well moisturized, and taking baths regularly (possibly with a small amount of bleach).

Gastrointestinal problems are usually mild, and include nausea, diarrhea, abdominal pain, or weight gain. Rare side effects include heart and eye issues, so these guidelines also propose regular monitoring with an echocardiogram and ophthalmology exam at the beginning of treatment, one month into treatment, and then every 3-6 months after that. If you have any other questions about side effects and monitoring for MEK inhibitors, please share this article with your doctor, and check out the free patient information sheet that is available online as a supplemental file to this article.

2. Clinical Trials for NF1-Associated Brain Tumors

The Bottom Line: Two large multicenter clinical trials show that selumetinib and everolimus are both promising options to try to shrink or stop the growth of low-grade gliomas that did not respond to prior chemotherapy in children and young adults with NF1.

Low-grade gliomas are brain tumors that originate from glial cells (the cells that help support neurons). Low grade gliomas are most commonly diagnosed in kids with NF1, and most are located in the optic pathway and/or hypothalamus, although they can occur throughout the brain. While they are unlikely to grow quickly or spread the way more malignant, or high-grade, cancers do, they can cause problems with vision, hormone levels, or motor function, based on where the tumor is located. Many people with low-grade gliomas do not require treatment, but for those who do, cytotoxic chemotherapy (drugs that stop cells from dividing, such as vincristine and carboplatin) are available. However, not all gliomas respond to these traditional chemotherapies, and kids may have undesirable side effects from taking them. For this reason, researchers are testing new treatments that target specific molecular pathways relevant to low-grade gliomas. Here we report on the results of two clinical trials for these new treatments – selumetinib (which targets the Raf-MEK-ERK pathway) and everolimus (which targets the mTOR pathway).

a. Clinical Trial of Selumetinib for Low Grade Gliomas in Children with NF1

Fangusaro et al. FREE, NIH (United States) report on a trial of selumetinib conducted by the Pediatric Brain Tumor Consortium. 25 children and young adults (ages 3-21) with NF1 and low-grade gliomas that did not respond to prior treatment (i.e. new areas of tumor appeared, tumors continued to grow and/or the person developed worsening vision) were treated with selumetinib. Patients received selumetinib twice a day as a pill for up to 2 years, unless they developed side effects that required them to stop taking the drug.

9/25 (36%) of patients had their tumors shrink 50% or more based on 2D measurements, with a median time to demonstrate this shrinkage of 3 ½ months. Patients' age or tumor size was not associated with which tumors responded to treatment. The progression-free survival at 2 years was 96%, meaning that after two years on treatment, only 4% had their tumors grow 25% or more in size. Patients were also followed after they stopped taking selumetinib. After an average of 4 years of observation, 17 people (68%) have tumors that were stable in size or smaller than when they started the trial. 8 patients (32%) had tumors that grew at least 25% in size, but for most of the people (7/8) this happened after they stopped taking selumetinib (either due to side effects or because the treatment period of the trial had ended.) Overall, these results show that selumetinib is effective at shrinking some low-grade gliomas in kids with NF1, just as it has been for plexiform neurofibromas (see the **Gross et al.** study above). The authors recommend that future studies of selumetinib for

low-grade gliomas include measures of vision, quality of life, and neuropsychologic outcomes in order to more comprehensively assess the benefits of treatment.

b. Clinical Trial of Everolimus for Low Grade Gliomas in Children with NF1

Ullrich et al. DoD, NIH (United States) report on a trial of everolimus conducted by the NF Clinical Trials Consortium. 22 children and young adults (ages 3-21) with NF1 and low-grade gliomas that were growing despite prior treatment with carboplatin were analyzed in the study. Patients took everolimus once a day as a pill or liquid for up to 48 weeks.

After 48 weeks of treatment, 3/22 (14%) participants had their tumors shrink 50% or more based on 2D measurements, 12/22 (55%) had tumors that were stable in size, and 7/22 (32%) of participants had their tumors grow 25% or more based on 2D measurements. After an average observation period of 33 months, 10/15 people continued to have their tumors stay at the reduced or stable size (while five had tumors that started growing again later). Also, side effects were mostly mild, with only one person experiencing most of the more severe side effects and no one having to stop the study due to side effects. The authors note that this is especially important in treatment of patients with NF1- associated low grade gliomas, who have good overall survival and thus often take treatment for longer than kids without NF1. The authors recommend future trials combine or compare everolimus with selumetinib or other targeted therapies to see if this improves efficacy and tolerability. The authors also agree with **Fangusaro et al.** that functional outcomes (rather than just measuring tumor size) will be key in these future trials.

3. What's New in NF1 Biology and Translational Science?

The Bottom Line: Minipigs with NF1 mutations develop many of the same symptoms as people with NF1 (including café au lait spots, freckling, and cutaneous neurofibromas), making them a promising tool to screen potential treatments for these symptoms; dietary supplements with L-carnitine seem to improve muscle function in a mouse model of NF1; more research reviews are available free online.

a. Developing Minipig Models of NF1 to Improve Drug Development

Animal models of human diseases are made by specifically breeding or otherwise genetically manipulating animals to have analogous genetic mutations to humans. Animal models allow scientists to study a disease in a controlled, laboratory environment in ways that are not possible in humans. The hope is that the knowledge gained from these animals will eventually result in improved care or treatment for humans with the same disease. Previous research studies have mostly used mice models to study NF1. Although mice models can be very helpful, mice are too small for many medical imaging systems and do not develop all of the same symptoms of NF1 as humans. This means that mice are not a strong animal model for detecting and monitoring the progression of some physical features associated with NF1.

Minipigs have been found to be a good animal model when studying other human diseases due to their anatomical and physiological similarities to humans. In addition, minipigs are large enough to be studied using the same imaging machines and tools used for humans. **Uthoff et al.** FREE, NIH (United States) imaged minipigs with a specific *NF1* mutation to monitor whether these pigs develop the physical features associated with NF1. When imaged over the first 12-months of life, the minipigs developed the same physical characteristics found in humans with NF1. For example, minipigs can develop café au lait spots, cutaneous and plexiform neurofibromas, and freckling in the armpit and groin. In addition, minipigs with this *NF1* mutation display decreased cognitive abilities, increased pain, and trouble sleeping, all symptoms that people with NF1 might struggle with.

What is most exciting about this research is the opportunities it presents for better understanding and treating NF1. In addition to previously established NF1 mouse models, there is now significant research supporting two different NF1 minipig models, giving researchers more tools to test potential treatments for different NF1 symptoms in the future.

b. Understanding the Effect of Diet on Muscle Function in NF1

Due to a variety of neurological, musculoskeletal, or vascular symptoms, people with NF1 may experience muscle problems including muscle weakness, reduced muscle tone, faster muscle fatigue, and poor coordination. Given the impact these muscle problems can have on people with NF1, there has been increasing interest in understanding muscle biology and potential treatments to improve muscle function. **Summers et al.** FREE, NIH (Australia) previously found that mice who lack NF1 gene expression in their skeletal muscles (the muscles that you can voluntarily flex) had too many intramyocellular lipids – fats that are stored as droplets within muscle cells to provide energy. They also found that this accumulation of intramyocellular lipids could be corrected in mice with a diet full of medium-chain fatty acids (called medium-chain because of the number of carbon atoms they have) and taking supplements of L-carnitine (which helps transport fatty acids into a cell's energy producing centers, the mitochondria).

Vasiljevski et al. FREE (Australia) built on this work to see whether various diets and supplements would also be effective at reducing intramyocellular lipids. The authors were particularly interested in knowing if taking L-carnitine supplements alone would help, because if this treatment is going to be tested in people with NF1, taking a supplement would be a lot easier than changing people's diets. The authors found that having a diet rich in medium-chain fatty acids by itself, taking a L-carnitine supplement by itself, or taking a combination of supplements (L-carnitine, CoQ10, creatine, and vitamin B2) were all roughly equally effective at reducing intramyocellular lipids. However, the effect stopped shortly after the mice stopped getting the supplements or special diet, suggesting that dietary changes likely have to be maintained long-term. Analyzing the specific fats stored in the mice's muscles suggests the reason these diets and supplements worked by inducing the muscle to break down lipids into their component parts rather than continue storing it. The authors conclude that that NF1 impairs lipid storage in a way that is potentially treatable using dietary changes. The authors recommend conducting a clinical trial in humans to see if the tested supplements can help improve muscle function in people with NF1.

c. Current Clinical and Biological Research in NF1 (Special Issue)

The journal of Neuro-Oncology Advances has published a special issue in July 2020 dedicated to NF1 called "A Contemporary Landscape of the Clinical and Biological Research in Neurofibromatosis Type 1." All of these articles are available for free online for those who would like to access them. The introduction by **Suppiah et al**. FREE, DOD (Canada) outline the topics of the included articles and the major questions in NF1 research they address.

One set of articles addresses the biology of neurofibromas – how do cutaneous and plexiform neurofibromas develop? Research suggest that tumors begin at a specific stage of Schwann cell development, where inflammation and the immune system play a role in the tumor continuing to grow. (Schwann cells are the cells that wrap around nerves throughout your body to help them conduct electrical signals better.) Another set of articles focuses on malignant peripheral nerve sheath tumors (MPNSTs), a cancer that about 10% of people with NF1 will develop in their lifetime. Authors reviewed the current knowledge about how MPNSTS should be diagnosed and treated, and highlight the need for additional studies to explore how radiotherapy and/or

chemotherapy might improve outcomes beyond the current gold-standard of surgery. Additional articles detail the molecular pathways by which MPNSTs form and metastasize (spread to other parts of the body), highlighting potential targets for new treatments.

Two articles focus on how we classify and manage cutaneous neurofibromas. One paper looked at how different pathologists describe and classify cutaneous neurofibromas based on their microscopic features. This is the first step towards coming up with a single classification system that everyone can use to standardize reporting in the future. Another paper reviewed current treatments for cutaneous neurofibromas, including surgical removal, laser treatments, electrodessication, or radiofrequency ablation. Unfortunately, many insurance companies in the United States do not pay for these treatments because they are classified as elective, cosmetic procedures. Hopefully in the future, strong patient advocacy building on research showing the impact of cutaneous neurofibromas on peoples' quality of life can change this.

Three more articles focus on other kinds of tumors in NF1, including brain tumors (such as optic pathway gliomas) and abdominal tumors (like pheochromocytomas and gastrointestinal stromal tumors). Authors note that because optic pathway gliomas are rarely biopsied or surgically resected, there is very little tumor tissue to study, making NF1 animal models like mice and pigs critical for research advances. The RAS-MAPK pathway was activated in several non-NF1 related optic pathway gliomas, suggesting this may be worth studying in NF1, too. In another paper, researchers propose setting up large, multi-hospital studies to see if routine screening for abdominal tumors might help improve the average lifespan of people with NF1, as it has done for people with another genetic syndrome called Li-Fraumeni syndrome.

The last set of articles addresses clinical trial design, including the importance of understanding how new treatments affect patients' day to day functioning and quality of life. One study in Canadian patients with NF1 and NF2 found that pain was the most significant driver of physical health, and disease visibility was the most significant driver of patients' mental health. Another article explores how we might use novel, noninvasive imaging techniques such as diffusion tensor imaging (which can illuminate how supporting brain cells are connected) to help find people who might benefit from treatment as early as possible.

4. Other Clinical Features of NF1

The Bottom Line: In a survey of European adults with NF1, the visibility of cutaneous neurofibromas and the unpredictability of their formation and growth were the most bothersome aspects of these tumors. Participants desire a new cream or pill that could block the growth of existing neurofibromas most.

a. Patients' Views on Cutaneous Neurofibromas

Guiraud et al. FREE (France) surveyed 170 adults with NF1 from across France, the United Kingdom, Spain and Germany. The focus of the survey was to better understand the real-world experiences of patients living with NF1, how patients felt about current treatment options for cutaneous neurofibromas (cNF), and what patients' expectations were for new treatment options. Understanding patients' lived experience of NF1 and what patients find the most burdensome about their cNF is important for shaping NF1 research priorities in the future.

The survey confirmed that the total number of cNF people have, including the number of cNF that people have on parts of the body that are visible to others, increases as patients age. Nearly all respondents (96%) reported having cNF on highly visible parts of their body, such as their face, neck, hands, and forearms. When asked to rank what aspects of cNF were most bothersome, the visibility

of these tumors and the stress of not knowing how they will evolve over time were the most highly ranked problems, followed by the number of cNF, the size of cNF, pain from cNF, and lastly, itching from cNF. While pain was on average a low priority across the whole sample, 22% of survey respondents did rank pain as their number one concern (second only in #1 ranks to the visibility of cNF), suggesting a wide range of experiences in this area. Participants also reported that cNF had a negative impact on their quality of life, with particularly noticeable effects on everyday mood and social life.

Currently, the only two treatment options for cNF are lasers and surgical removal. More than 76% of the study population reported trying at least one of these two methods. Overall, patients reported being fairly satisfied with these treatments. However, the frequency of surgery and the rate of cNF regrowth after surgery were identified as the least satisfactory aspects of current treatment options.

One of the most important findings in this study is the information gained about patients' expectations towards future treatment options. Overall, patients were interested in topical creams, pills, or implants for future cNF treatment options. Patients were generally the least interested in injection treatments. According to patients, the top criteria for deciding if a new treatment worked would be (in decreasing order of importance) blocking cNF from growing, reducing the number of existing cNF, and preventing the appearance of new cNF. The majority of patients reported that they would consider a treatment to be moderately or very effective if the treatment could clear 30% of cNF. 60% of patients said they would take an effective treatment for the rest for their life, with people who have more cNF to start with more willing to take treatment for life than those with few cNF.

This survey presents clinicians and researchers with a clear idea of not only what types of treatments NF1 patients are most interested in to treat or prevent their cNF, but also the criteria those treatments would have to meet in order to be considered successful. This information is crucial for shaping future NF1 clinical trials that prioritize patients' interests in the management and treatment of their disease.

5. NF2 Update

The Bottom Line: Higher-doses of bevacizumab are no more effective than standard doses in treating vestibular schwannomas; laboratory works suggests combining AZD2014 (an mTOR inhibitor drug) and dasatinib may be an effective treatment strategy for meningiomas and vestibular schwannomas; meningiomas that are most likely to grow and need treatment are those that are bigger, have swelling around them but no calcified mineral deposits, and are brighter on specific types of MRI sequences.

a. Clinical Trial of High-Dose Bevacizumab for Vestibular Schwannomas in People with NF2

Many patients with Neurofibromatosis type 2 (NF2) develop vestibular schwannomas. Vestibular schwannomas are a type of tumor that develops from the balance and hearing nerves within the inner ear. Although these tumors are benign (non-cancerous), they can significantly impair patient's functioning and quality of life as they grow larger. Vestibular schwannomas can cause hearing loss, dizziness, balance difficulties, and tinnitus (ringing in the ear). Furthermore, vestibular schwannomas can interfere with face sensation and function, leading to facial numbness, weakness, or paralysis.

Previous studies have documented the benefits of using a chemotherapy called bevacizumab to shrink vestibular schwannomas and improve hearing. Bevacizumab acts as an antibody against vascular endothelial growth factor (VEGF), a signaling protein expressed by vestibular schwannomas. Previous studies have documented tumor shrinkage and hearing improvement in 30-60% of NF2 patients with growing vestibular schwannomas or hearing loss who were treated with 5 mg/kg every two weeks or 7.5 mg/kg every three weeks of bevacizumab.

Within other neuro-oncology populations (not NF2 patients), treatment with bevacizumab at 10 mg/kg every two weeks was found to be safe. **Plotkin et al.** [FREE, DoD] (United States) designed a clinical trial to see whether starting off with this higher dose of bevacizumab would increase the number of NF2 patients who responded to treatment. This trial was run through the Department of Defense-funded NF Clinical Trial Consortium, and enrolled 22 participants with NF2 from across the U.S., ranging in age from 12 to 62 years. Seven participants were considered to be pediatric (under 21 years) and the remaining 15 were considered adult participants (over 21 years of age).

The study used word recognition scores (a hearing test of how well people can understand speech), tumor volume, and quality of life surveys to assess the impact of bevacizumab treatment. For the first six months of the study, bevacizumab was given intravenously at a dose of 10 mg/kg every 2 weeks. Afterwards, participants with stable or improved word recognition scores were treated with 5 mg/kg of bevacizumab every 3 weeks for 18 months.

The study found that treating participants with 10 mg/kg of bevacizumab every 2 weeks led to improved hearing in 41% of participants and tumor shrinkage in 34% of targeted vestibular schwannomas. These rates are similar to previous studies using lower doses of bevacizumab. This suggests that the use of high-dose bevacizumab does not significantly improve outcomes compared to the lower doses utilized in previous studies.

There were also notable differences in responses among adult and pediatric participants. Almost all of the participants who saw improvement in hearing and tumor shrinkage were adults. 8/15 adults (53%) but only 1/7 (14%) pediatric patients had improved hearing; 7/15 (47%) adults but zero children had vestibular schwannomas shrink at least 20% in volume. These findings support previous studies that suggest children may respond less well to bevacizumab than adults. However, both adults and pediatric participants reported significant improvement in quality of life scores during bevacizumab treatment. The authors note this means it is possible that bevacizumab might be beneficial for people with NF2 and worsening vestibular schwannomas even if there is no detectable improvement in hearing or tumor volume.

b. Testing New Treatment Combinations for Vestibular Schwannomas in the Lab

Many people with NF2 have vestibular schwannomas and meningiomas, so finding treatments that are effective against both types of tumors would be helpful. Previous research has shown that using two drugs together - AZD2014 and dasatinib - was effective at slowing the growth of meningioma cells in the laboratory. Now, **Sagers et al.** [FREE, DoD, NIH] (United States) tested whether these same two drugs were effective at treating vestibular schwannomas.

AZD2014 is an mTOR inhibitor which works against two protein complexes (called mTORC1 and mTORC2) that regulate cell growth and cell proliferation (when cells divide faster than they die or differentiate into other cell types, increasing the total number of cells). AZD0214 is not FDA-approved for any use. Dasatinib is a tyrosine kinase inhibitor that helps stop enzymes from activating proteins, including multiple targets that seem overactive in cells without functioning NF2 genes (namely, erythropoietin-producing hepatocellular (EPH) receptors, SRC family kinases, and c-Kit).

Dasatinib is FDA-approved to treat certain kinds of leukemia (but has not been used in NF2).

The authors found that combining AZD2014 and dasatinib was more effective than either drug alone at reducing the metabolic activity of human vestibular schwannoma cells in a dish and in slowing down tumor growth in schwannomas in mice. This suggests that targeting multiple molecular pathways (the mTOR pathway and the EPH receptor pathway) that are dysregulated in people with NF2 simultaneously may be an effective strategy to treat vestibular schwannomas.

While no clinical trials for this combination of drugs have started yet, AZD2014 by itself is currently being tested in two phase 2 clinical trials – one for people with NF2 who have growing or symptomatic meningiomas (NCT02831257) and one for people with NF2 that have higher-grade meningiomas that have come back or grown despite treatment with surgery and radiation (NCT03071874). The trial in people with NF2 will also look at changes in vestibular schwannoma as a secondary outcome, hopefully providing information on the safety and preliminary efficacy of this treatment.

c. Predicting Which Meningiomas Will Grow Rapidly

Over half of patients with neurofibromatosis type 2 (NF2) develop intracranial meningiomas, a type of benign brain tumor. Some meningiomas do not cause any symptoms and can be observed using MRI, but some meningiomas, especially those that are growing quickly, may need treatment with surgery or radiation. **Abi Jaoude et al.** (France) designed a study to look at what characteristics may be associated with faster meningioma growth in patients with NF2.

The authors looked back at their hospital's medical records from 2012 to 2018, and found 92 NF2 patients who had a total of 358 intracranial meningiomas with images over at least 2 years. Sixty tumors (17%) in the study cohort were considered rapidly growing tumors (growing more than 2 cubic centimeters per year). Using statistical models, the authors found that the following characteristics were associated with faster meningioma growth: larger tumor volume at diagnosis, swelling around the tumor, the absence of calcifications (mineral deposits around the tumor), and brightly colored areas surrounding the tumor visible on MRI.

Current NF2 meningioma management options include observation, radiotherapy or radiosurgery, and traditional surgery. Many NF2 patients who develop meningiomas develop more than one, which can result in multiple procedures or surgeries throughout a patient's lifetime. In this instance, knowing how to prioritize surgery for certain tumors over others, based on their expected growth, can be extremely impactful for a patient's health and quality of life. In addition, patients with fast growing meningiomas might be good candidates for clinical trials. **Abi Jaoude et al.**'s study offers promising information on how to identify fast growing meningiomas so that patients and clinicians can make better informed decisions regarding the possible types and timing of meningioma treatment.

6. Schwannomatosis Update

The Bottom Line: Researchers continue to search for additional genes that cause schwannomatosis and understand why pain is so common in people with schwannomatosis; damage to small nerve fibers called C-fibers may play a role in causing pain.

a. Understanding the Cause of Neuropathic Pain in People with Schwannomatosis

The main symptom reported by people with schwannomatosis is pain, although the cause of this pain is not always known. For some people, the pain can be traced to a specific schwannoma that is compressing or irritating a specific nerve. But for many people, their pain is not near a schwannoma or it occurs across their whole body. To try to understand why people with schwannomatosis get this pain, **Farschtschi et al**. FREE (Germany) comprehensively examined 20 patients with chronic pain and compared their data to 20 people of the same age and gender who did not have schwannomatosis.

All participants in the study answered questions about their pain and received nerve testing (called quantitative sensory testing and measurement of laser evoked potentials) to measure the functioning of different sizes of nerve fibers. People with schwannomatosis also got whole-body MRIs to measure their schwannomas, magnetic resonance neurography (a special type of MRI that looks closely at your nerves) to look for any small irregularities in nerve bundles, and skin biopsies to assess intra-epidermal nerve fiber density (how thickly packed the nerves in the skin are).

The number, size and location of people's schwannomas did not seem to predict their pain. Only one person with schwannomatosis had a classic sensorimotor polyneuropathy (where nerves controlling both sensation and movement are damaged across multiple parts of the body), and three people had evidence of neuropathy (nerve damage) in just one or two nerves associated with a current or previously resected schwannoma. However, most people with schwannomatosis had very small lesions (called fascicular nerve lesions) in certain bundles of nerve fibers within the larger nerves. Based on their analyses of nerve function and density, the authors believe that specific nerve fibers called C- fibers are the most likely to be damaged in people with schwannomatosis. C-fibers are small nerves without myelin sheaths (the insulation that helps nerves conduct electricity faster) which are known to cause a more slow, diffuse sensation of pain. Future research confirming the role of C-fiber damage in schwannomatosis-related pain and exploring why this damage happens will hopefully help move us closer to discovering effective pain treatments for people with schwannomatosis.

b. The Search for Additional Genes that Cause Schwannomatosis

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. In Volume 14 of the Network Edge, we shared a free review of the genetics of schwannomatosis by **Kehrer-Sawatzki et al**. FREE (Germany). In this paper, the authors estimated that a large percentage of people with schwannomatosis have mutations in currently unknown genes. 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 first person in their family to have schwannomatosis, 30% will have an LZTR1 mutations, 10% will have SMARCB1 mutations, and the remaining 60% may have mutations in another gene or genes.

A new article by **Min et al.** (Korea) details some of the research being done to try to identify the additional genes that may cause schwannomatosis. This research group performed whole exome sequencing on the blood of ten people with sporadic schwannomatosis (meaning they were the first in their families to be diagnosed) who did not have any mutations in SMARCB1 or LZTR1. Unfortunately, there was no clear gene identified as being associated with schwannomatosis. Patients had potentially harmful mutations in a variety of genes that help repair DNA damage or genes that are tumor suppressors (called this name because they inhibit cell growth or promote cell death). The authors suggest that decreased DNA repair may cause genomic instability – an environment where gene mutations in cells are more frequent - which could make schwannomas

more likely to develop. But without analyzing matched blood and tumor samples from the same patients, we can't be sure these observed mutations directly cause schwannomas to form. Future research with detailed sequencing of both blood and tumor tissue from sporadic schwannomatosis patients will hopefully illuminate the other genetic causes of schwannomatosis soon.

8. Quality of Life in NF1, NF2, and Schwannomatosis

The Bottom Line: A small-group, live-video intervention to teach resiliency and stress management skills was successfully adapted for teenagers with NF and was able to improve their quality of life.

Clinical Trial of Virtual Group Resiliency Training in Teens with NF1 or NF2

In Volume 13 of the Network Edge, we shared results from a randomized trial by **Vranceanu et al.** (United States) which compared two stress management interventions delivered via group video- chats. This trial showed that a program called the Relaxation Response and Resiliency Program (3RP) may be effective at improving quality of life for adults with NF1, NF2, and schwannomatosis. Since that time, Dr. Vranceanu and colleagues have adapted the 3RP program to reach a wider group of NF patients.

First, they adapted the program to be compatible with Communication Access Real-time Translation (CART) services, so that people with NF2 and hearing loss could participate in the discussion. The successful randomized trial of this version of the 3RP program was reported by **Funes et al.** FREE (United States) and reported on in Volume 17 of the Network Edge. The team also adapted the program for teenagers with NF1 and NF2, into a program called Resilient Youth with NF. Now, **Lester et al.** FREE, DoD (United States) share the results of a pilot clinical trial to test this new program in kids ages 12- 17 with NF1 and NF2 from across the U.S. and Canada.

The Resilient Youth with NF program was similar to the adult 3RP program in that it teaches mindfulness, stress management, coping skills, and personal growth practices in small-group sessions conducted over live video. Participants learned these skills through a mixture of lessons and teaching games led by a psychologist, practical meditation exercises, and talking with other group members about their experiences. However, in the teen version of the program, the sessions were shorter (45 minutes instead of 90 minutes), the program manual was written using simpler language and more examples relevant to teenagers' lives, and the team developed in-session games to teach new skills that had built-in rewards to help reinforce learning.

For the clinical trial, 51 kids were randomized into a group following the Resilient Youth with NF curriculum or a group following a health education program that included information on NF, stress, and lifestyle modifications for healthy eating, exercise, and sleep. All groups had 5 kids with NF who met with a clinical psychologist to do the group sessions using free videoconferencing software (Skype). Teenagers in the Resilient Youth with NF program improved significantly in their physical, psychological, social, and environmental aspects of quality of life, whereas children in the standard health education program did not improve. This suggests that simply meeting as a group and discussing educational information is not enough to improve kids' quality of life. Also, when the researchers checked in with participants six months after the sessions ended, these improvements in quality of life were still apparent. This suggests that the specific skills taught in the Resilient Youth with NF programs around resiliency, mindfulness, and coping skills continue to benefit kids with NF even after the program ends.

Based on these results, the researchers are conducting a larger scale trial of the 3RP for NF patients to confirm these quality of life benefits, see if there are any additional benefits for participants' pain

and mental health, and to test if different psychologists can be trained to deliver the program. For information on the ongoing clinical trial for teens with NF, go to https://clinicaltrials.gov and search for trial number NCT03873610.

*Disclosure: The author of this newsletter is also a co-author on the paper by Vranceanu et al.

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The Network Edge **Archive**

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