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.

- 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.

- FREE Publications: Many scientific publications are now available at no charge. These are tagged in the text as FREE. To download full articles visit www.pubmed.gov and "search" for the publication title, then follow the links to download.

Highlights from Volume 13 of *The Network Edge*:

- **Congressional Update**: Twenty-one new NF projects are being funded by the Congressionally Directed Medical Research Program - Neurofibromatosis Research Program (CDMRP-NFRP).
- **NF Clinical Trials:** Pegylated interferon slows down the growth of plexiform neurofibromas in young people with NF1; vinblastine may be an effective treatment for optic pathway glioma.
- **NF1 Biology**: Researchers study how neurofibromas begin and later transform into MPNSTs, with some success identifying potential genes and pathways that new drugs can target.
- **NF2 Clinical Management**: Researchers review auditory brainstem implants in NF2.
- **NF2 Biology**: Research using two FDA-approved drugs, celecoxib and crizotinib, to treat schwannomas shows promising results in the lab and in mice.
- **Schwannomatosis Update**: A special type of MRI reveals nerve abnormalities in people with segmental schwannomatosis.
- **Quality of Life**: The Relaxation Response Resiliency Program (3RP) delivered over Skype shows promising results in improving quality of life of adults with NF1, NF2, and schwannomatosis.

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1. CDMRP Neurofibromatosis Research Program Update

The Bottom Line: A sneak peek at the innovative NF research recently funded by the CDMRP program

In this new section of *The Network Edge*, we'll highlight recently-funded research from the Congressionally Directed Medical Research Program (CDMRP) Neurofibromatosis Research Program (NFRP), which is overseen by the U.S. Department of Defense. Thanks in large part to the dedicated efforts of individuals with NF, their family and friends, and NF advocacy organizations like the NF Network, Congress approved $15 million in funding for NF research projects for fiscal year 2015. In this update, we will describe the exciting and innovative new projects chosen to receive that funding.

As of September 2016, 21 NF projects with a total budget of $13.5 million have been approved and finalized. These projects range from small grants to develop new ideas to large clinical trials of potential new treatments. Additional studies may be approved in the coming weeks.

So far, one clinical trial has received funding: This trial, led by Dr. Scott Plotkin of Massachusetts General Hospital, will test whether a drug called AZD2014 can help treat meningiomas in individuals with NF2. AZD2014 is a new drug that blocks two different parts of the mTOR signaling pathway, a biological pathway that contributes to the growth of meningiomas. In this Phase 2 clinical trial, eighteen individuals with NF2 and a meningioma that is growing or causing symptoms will take AZD2014. Participants will receive MRIs of the brain every three months, and researchers will measure whether their respective meningiomas shrink, remain the same size, or continue to grow. Researchers will also investigate whether AZD2014 has an impact on the size of vestibular schwannomas and participants' quality of life.

A second clinical trial, led by AeRang Kim of the Sarcoma Alliance for Research through Collaboration, was also recommended to receive funding but has not been finalized yet. (As such, it is not counted in the total of 21 projects that have been approved, mentioned above.) If approved, this trial will test whether a combination of two drugs, selumetinib and vistusertib, can help treat malignant peripheral nerve sheath tumors (MPNSTs) that can't be removed with surgery.

Fourteen projects will examine different aspects of NF1. Dr. John Albeck will use new methods to look at how messages in the RAS pathway (a major biological pathway affected in NF1) pass through live cells with and without NF1. This will help researchers to better understand how the messages are disrupted in individuals with NF1 and will also allow them to test potential new drugs for the ability to fix the message system. Dr. Harini Sundararaghavan will develop a new system to test whether potential drugs will effectively treat NF1. Instead of testing drugs on cells grown in a plastic dish, Dr. Sundararaghavan and his team will create a 3-dimensional model with multiple types of cells in order to better represent a real neurofibroma and its environment.

Multiple researchers will test potential drug treatments in animal models of NF1. Dr. Thomas Look will use zebrafish to test a large number of potential drugs to treat MPNST. Dr. Chengkai Dai will investigate whether a combination of two already-FDA-approved drugs can help stop the development and growth of neurofibromas and MPNSTs in mice. Dr. Matthew Greenblatt will study a molecule called MEKK2 and investigate whether drugs aimed at this molecule can treat bone problems in mice with NF1.

Dr. Chetan Bettegowda and Dr. Luis Parada are both studying how and when plexiform neurofibromas turn into MPNSTs. Dr. Parada's team will investigate cancer stem cells and their possible role in turning plexiform neurofibromas into MPNSTS. Dr. Bettegowda's team will look at tiny bits of tumor DNA that enter the bloodstream of an individual with NF1 to test whether it is possible to distinguish between a plexiform neurofibroma and an MPNST just by looking at a patient's blood.

Dr. Lu Le and Dr. Hector Peinado Selgas will both look at how the tumor microenvironment (the normal cells, molecules, and blood vessels that surround a tumor) contributes to the development and growth of neurofibromas. Dr. Le's team will look at fibroblasts, a type of cell that makes collagen; Dr. Peinado Selgas's team will look at exosomes, tiny sacs released by cells to carry proteins from one part of the body to another.

Multiple researchers are working on issues related to learning disabilities and other cognitive problems in NF1. Dr. Marc Wolman is investigating a new signaling pathway by which NF1 mutations lead to problems with attention and learning. Dr. Hongjun Song and Dr. James Walker will both use stem cell technology to grow brain cells (neurons) with the same mutation as NF1 patients, in order to better understand learning disabilities in NF1. Dr. Anantha Shekhar will study social learning and communication problems in mice with NF1. Dr. Jonathan Payne will try to understand why children with NF1 experience learning problems by using a special type of MRI that can pinpoint the activity of certain chemicals in the brain.

The CDMRP has also funded five projects related to NF2 (in addition to the clinical trial of AZD2014 mentioned above). Dr. Sarah Hughes will look at the ways in which Merlin, the protein made by the NF2 gene, works with other proteins to control how cells grow and stick together in the nervous system. Dr. Long-Sheng Chang will study a gene called NUP98 to see how changes in this gene might affect the size and growth of vestibular schwannomas. Dr. Marco Giovannini will study how the molecular landscape of schwannomas changes as the tumor grows, which might explain why drug treatments work on some NF2 tumors but not all. Dr. Andrea McClatchey will study how drugs that affect cell division work against NF2 tumors (schwannomas and meningiomas) and sporadic cancers that also have problems in the NF2 gene. Dr. Lei Xu will study immunotherapy (a way of boosting the body's own immune system to fight tumors) as a treatment for schwannomas in mice. Dr. Xu's team will test whether combining immunotherapy with anti-VEGF treatments (such as bevacizumab) is more effective than either treatment alone.

Finally, the CDMRP has approved one project specifically on schwannomatosis: There are currently two genes known to be associated with schwannomatosis – SMARCB1 and LZTR1. However, most individuals with schwannomatosis do not have a mutation in either of these genes. Dr. Ludwine Messiaen will try to find the additional gene or genes that cause schwannomatosis in these patients.

If you would like to learn more about any of the projects mentioned here, a full description of the studies that received funding is available online at http://cdmrp.army.mil/search.aspx. (Under "Research Program," select "Neurofibromatosis Research Program." Then, under "Fiscal Year," select "2015." Finally, select the "Search Awards" link and click on the title of any proposal to reveal a short description of the project, which researchers write specifically for a general, non-scientific audience.)

2. Recommendations from the REiNS International Collaboration to Improve Outcome Measures for NF Clinical Trials

The Bottom Line: An international group of researchers and clinicians recommend new outcome measures to use in NF1, NF2, and schwannomatosis clinical trials.

The Response Endpoints in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration is an international group consisting of NF clinicians and researchers who work together to determine the best outcome measures for NF clinical trials. The REiNS group published their first set of clinical trial recommendations in 2013 (a summary of which can be found in Volume 5 of *The Network Edge*.) Now, the REiNS group has released a second set of recommendations, all of which are available for free online.

In the introduction to this special publication, Widemann and Plotkin[FREE] (United States) give a brief overview of the activities of the REiNS International Collaboration. They note that the outcome measures REiNS recommended in 2013 have been used in multiple NF clinical trials already. As more trials use the same outcome measures, it will be easier to compare results across research studies to decide which treatments work best. The recommendations of different REiNS subgroups are as follows…

Patient-reported outcomes group: Wolters et al.[FREE] present recommendations for measuring pain and physical functioning in NF clinical trials. To measure the intensity of an individual's pain, the group recommended the Numeric Rating Scale-11, which asks patients to rate their respective pain on a scale from 0 to 10. To measure how much pain interferes with an individual's life, the group recommended two surveys: the PROMIS Pain Interference scale for adults and the Pain Interference Index for children and adolescents. To measure physical functioning, the group recommended the PROMIS Pain Interference scale for both adults and children. The group notes that researchers have to do more work to compare paper surveys of the recommended measures with new, computer-adaptive versions that are completed on a tablet or computer. *Disclosure – The author of this newsletter is also a co-author on the paper by Wolters et al.

Functional outcomes group: Plotkin et al.[FREE] present recommendations for measuring lung function and sleep in individuals with plexiform neurofibromas near their respective airways. The group recommended two measures of lung function: forced expiratory volume (FEV) and airway resistance. FEV is the amount of air an individual can push out of his or her lungs over a specified amount of time (0.75 seconds for preschoolers and one second for older children and adults). To measure sleep, the group recommended the apnea-hyponea index, which measures how many times individuals temporarily stop breathing or have very shallow breathing during sleep. The group also recommended a number of other, secondary measurements of breathing and sleep that researchers can use to gather extra information about a new treatment.

Neurocognitive group: Walsh et al. [FREE] describes how the members of the neurocognitive group review outcome measures related to cognitive functioning and presents recommendations for measuring attention. The group recommended using the WAIS Digit Span task and the Connors rating scales to measure attention. In the Digit Span task, an individual is given a string of numbers and asked to repeat them back, either in the same order or in reverse. The Connors rating scales are surveys that ask an individual (or in the case of children, the child's parent or teacher) to answer questions about everyday behaviors related to attention (for example, "How hard is it for you (or your child) to focus on homework assignments?").

Whole-body MRI group: Ahlawat et al. [FREE] reviewed the use of whole-body MRIs in individuals with NF1, NF2, and schwannomatosis to date. They identified multiple research questions that need to be studied more before one single recommendation can be made regarding how to use whole body MRI in clinical trials. One of the biggest questions is how whole body MRIs compare to MRIs of a single body part.

Biomarker group: Hanemann et al. [FREE] reviewed the use of biomarkers in studies of NF1, NF2, and schwannomatosis to date and made recommendations on how to collect biomarkers in future studies. Biomarkers are molecules in the blood, urine, tumors, or other bodily tissues that show how a hidden process in the body is working (for example, researchers might attempt to test whether the levels of proteins in the blood change when a person's plexiform neurofibroma has transformed into an MPNST). If changes in the protein reliably reflect changes in the tumor, then the protein would be considered a good biomarker.

3. NF1 Clinical Trials

a. Pegylated Interferon for Plexiform Neurofibroma in Young People with NF1

The Bottom Line: Pegylated interferon may slow down the growth of plexiform neurofibromas in young people with NF1.

Jakacki et al. (United States) report the results of a clinical trial of pegylated interferon in children and young adults with NF1 with plexiform neurofibromas (PN). Overall, 82 individuals age one-and-a-half to 21 years were enrolled in the study and provided data that could be analyzed. Of that number, only two individuals experienced significant reduction in the size of the plexiform neurofibroma (>20% in volume).

However, in the 29 individuals who joined the trial specifically because their respective PNs were growing, treatment with pegylated interferon seemed to slow down tumor growth. It took an average of 29.4 months for the plexiform neurofibromas in these individuals to increase 20% in volume, which is more than double the time it took for tumors to grow in similar individuals involved in another study receiving no treatment (In those individuals, it took an average of 11.8 months for the plexiform neurofibroma to increase 20% in volume.).

Given that there are no drugs currently approved to treat plexiform neurofibromas, the authors suggest that pegylated interferon may be a reasonable treatment choice for young people with actively growing PNs at risk of causing clinical problems. However, they also note that other drugs (like selumetinib and imatinib) have shown an ability to shrink tumors in early clinical trials. If larger clinical trials prove that other drugs can shrink tumors, and not just slow their growth like pegylated interferon, those drugs would likely be more attractive treatment options.

b. Vinblastine for children with low-grade gliomas

The Bottom Line: In a small group of children with NF1 and optic pathway glioma, vinblastine seems to be an effective first-line treatment.

Lassaletta et al. FREE (Canada) studied the how well a chemotherapy called vinblastine worked for children with low grade gliomas (brain tumors). To join the clinical trial, children could not have received radiation or any other chemotherapies. The clinical trial lasted 70 weeks, with children receiving vinblastine as an infusion once a week.

Fifty-four children age eight months to 17 years received treatment, and 13 of those children had NF1. All 13 children with NF1 had an optic pathway glioma. Children with NF1 were younger than the other children in the trial, with a median age of 3.8 years. Four of the 13 children with NF1 experienced a decrease in the size of their respective tumors, and the other nine children did not experience any fluctuation in tumor size. No individuals with NF1 experienced tumor growth while receiving vinblastine, but after finishing treatment, two children experienced tumor growth. The researchers don't specifically report how vision was affected in children with NF1, but in the overall group of 23 children with optic pathway gliomas and visual problems, five experienced improved vision, 13 experienced no change in vision, four experienced worsening of vision, and vision-related information was not recorded for one individual. The most common side effect of treatment was neutropenia (when individuals have a low number of a certain type of white blood cells, which makes them more vulnerable to getting infections).

Overall, the results of this study suggest that vinblastine might be a good choice of chemotherapy for children with low-grade gliomas, including children with optic pathway gliomas due to NF1. Vinblastine has less severe side effects than some of the other drugs used to treat low-grade gliomas, making it an attractive choice of treatment. However, a larger study with more children with NF1 and specific information about vision is needed before making stronger recommendations.

4. Learning Disabilities and Social Functioning in NF1

The Bottom Line: Researchers use MRIs and other advanced imaging techniques to better understand how the brain works in mice and humans with NF1.

Violante et al. FREE (Portugal, United Kingdom) used advanced imaging techniques to understand how a neurotransmitter called GABA works in individuals with NF1. Neurotransmitters are chemicals that are released by neurons to transmit messages to nearby neurons. To receive the message, nearby neurons need special receptors to catch hold of the neurotransmitters.

In this study, the brains of 14 adults with NF1 and 13 adults who did not have NF1 were imaged using two techniques: The first is called magnetic resonance spectroscopy (MRS), which can track the concentration of neurotransmitters in the brain; the second was a special type of PET scan in which individuals were injected with a contrast dye that shows where GABA receptors are located. The combination of scans showed that individuals with NF1 have less GABA and fewer GABA receptors in some areas of the brain than people without NF1. This study is important because it shows that problems with GABA are occurring both in the neurons that are sending messages and in the neurons that should be receiving messages.

Petrella et al. (Portugal, United States) use MRI scans of the brains of mice with and without NF1 to learn more about which areas of the brain are involved with social memory and spatial learning. The brains of mice with NF1 were larger in certain areas compared to mice without NF1. In mice with NF1, the size of one area of the brain, the prefrontal cortex, was associated with social memory. To test social memory, the researchers measured how much time a mouse spends with a mouse it has already met compared to time spent with an unfamiliar mouse. Mice without NF1 spent more time with the unfamiliar mouse, but mice with NF1 spent an almost equal amount of time with both the unfamiliar mouse and the mouse that had been introduced previously. This study shows that the brain's structure, and not just its function, may be important in NF1. Future research will have to determine whether the size of the prefrontal cortex is related to social functioning in humans.

5. What's New in NF1 Biology?

a. Neurofibromas

The Bottom Line: Researchers try to better understand how neurofibromas begin to form.

The cells in our bodies carry two copies of every gene in our genome. In individuals with NF1, each cell has a mutation in one copy of the NF1 gene. If an individual experiences a mutation in the second copy of the NF1 gene, the cell stops making the NF1 protein. When Schwann cells (the cells the wrap around nerves) stop making the NF1 protein, neurofibromas can form.

Wu et al. FREE, NIH (United States) mapped some of the specific biological steps by which loss of the NF1 protein leads to neurofibroma forming. They found that two pathways, called JAK/STAT and Wnt/Beta-catenin, are critical for a neurofibroma to initially form and begin to grow. Future research should look at drugs that affect these two pathways in order to determine whether they can help prevent or slow the growth of neurofibromas.

Liao et al. FREE, NIH, CDMRP (United States) looked at factors outside the Schwann cell that impact the formation and growth of neurofibromas. They found that in order for Schwann cells to turn into neurofibromas, nerve cells must be located nearby. This might be because the nerve cells are releasing growth factors that help support the tumor's growth. If so, these growth factors would be another possible drug target in the treatment of benign neurofibromas.

b. Malignant Peripheral Nerve Sheath Tumors (MPNST)

The Bottom Line: Multiple researchers are studying how neurofibromas transform into MPNSTs, with some success identifying potential genes and pathways that new drugs can target.

As mentioned in the section above, when Schwann cells have mutations in both copies of the NF1 gene, they can turn into neurofibromas. If the cells in the neurofibroma have additional mutations in certain cancer-promoting genes, the neurofibroma can turn into an MPNST.

Multiple research groups are studying how these cancer-promoting genes lead to the formation and growth of MPNSTs. For instance, **Patel et al.** FREE, NIH, CDMRP (United States) found that a gene called MEIS1, which is known to be involved in leukemia, is an important player in MPNST growth. Using research with zebrafish, **Ki et al.** FREE, CDMRP (United States) found that having too much PDGFRA, a receptor for a type of growth factor, leads to more aggressive MPNSTs.

By understanding the biological pathways these genes are involved in, researchers hope to find targets for drugs that can eventually be used to treat MPNST. **Kendall et al.** FREE, NIH (United States) studied whether blocking an enzyme called CK2 could help prevent MPNST cell growth. After performing tests in MPNST cells to show how CK2 works, they tested a drug that blocks CK2 in mice with MPNSTs. This drug, called Silmitasertib, slowed the growth of the MPNST and led to the mice living longer. However, the drug didn't actually kill the MPNST cells in mice. Overall, these results show that blocking CK2 might be a useful strategy for treating MPNSTs but that this area requires more research in order to find the best drug or combination of drugs to use.

Thinking about utilizing a combination of drugs**, Ahsan et al.** FREE (United States) studied whether targeting two different signaling pathways could effectively kill MPNST cells. They found that that MPNST cells treated with the combination of selumetinib (which targets MEK) and another drug that targets BMP2 grew more slowly, were more likely to die, and were less likely to invade nearby areas. The combination of drugs worked better than either drug did alone, leading the authors to suggest that combining drugs that target different pathways in MPNST is likely to be the most effective way to treat patients in the future.

6. NF2 Clinical Management

The Bottom Line: Auditory brain implants can help improve hearing in some individuals with NF2.

Auditory brainstem implants (ABI) are electronic devices that help transmit sound directly to the brain of individuals who have damage to the inner ear and auditory nerves. An ABI has three parts: a processor with a small microphone that is worn around an individual's ear, a receiver that is surgically implanted under the skin, and a wire that runs from the receiver to the brain. The processor turns sounds into electrical signals and transmits them wirelessly to the receiver and through the wires. Then, the wires can directly stimulate the hearing area of the brainstem.

Ramsden et al. (United Kingdom) reviewed the outcomes of all of the patients with NF2 who received an ABI between 1994 and 2009 at the NF2 clinic in Manchester, England. Forty-nine individuals received an ABI, but only 41 actually turned on the device. (Eight individuals did not turn on the ABI because they still experienced good hearing in their opposite ears, and they didn't want the signals from the ABI to confuse hearing in the other ear.) Of the 41 who turned on the ABI, 29 (71%) use it full time.

On average, individuals who use the ABI could correctly identify a sound in the environment (like a doorbell ringing or a car horn honking) 51% of the time. However, accuracy varied significantly: some individuals could only identify about 25% of sounds, while others could identify almost 80%.

Understanding speech was more difficult than hearing noises in the environment. Using just the ABI, individuals could on average understand 22% of speech sounds (like the letter "m" or the sound "sh") and 13% of key words in a sentence. However, when signals from the ABI were combined with lip reading, hearing test results improved significantly; on average, individuals could understand 65% of speech sounds and 54% of key words in a sentence. As was the case with tests measuring perception of noises in the environment, these outcomes varied widely between individuals.

Overall, these results show that ABIs can lead to good hearing outcomes in some patients with NF2, especially if patients combine use of the ABI with lip-reading. However, results vary widely, with some individuals hearing very little or never using the ABI at all. The researchers investigated whether any factors could predict who would benefit most from an ABI; however, tumor size, age, and duration of hearing loss at the time of surgery proved to be largely unrelated to hearing outcome.

7. What's New in NF2 Biology?

The Bottom Line: Research using two FDA-approved drugs, celecoxib and crizotinib, to treat schwannomas has promising results in the lab and in mice.

Guerrant et al. NIH (United States) looked at the YAP signaling pathway, which is important in a variety of tumor types, to see what role it plays in NF2. They found that the YAP pathway is necessary for NF2 Schwann cells (the cells the surround nerves and grow into schwannomas in individuals with NF2) to survive and grow. One of the things the YAP pathway does is increase levels of the enzyme COX-2. When the researchers treated mice with a drug that works against COX-2 (celecoxib), schwannomas in the mice that received celecoxib grew more slowly that schwannomas in the mice that did not receive treatment. Celecoxib is currently approved by the FDA to treat multiple forms of arthritis as well as other issues.

Troutman et al. FREE, NIH (United States) studied the effect of crizotinib on NF2 Schwann cells and schwannomas in mice. Crizotinib is a drug that has been approved by the FDA to treat a form of lung cancer and is in clinical trials for a variety of other diseases. The researchers found that crizotinib keeps NF2 Schwann cells from growing, primarily through an effect on the enzyme FAK1. Similar to **Guerrant et al.**'s experiment with celecoxib, mice treated with crizotonib experienced slower schwannoma growth than mice that did not receive treatment.

Together, these articles provide exciting evidence for further study of crizontinib and celecoxib in treating schwannomas in individuals with NF2. Researchers hope it will be easier to study the effect of these drugs in humans because the drugs have already been FDA-approved to treat other diseases, which means that there is already basic information available regarding the safety and appropriate dosage of the drug.

8. Schwannomatosis Update

The Bottom Line: A special type of MRI reveals nerve abnormalities in individuals with segmental schwannomatosis.

About one-third of individuals with schwannomatosis are thought to have segmental schwannomatosis. In segmental schwannomatosis (sometimes called mosaic schwannomatosis), tumors are found only in one part of the body, such as a single arm or one area of the spine. This is thought to happen if only a portion of an individual's cells have the genetic mutations that cause schwannomatosis (a condition called genetic mosaicism).

Farschtschi et al. (Germany) report on five individuals with segmental schwannomatosis. Each individual underwent a whole-body MRI that showed tumors resided in only one area of the body. Each individual also underwent a microstructural magnetic resonance neurography (MRN) scan – a type of MRI that looks very closely at the nerves and the cells surrounding the nerves. In four of the five individuals, there were small nerve abnormalities in areas of the body other than where a tumor was located. These nerve abnormalities were not seen/were very rare in a group of 25 individuals without schwannomatosis who also underwent MRNs, strengthening the claim that these nerve abnormalities are related to schwannomatosis.

If this is true, it means that individuals who appear to only have tumors in one part of the body may actually have other affected body parts that cannot yet be detected on an MRI. This also means that individuals with segmental schwannomatosis may not actually have genetic mosaicism. Indeed, two of the individuals in the study were found to have LZTR1 mutations in their blood, skin, and other tissues, suggesting that the mutations that cause schwannomatosis were present in the entire body.

It is important to remember that clinicians don't know whether the nerve abnormalities will ever grow into larger schwannomas or cause symptoms. Future research will be necessary to explore this area in more depth, as well as the relationship between a person's genetic mutations and the location of his or her tumors.

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

The Bottom Line: The Relaxation Response Resiliency Program (3RP) delivered over Skype shows promising results in improving quality of life in adults with NF1, NF2, and schwannomatosis.

In the past few years, the NF community has increasingly recognized the importance of psychological and social treatments in improving quality of life in individuals with NF. Multiple groups are working to adapt existing, well-researched programs to suit the unique challenges faced by individuals with NF. In the last issue of *The Network Edge*, a preliminary study of Acceptance and Commitment Therapy for adolescents with NF1, plexiform neurofibromas, and pain was presented. In this issue, we're excited to report on a different type of psychosocial skills program, called the Relaxation Response Resiliency program (3RP), which was adapted for adults with all forms of NF.

Vranceanu et al. (United States) performed a randomized trial of two stress-management programs to determine whether they could improve quality of life in adults with NF1, NF2, and schwannomatosis. Participants completed eight 90-minute group sessions using the free videoconferencing software Skype. A clinical psychologist led each session, and groups included six-to-eight individuals, who could log into the sessions from their respective home computers. Half of the group followed the curriculum from the 3RP, which focused on skills to increase relaxation, mindfulness, coping with stress and uncertainty, and positive thinking. Half of the group followed the curriculum from a more general health program, which focused on educational information about NF, healthy eating and exercise, and communicating with doctors.

Sixty-three individuals total participated in the study. Individuals in both groups improved in regard to psychological quality of life, but individuals in the 3RP showed greater levels of improvement. Individuals in the 3RP also improved in their physical, social, and environmental aspects of quality of life, as well as anxiety and depression, whereas individuals in the general health education program did not. Based on these results, the researchers recommend conducting a larger trial of the 3RP for NF patients to confirm these benefits and test whether different psychologists can be trained to deliver the program.

Two more clinical trials of the 3RP are currently underway or about to begin. The first trial is testing a version of the program adapted for adolescents age 12-17 with NF1 or NF2. More information about this study can be found at https://clinicaltrials.gov/ct2/show/NCT02387177. The second trial is testing a version of the program adapted for adults with NF2 and hearing loss. This group will use real-time captioning (through Communication Access Real-time Translation [CART]) and/or American Sign Language interpreters to facilitate the group sessions. More information about this study can be found at https://clinicaltrials.gov/ct2/show/NCT02811718

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

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