TheNetworkEdge
NF Network and NF Northeast present a periodic research review
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The Network Edge Volume 20: Fall, 2021

***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.

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Highlights from Volume 20 of *The Network Edge*:

- **NF1 Clinical Trials:** L-carnitine supplements were safe and well-tolerated by children with NF1 in a small clinical trial; future trials will confirm whether these supplements can improve children's muscle strength and endurance.
- **NF1 Learning Disabilities:** Initial testing shows that MEK inhibitors like selumetinib and computer training games like Cogmed might improve cognitive functioning in children with NF1.
- **NF1 MPNSTs:** A new blood test analyzing cell-free DNA from tumors that floats in our bloodstream holds exciting promise for early detection and monitoring of MPNSTs.
- **NF1 Optic Pathway Gliomas**: Treating mice with MEK inhibitors like mirdametinib shortly after birth may prevent optic pathway gliomas from forming.
- **NF2 Clinical Trials**: Analyzing resected tumors from NF2 patients taking everolimus helps uncover why the drug was not as effective as hoped in shrinking vestibular schwannomas.
- **NF2 Biology**: Two FDA-approved drugs - brigatinib and losartan – hold promise for being repurposed to treat vestibular schwannomas and other NF2-related tumors.
- **Quality of Life:** Treating depression may help buffer the impact of pain on people's everyday lives; similarly, building resiliency may help reduce the impact of stress on people's quality of life.
- **REiNS Update**: A new series of articles highlights NF clinical trial recommendations, including how NF patients and their family members have contributed to REiNS research.

The Network Edge: Volume 20 – Contents

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1. NF1 Clinical Trials

The Bottom Line: L-carnitine supplements were safe and well-tolerated by children with NF1 in a small Phase 2 clinical trial; a larger, more rigorous trial is needed to determine if these supplements can improve muscle strength and endurance in kids with NF1.

People with NF1 may experience a variety of muscle problems including muscle weakness, reduced muscle tone, and physical fatigue. This may be due to an excess of intramyocellular lipids - fats that are stored as droplets within muscle cells to provide energy to the cells. In Volume 18 of the Network Edge, we shared an article by **Vasiljevski et al.** FREE (Australia) that showed L-carnitine supplements were effective at reducing intramyocellular lipids in mice with NF1. Now, the researchers have built on this preclinical work to launch a clinical trial of L-carnitine supplements in children with NF1. In this small, Phase 2, proof-of-concept clinical trial, **Vasiljevski et al.** (Australia) studied the safety and feasibility of L-carnitine supplements in six children ages 8 to 12 with NF1 who had a history of muscle weakness or fatigue. The kids in the trial took over the counter L-carnitine supplements by mouth twice a day for 12 weeks. Taking the supplements was safe and relatively easy to do, and preliminary efficacy data showed that the children might have increased muscle strength and improved motor function (as measured by walking and jumping performance). To make sure these benefits were truly due to the supplements, the researchers recommend performing a larger, randomized, placebo-controlled Phase 3 clinical trial in children across a wider age range.

2. NF1 Learning Disabilities

The Bottom Line: Initial testing shows that MEK inhibitors like selumetinib and computer training games like Cogmed might improve working memory and executive functioning in children with NF1.

Walsh et al. FREE, NIH (United States) evaluated the cognitive function of 59 children and young adults with NF1 who were participating in clinical trials of MEK inhibitors to treat their plexiform neurofibromas. (Most people (92%) were receiving selumetinib, but five participants were in clinical trials for mirdametinib or trametinib.) The study found no evidence of any negative side effects of MEK inhibitors on cognitive function over the first 48 weeks of treatment. In fact, it appeared that drugs may even improve working memory and executive functioning, especially in children who had difficulties in these areas to begin with. Future research should directly compare the cognitive changes seen during treatment with MEK inhibitors to changes seen in people receiving no treatment or other types of medications to prove whether these cognitive improvements are real and durable.

Hardy et al. (United States) did an initial pilot test of whether Cogmed^{RM}, a computer-game like training program, could be a useful intervention to improve cognitive functioning in kids with NF1. Twenty-seven children with NF1 ages 8 to 15 with impairments in working memory scores tried out the program at home. Sixty nine percent of kids were able to complete the minimum number of sessions (20 sessions over 9 weeks), and promisingly showed short-term improvements in memory, attention, and executive functioning. Ninety percent of parents said they were 'somewhat' or 'very' satisfied with the program, although 45% noted their kids 'often' or 'always' complained about having to do the training. Based on these findings, the researchers propose conducting a larger, randomized clinical trial to more robustly study the benefits of Cogmed, and explore how computer training may supplement treatment with medications.

3. NF1 Malignant Peripheral Nerve Sheath Tumors

The Bottom Line: A new blood test holds exciting promise to detect MPNSTs and monitor people's response to treatment; new insight into MPNST biology identifies potential targets for treatment.

About 8-10% of people with NF1 will develop malignant peripheral nerve sheath tumors (MPNSTs) in their lifetime, but it can be difficult to tell based on imaging alone whether a tumor is a benign plexiform neurofibroma or a cancerous MPNST. **Szymanski et al**. FREE, NIH (United States) are working to develop a blood test that can reliably differentiate plexiform neurofibromas from MPNSTs by analyzing plasma cell-free DNA– small fragments of DNA that float in the bloodstream. In their small initial test sample, a one-time blood test was 86% accurate in distinguishing people with plexiform neurofibromas from people with MPNSTs. Over time, the amount of tumor-related plasma cell-free DNA also went up or down with the size of the MPNSTs. If this technology can be validated and scaled up, it will be a promising tool to non-invasively detect MPNSTs earlier and monitor people's response to treatment. For those who would like a more detailed review on how cell-free DNA could potentially be used in diagnosing and monitoring MPNSTs in people with NF1, please see **Jones et al.** (Australia).

Mutations in NF1 lead to disruptions in the RAS signaling pathway, which is why NF1 is considered a "RASopathy syndrome." **Weber et al**. FREE, NIH, CDMRP (United States) are studying how different forms of the RAS protein affect signaling in NF1-related MPNST cells. They found that different forms of RAS act on different downstream targets that lead to tumor growth. These targets – including R-Ras driven changes in ROCK1 signaling – could be a potential new target for MPNST treatments.

4. NF1 Optic Pathway Gliomas

The Bottom Line: Researchers identify the excess cell types and proteins that lead to optic pathway gliomas, and show that intervening early in mice development with MEK-inhibitors like mirdametinib may be able to prevent these tumors from forming.

Jecrois et al. NIH, CDMRP (United States) found that optic pathway gliomas in mice arise from a specific type of cell (called "migrating glial progenitors") found within the optic nerve during early development. Mice with NF1 had too much signaling in the Mek-Erk/MAPK pathway, leading to overproduction of these glial progenitors cells and eventual tumor formation. Excitingly, temporary treatment with the MEK-inhibitor mirdametinib for the first three weeks after birth prevented optic glioma formation in the mice. This provides proof-of-concept that chemotherapy treatment delivered during early development in humans may be able to prevent optic pathway gliomas before any irreversible neuronal damage occurs, although the exact time window for treatment and a safe dose of chemotherapy would still have to be determined.

Pan et al.NIH, CDMRP (United States) also sought to explore why optic pathway gliomas form. They found that optic nerve activity promotes tumor growth, and that optic pathway gliomas will only form in mice with NF1 if the optic nerve is stimulated by visual experiences during a specific period in early development. This is because mice with NF1 shed too much of a protein called neuroligin 3 within the optic nerve in response to light stimulating the retina. However, blocking neuroligin 3 during this early developmental window helped prevent optic pathway gliomas from forming in new mice. This provides another important window into ways we might be able to prevent optic pathway gliomas from occurring.

5. Other Clinical Features of NF1

The Bottom Line: Publications confirm that people with NF1 have a higher risk of developing spinal problems (like scoliosis and dural ectasia) and neuroendocrine tumors (like pheochromocytomas).

Well et al. FREE (Germany) confirmed that scoliosis (curvature of the spine), dural ectasia (when the membrane surrounding the spinal cord balloons out with cerebrospinal fluid), and veterbral scalloping (erosion of the bone, often due to a nearby tumor) are more common in people with NF1 than people the same age and gender without NF1. However, the researchers did not find any association between what type of NF1 gene mutation people had and what type of spinal abnormalities they had.

Alkhayyat et al. FREE, NIH (United States) found the people with NF1 have a higher risk of developing neuroendocrine tumors (like pheochromocytomas) than the general population, but that the absolute number of people with NF1 who have these tumors is still quite low (about 1 in 750 people with NF1 in a large, U.S. medical records database).

6. What's New in NF1 Biology?

The Bottom Line: Research in flies and mice explores how the NF1 gene affects metabolism and response to drug treatments.

Emerging research is looking at how NF1 affects metabolism and growth. Prior studies have shown that when the NF1 gene is not functioning it can affect how cells create energy out of the oxygen we breathe and food we eat. Mice with NF1 mutations can have less fat in their bodies, an increased sensitivity to insulin, and are less susceptible to obesity. Perhaps relatedly, people with NF1 can sometimes be shorter than expected. **Botero et al.** FREE, NIH, CDMRP (United States) studies what mechanisms might be driving these differences in metabolism using flies with NF1 mutations. They found that neurofibromin, the protein encoded by the NF1 gene, increases flies' metabolic rates – how much energy they need to expend to keep their bodily functions going at rest – via a specific set of neurons in the flies' brains. This suggests metabolism problems in NF1 may be centrally regulated in the brain, rather than being a problem with how tissues in the rest of the body are processing insulin and other factors.

Krenik et al. CDMRP (United States) found that which parent a mouse inherits NF1 from can affect its behavior and response to drug treatment. Mice who inherited an NF1 mutation from their father showed behavioral and cognitive changes in response to treatment with an ALK inhibitor that similar mice who inherited an NF1 mutation from their mother did not. The researchers speculate that this difference may have to do with differences in mitochondrial function, as mitochondrial DNA is only passed down from mothers. The results also speak to the value of replicating study findings across mouse models with different genetic backgrounds to better understand variability in responses to treatment.

7. NF2 Clinical Trials

The Bottom Line: Analyzing resected tumors from NF2 patients taking everolimus helps uncover why the drug was not as effective as hoped in shrinking vestibular schwannomas.

In prior Phase 2 clinical trials, everolimus did not significantly shrink vestibular schwannomas in people with NF2, although there was some evidence suggesting that this drug might help slow the growth rate of tumors. To better understand why these results occurred despite promising preclinical studies showing tumor shrinkage in mice, **Karajannis et al**. [NIH] (United States) ran a Phase 0 clinical trial to see whether everolimus actually reaches people's tumors at a sufficient concentration. Ten people with NF2 who were already scheduled to get surgery for a vestibular schwannoma or meningioma were asked to take everolimus for 10 days before surgery, so that the researchers could study the drug's effects on their tumor samples. They found that while everolimus does reach people's tumors, it only partially inhibits the necessary biological pathways to stop tumor growth. This suggests that using everolimus in combination with other medications or finding brand new medications that target the same pathways more effectively might be necessary to treat tumors in people with NF2.

8. NF2 Clinical Management

The Bottom Line: Looking back at the medical records of NF2 patients shows that stereotactic radiosurgery may be more effective at treating meningiomas than vestibular schwannomas.

Mohammed et al. (United States, Czech Republic, India, Canada, Dominican Republic) looked at the medical records of NF2 patients across seven hospitals to see how people did after receiving gamma knife radiosurgery to treat meningiomas. They identified 39 patients who had a total of 204 meningiomas treated with gamma knife. In these selected cases for which gamma knife was recommended by the clinical team, tumor growth was very minimal, with 95% of patients not seeing any significant growth over the first ten years after treatment. Four patients (10%) did have some radiation-induced side effects (with edema, or swelling in the brain, being the most common), but these side effects were transient and could be managed with steroid medications. Finally, none of these patients had their meningioma transform into a malignant tumor during the follow-up period. Altogether, this suggests that gamma knife radiosurgery could be a good treatment option for some people with NF2-related meningiomas.

Similarly, **Santa Maria et al.** [NIH] (United States) looked back at the medical records of everyone who received stereotactic radiosurgery for a vestibular schwannoma at a single hospital between 1992 and 2013. Twenty-one of these people had NF2, while the rest had sporadic vestibular schwannomas. At three years post-treatment, 57% of people with NF2 had their vestibular schwannoma regrow and/or require additional treatments, compared to only 11% of people with sporadic tumors. While the number of people with NF2 in this cohort is small, limiting the ability to draw robust conclusions, it seemed like the size of the tumor and whether it was growing before radiation did not predict whether stereotactic radiosurgery would be effective in people with NF2.

Egra-Dagan et al. [NIH, CDMRP] (United States) looked back at the CT scans of 20 people who had received auditory brainstem implants (17 of whom had NF2) to see what factors correlated with hearing outcomes. They found that ABIs performed best if they were tilted superiorly on imaging, had more active electrodes, and needed less electrical charge to stimulate each electrode.

9. What's New in NF2 Biology?

The Bottom Line: Two FDA-approved drugs - brigatinib and losartan – hold promise for being repurposed to treat vestibular schwannomas and other NF2-related tumors.

Chang et al. FREE (United States, Germany) found that brigatinib, an oral medication that is FDA-approved to treat certain types of metastatic lung cancer, was effective at inhibiting tumor growth of NF2-related meningiomas and schwannomas in mice. This was surprising because the main effect for which brigatinib is approved in lung cancer is targeting the ALK protein, which is not expressed in schwannomas or meningiomas. However, the researchers found that this medication also acts on multiple tyrosine kinases (enzymes that that help turn other proteins on or off, specifically by adding or removing molecules attached to the amino acid tyrosine). These tyrosine kinases seemed to play a role in schwannomas and meningiomas, showing the potential of screening large libraries of existing drugs for potential use in treating NF2. Based on this promising data, brigatinib was advanced to the next stage of testing in human clinical trials. Brigatinib is the first treatment being tested as part of the INTUITT-NF2 trial (which stands for "Innovative Trial for Understanding the Impact of Targeted Therapies in NF2"). This trial is a platform trial that will test multiple medications over time in NF2 patients with growing vestibular schwannomas, non-vestibular schwannomas, meningiomas, or ependymomas. This trial will be open at six sites across the U.S. and more information can be found at: https://clinicaltrials.gov/ct2/show/NCT04374305.

A previous study of 274 people with vestibular schwannomas showed that the degree of hearing loss people experienced was correlated with the amount of fibrosis (thickening or scarring) around their tumor. This led **Wu et al**. NIH, CDMRP (United States, China) to investigate the drug losartan, which is FDA-approved to treat high blood pressure, but also acts on molecular pathways involved in fibrosis and inflammation. They administered losartan to mice with NF2, and found that it prevented hearing loss by reducing inflammation, which helped normalize the blood vessels and reduce swelling around the tumor. It was even more effective when combined with radiation treatment. Preliminary studies with NF2 patient samples showed the same inflammatory pathways that losartan blocked in mice are correlated with hearing function in people with NF2. The authors also looked back at the medical records of 45 people with vestibular schwannomas who also had high blood pressure. The seven people taking losartan or drugs like it seemed to have less hearing loss over 3-4 years than people taking other medications. Based on this data, the authors propose starting a clinical trial of losartan (either alone or in combination with radiation) in people with NF2.

Hawkey et al. NIH, CDMRP (United States) are working to understand how Merlin (the protein encoded by the NF2 gene) interacts with a group of proteins called "p21-activated kinases" or PAKs in mouse models of NF1. They found that while both PAK1 and PAK2 are over-activated in mice schwannomas, these two PAKS function differently. Eliminating PAK1 reduced tumor size and extended the lifespan of mice with few side effects, but eliminating PAK2 led to significant side effects and even early death. This work shows the importance of targeting very specific molecules, even when they otherwise appear very similar, and supports the further investigation of PAK1 inhibitors to treat vestibular schwannomas.

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

The Bottom Line: The COVID-19 pandemic was challenging for many people's mental health and ability to get NF care. Treating depressive symptoms may help buffer the impact of pain on people's everyday lives; similarly, building resiliency and coping skills may help reduce the impact of anxiety and stress on people's quality of life.

Quality of Life in NF1, NF2, and Schwannomatosis

Wolters et al. [NIH] (United States) surveyed 613 adults with NF1, NF2, and schwannomatosis in the summer of 2020 about the impact of the COVID-19 pandemic on people's mental health and use of NF healthcare. They found that people with mental health disorders, people with moderate to severe NF symptoms, and women were more likely to have high levels of stress about COVID-19. These groups of people may need extra psychosocial support as the pandemic continues. The researchers also found that 30% of people missed in-person doctor's appointments during the early pandemic, but less than half of these people replaced their in-person visit with a telehealth appointment. Of the people who did use telehealth, about 80% said it met their needs to a moderate or high degree, suggesting telehealth could be effectively used for some NF patients in the future. (Disclaimer: the author of this newsletter is also a co-author of this paper).

Researchers from Massachusetts General Hospital used patient-reported data from over 200 adults with NF1, NF2, and schwannomatosis who participated in a virtual trial of a mind-body intervention to better understand the relationships between various factors that impact quality of life. **Doorley et al**. [NIH, CDMRP] (United States) focused on pain intensity (how severe pain is) and pain interference (how much pain prevents you from doing your daily activities). They found that depression, but not anxiety, partially explains why people with higher pain intensity have higher pain interference. This suggests that treating people's depressive symptoms may reduce the negative effects of pain on people's lives, allowing them to carry out more of their daily activities despite their high pain levels. Similarly, **Mace et al**. [CDMRP] (United States) analyzed how emotional distress (including depression, anxiety, stress) and resiliency skills (like optimism, gratitude, mindfulness, and other coping skills) are related to people's quality of life. They found that resiliency skills could buffer some of the effects of emotional distress on quality of life, supporting the idea that psychological interventions building resiliency skills could be helpful to reduce the impact of mental health disorders on the day to day lives of people with NF.

Kenborg et al. [CDMRP] (Denmark) took advantage of the extensive health databases in Denmark to look at psychiatric and neurodevelopmental disorders in 905 people with NF1 and 7614 people without NF1 of similar age and sex at birth. They confirmed that boys and girls with NF1 had a higher risk of ADHD, autism spectrum disorder, and intellectual disabilities than people without NF1. They also found that only girls with NF1 had an increased risk for being diagnosed with and seen at a hospital for depression, severe stress reaction and adjustment disorders. Neither boys nor girls with NF1 were at higher risk for schizophrenia, bipolar disorder, or substance abuse than people without NF1. As these psychiatric and neurodevelopmental issues could occur from childhood through young adulthood, the authors encourage mental health support services and treatment in all age groups.

11. NF Genetics Update

The Bottom Line: Geneticists search for mutations that cause NF1, NF2, schwannomatosis in non-coding DNA regions.

Only a small fraction of our DNA directly encodes specific proteins. The rest of our DNA is considered "non-coding DNA", and its function has been harder to unravel. Because of this, it can also be hard to tell if specific genetic sequences in non-coding DNA are insignificant variations between people, or actually a disease-causing mutation. **Perez-Becerril et al.** CDMRP (United Kingdom) summarize the different types of mutations that have been already found in non-coding portions of the NF1, NF2, SMARCB1, and LZTR1 genes, and suggest that further characterizing of non-coding DNA could help diagnose additional people with NF1, NF2, and schwannomatosis.

12. REiNS Collaboration Update

The Bottom Line: The REiNS Collaboration published its third issue of NF clinical trial recommendations, including multiple articles on cutaneous neurofibromas, quality of life surveys, and cognitive tests. Overview articles highlight the impact of REiNS recommendations on NF clinical trials to date and how NF patients and their family members have contributed to REiNS research.

The Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration is a group of researchers, clinicians and patients who work to improve the design of clinical trials for NF. The group recently published its third set of papers on clinical trial outcomes and other topics, all of which are available for free online at the Neurology journal's website and on the REINS website at https://ccrod.cancer.gov/confluence/display/REINS/Home.

In two introductory articles, **Gross et al**. FREE, NIH (United States) highlight how REiNS-recommended outcome measures on tumor shrinkage and pain were used successfully in the clinical trial that led to the approval of selumetinib for treatment of plexiform neurofibromas in kids with NF1. **Merker et al**. FREE, NIH (United States) evaluated the REINS patient representative program which began in fall 2017 to engage patients with NF1, NF2, and schwannomatosis and their family members in clinical trial design. Their paper highlights the positive impact that patient representatives can have as members of research teams, including helping REiNS to select more meaningful, relevant, and feasible clinical trial outcome measures.

Four articles focused on cutaneous neurofibromas (cNF). **Cannon et al.** FREE, NIH (United States, Vienna) surveyed 548 adults with NF1 about their preferences for cNF clinical trials. Two-thirds of respondents were very much or extremely willing to try experimental treatments for cNF, with people favoring topical medications the most and oral medications second. Most people hoped to see at least a moderate decrease (33%-66% decrease) in the number or volume of their tumors to consider a new treatment a success. **Thalheimer et al.** FREE (United States) offer recommendations for how to measure the size of cNF in future clinical trials, including pros and cons of different measurement techniques. High frequency ultrasound is the most expensive and time consuming, but it's the only technique that can see small cNF underneath the skin, making it appealing for trials trying to prevent cNF from developing. 3D photography is a quick and reliable way to measure cNF that stick out above the skin, making it appealing for trials looking to shrink or remove already visible cNF. Finally, digital calipers (which are used somewhat like tweezers to physically grasp the tumors and measure their width) are somewhat less reliable but affordable and easy to use, making them appealing for more widespread trials where people are monitored

outside expert centers. **Wallis et al.** [FREE, NIH] (United States, Australia) made recommendations on how to collect cNF samples during trials in order to study them and hopefully identify biomarkers that can show whether a new drug is working as intended and predict who will benefit from new treatments. Finally, **Maguiness et al.** [FREE, NIH] (United States, Australia) explored the use of the Skindex as a quality of life questionnaire. They found that people with many cNF, people with cNF on their face, and women have lower quality of life, regardless of their overall NF1 disease severity.

Four articles focused on how best to gather data directly from patients or their parents about their symptoms during clinical trials. **Wolters et al.** [FREE, NIH, NFRP] (United States, Canada, Netherlands) made recommendations for quality of life questionnaires, including general quality of life measures that can be used across all types of NF, and specific measures for NF1 (the PedsQL NF1 module) and for NF2 (the NFTI-QoL). **Thompson et al.** [FREE] (United States) recommended using a patient questionnaire called the Self-Assessment of Communication to measure improvements in hearing during NF2 clinical trials. **Janusz et al.** [FREE] (United States, Australia) recommended two questionnaires for parents to help assess their children's social skills in NF1 clinical trials – 1) the Social Skills Improvement System Rating Scale to assess social functioning broadly, and 2) the Social Responsiveness Scale-2 to specifically look at social behaviors associated with autism spectrum disorder. **Klein-Tasman et al.** [FREE] (United States, Australia) recommended measures that can be used to gauge attention difficulties in preschool aged children with NF1, including the AD/HD Rating Scale – Preschool version.

The final three articles covered a variety of topics. **Akshintala et al.** [FREE] (United States) discuss considerations for measuring muscle strength in clinical trials for people with NF1 and NF2. They found that handheld dynamometers – a small, mechanical device that a researcher presses against a person's muscle to measure the force it exerts during contraction – are a reliable method of measuring strength. **Ahlawat et al.** [FREE] (United States, Germany) surveyed NF experts about imaging protocols for people with NF1. While 90% of people agreed they would get a regional (*e.g.,* body-part specific) MRI to evaluate someone having symptoms without a known plexiform neurofibroma, other imaging situations had little consensus, suggesting the NF1 imaging guidelines might be helpful to suggest when to start imaging, how often to get imaging, and what modality of imaging to choose. **Bettegowda** [FREE, NIH, NFRP] (United States, United Kingdom) review available evidence on genotype-phenotype correlations in NF (whether people's specific genetic mutation is related to the symptoms they develop). For NF2, there are four categories of mutations that can roughly predict how severe someone's disease will be, but for NF1 there are only a few known genotype-phenotype correlations at this time.

(Disclaimer: the author of this newsletter is a co-author on the papers by Merker et al., Wolters et al., Thompson et al., and Thalheimer et al.).

The Network Edge Archive

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References

Ahlawat S, Ly KI, Fayad LM, Fisher MJ, Lessing AJ, Berg DJ, Salamon JM, Mautner VF, Babovic-Vuksanovic D, Dombi E, Harris G, Plotkin SR, Blakeley J; REiNS International Collaboration. Imaging Evaluation of Plexiform Neurofibromas in Neurofibromatosis Type 1: A Survey-Based Assessment. Neurology. 2021 Aug 17;97(7 Suppl 1):S111-S119.

Akshintala S, Khalil N, Yohay K, Muzikansky A, Allen J, Yaffe A, Gross AM, Fisher MJ, Blakeley JO, Oberlander B, Pudel M, Engelson C, Obletz J, Mitchell C, Widemann BC, Stevenson DA, Plotkin SR; REiNS International Collaboration. Reliability of Handheld Dynamometry to Measure Focal Muscle Weakness in Neurofibromatosis Types 1 and 2. Neurology. 2021 Aug 17;97(7 Suppl 1):S99-S110.

Alkhayyat M, Saleh MA, Coronado W, Abureesh M, Zmaili M, Qapaja T, Almomani A, Khoudari G, Mansoor E, Cooper G. Epidemiology of neuroendocrine tumors of the appendix in the USA: a population-based national study (2014-2019). Ann Gastroenterol. 2021 Sep-Oct;34(5):713-720.

Bettegowda C, Upadhayaya M, Evans DG, Kim A, Mathios D, Hanemann CO; REiNS International Collaboration. Genotype-Phenotype Correlations in Neurofibromatosis and Their Potential Clinical Use. Neurology. 2021 Aug 17;97(7 Suppl 1):S91-S98.

Borrie SC, Plasschaert E, Callaerts-Vegh Z, Yoshimura A, D'Hooge R, Elgersma Y, Kushner SA, Legius E, Brems H. MEK inhibition ameliorates social behavior phenotypes in a Spred1 knockout mouse model for RASopathy disorders. Mol Autism. 2021 Jul 26;12(1):53.

Botero V, Stanhope BA, Brown EB, Grenci EC, Boto T, Park SJ, King LB, Murphy KR, Colodner KJ, Walker JA, Keene AC, Ja WW, Tomchik SM. Neurofibromin regulates metabolic rate via neuronal mechanisms in Drosophila. Nat Commun. 2021 Jul 13;12(1):4285.

Cannon A, Pichard DC, Wolters PL, Adsit S, Erickson G, Lessing AJ, Li P, Narmore W, Röhl C, Rosser T, Widemann BC, Blakeley JO, Plotkin SR; REiNS International Collaboration. Perspective of Adults With Neurofibromatosis 1 and Cutaneous Neurofibromas: Implications for Clinical Trials. Neurology. 2021 Aug 17;97(7 Suppl 1):S15-S24.

Chang LS, Oblinger JL, Smith AE, Ferrer M, Angus SP, Hawley E, Petrilli AM, Beauchamp RL, Riecken LB, Erdin S, Poi M, Huang J, Bessler WK, Zhang X, Guha R, Thomas C, Burns SS, Gilbert TSK, Jiang L, Li X, Lu Q, Yuan J, He Y, Dixon SAH, Masters A, Jones DR, Yates CW, Haggarty SJ, La Rosa S, Welling DB, Stemmer-Rachamimov AO, Plotkin SR, Gusella JF, Guinney J, Morrison H, Ramesh V, Fernandez-Valle C, Johnson GL, Blakeley JO, Clapp DW; Synodos for NF2 Consortium. Brigatinib causes tumor shrinkage in both NF2-deficient meningioma and schwannoma through inhibition of multiple tyrosine kinases but not ALK. PLoS One. 2021 Jul 15;16(7):e0252048.

Doorley JD, Greenberg J, Bakhshaie J, Fishbein NS, Vranceanu AM. Depression explains the association between pain intensity and pain interference among adults with neurofibromatosis. J Neurooncol. 2021 Aug 19. Online ahead of print.

Egra-Dagan D, van Beurden I, Barber SR, Carter CL, Cunnane ME, Brown MC, Herrmann BS, Lee DJ. Adult Auditory Brainstem Implant Outcomes and Three-Dimensional Electrode Array Position on Computed Tomography. Ear Hear. 2021 Jul 16. Online ahead of print.

Gross AM, Plotkin SR, Widemann BC; REiNS International Collaboration. NF Clinical Trials - REiNS Collaboration 2020 Recommendations: Looking Back and Moving Ahead. Neurology. Neurology. 2021 Aug 17;97(7 Suppl 1):S1-3.

Hardy KK, Berger C, Griffin D, Walsh KS, Sharkey CM, Weisman H, Gioia A, Packer RJ, Acosta MT. Computerized Working Memory Training for Children With Neurofibromatosis Type 1 (NF1): A Pilot Study. J Child Neurol. 2021 Sep 2:8830738211038083.

Hawley E, Gehlhausen J, Karchugina S, Chow HY, Araiza-Olivera D, Radu M, Smith A, Burks C, Jiang L, Li X, Bessler W, Masters A, Edwards D, Burgin C, Jones D, Yates C, Clapp DW, Chernoff J, Park SJ. PAK1 inhibition reduces tumor size and extends the lifespan of mice in a genetically engineered mouse model of Neurofibromatosis Type 2 (NF2). Hum Mol Genet. 2021 Aug 12;30(17):1607-1617.

Janusz JA, Klein-Tasman BP, Payne JM, Wolters PL, Thompson HL, Martin S, de Blank P, Ullrich N, Del Castillo A, Hussey M, Hardy KK, Haebich K, Rosser T, Toledo-Tamula MA, Walsh KS; REiNS International Collaboration. Recommendations for Social Skills End Points for Clinical Trials in Neurofibromatosis Type 1. Neurology. 2021 Aug 17;97(7 Suppl 1):S73-S80.

Jecrois ES, Zheng W, Bornhorst M, Li Y, Treisman DM, Muguyo D, Huynh S, Andrew SF, Wang Y, Jiang J, Pierce BR, Mao H, Krause MK, Friend A, Nadal-Nicolas F, Stasheff SF, Li W, Zong H, Packer RJ, Zhu Y. Treatment during a developmental window prevents NF1-associated optic pathway gliomas by targeting Erk-dependent migrating glial progenitors. Dev Cell. 2021 Aug 20:S1534-5807(21)00634-1.

Jones J, Cain S, Pesic-Smith J, Choong PFM, Morokoff AP, Drummond KJ, Dabscheck G. Circulating tumor DNA for malignant peripheral nerve sheath tumors in neurofibromatosis type 1. J Neurooncol. 2021 Sep 16. Online ahead of print.

Karajannis MA, Mauguen A, Maloku E, Xu Q, Dunbar EM, Plotkin SR, Yaffee A, Wang S, Roland JT, Sen C, Placantonakis DG, Golfinos JG, Allen JC, Vitanza NA, Chiriboga LA, Schneider RJ, Deng J, Neubert TA, Goldberg JD, Zagzag D, Giancotti FG, Blakeley JO. Phase 0 Clinical Trial of Everolimus in Patients with Vestibular Schwannoma or Meningioma. Mol Cancer Ther. 2021 Sep;20(9):1584-1591.

Kenborg L, Andersen EW, Duun-Henriksen AK, Jepsen JRM, Doser K, Dalton SO, Bidstrup PE, Krøyer A, Frederiksen LE, Johansen C, Østergaard JR, Hove H, Sørensen SA, Riccardi VM, Mulvihill JJ, Winther JF. Psychiatric disorders in individuals with neurofibromatosis 1 in Denmark: A nationwide register-based cohort study. Am J Med Genet A. 2021 Jul 29. Online ahead of print.

Klein-Tasman BP, Lee K, Thompson HL, Janusz J, Payne JM, Pardej S, de Blank P, Kennedy T, Janke KM, Castillo AD, Walsh KS; REiNS International Collaboration. Recommendations for Measurement of Attention Outcomes in Preschoolers With Neurofibromatosis. Neurology. 2021 Aug 17;97(7 Suppl 1):S81-S90.

Krenik D, Weiss JB, Raber J. Role of the parental NF1 carrier in effects of pharmacological inhibition of anaplastic lymphoma kinase in Neurofibromatosis 1 mutant mice. Brain Res. 2021 Oct 15;1769:147594.

Mace RA, Doorley J, Bakhshaie J, Cohen JE, Vranceanu AM. Psychological resiliency explains the relationship between emotional distress and quality of life in neurofibromatosis. J Neurooncol. 2021 Sep 27. Online ahead of print.

Maguiness S, Berman Y, Rubin N, Dodds M, Plotkin SR, Wong C, Moertel C; REiNS International Collaboration. Measuring the Effect of Cutaneous Neurofibromas on Quality of Life in Neurofibromatosis Type 1. Neurology. 2021 Aug 17;97(7 Suppl 1):S25-S31.

Merker VL, Lessing AJ, Moss I, Hussey M, Oberlander B, Rose T, Thalheimer R, Wirtanen T, Wolters PL, Gross AM, Plotkin SR; REiNS International Collaboration. Enhancing Neurofibromatosis Clinical Trial Outcome Measures Through Patient Engagement: Lessons From REiNS. Neurology. 2021 Aug 17;97(7 Suppl 1):S4-S14.

Mohammed N, Hung YC, Xu Z, Chytka T, Liscak R, Tripathi M, Arsanious D, Cifarelli CP, Perez Caceres M, Mathieu D, Speckter H, Mehta GU, Lekovic GP, Sheehan JP. Neurofibromatosis type 2-associated meningiomas: an international multicenter study of outcomes after Gamma Knife stereotactic radiosurgery. J Neurosurg. 2021 Jun 18:1-6.

Pan Y, Hysinger JD, Barron T, Schindler NF, Cobb O, Guo X, Yalçın B, Anastasaki C, Mulinyawe SB, Ponnuswami A, Scheaffer S, Ma Y, Chang KC, Xia X, Toonen JA, Lennon JJ, Gibson EM, Huguenard JR, Liau LM, Goldberg JL, Monje M, Gutmann DH. NF1 mutation drives neuronal activity-dependent initiation of optic glioma. Nature. 2021 Jun;594(7862):277-282.

Perez-Becerril C, Evans DG, Smith MJ. Pathogenic noncoding variants in the neurofibromatosis and schwannomatosis predisposition genes. Hum Mutat. 2021 Oct;42(10):1187-1207.

Santa Maria PL, Shi Y, Aaron KA, Gurgel RK, Corrales CE, Soltys SG, Santa Maria C, Chang SD, Blevins NH, Jackler RK, Gibbs IC. Tumor Control Following Stereotactic Radiosurgery in Patients with Vestibular Schwannomas - A Retrospective Cohort Study. Otol Neurotol. 2021 Aug 4. Online ahead of print.

Szymanski JJ, Sundby RT, Jones PA, Srihari D, Earland N, Harris PK, Feng W, Qaium F, Lei H, Roberts D, Landeau M, Bell J, Huang Y, Hoffman L, Spencer M, Spraker MB, Ding L, Widemann BC, Shern JF, Hirbe AC, Chaudhuri AA. Cell-free DNA ultra-low-pass whole genome sequencing to distinguish malignant peripheral nerve sheath tumor (MPNST) from its benign precursor lesion: A cross-sectional study. PLoS Med. 2021 Aug 31;18(8):e1003734.

Thalheimer RD, Merker VL, Ly KI, Champlain A, Sawaya J, Askenazi NL, Herr HP, Da JLW, Jordan JT, Muzikansky A, Pearce EM, Sakamoto FH, Blakeley JO, Anderson RR, Plotkin SR; REiNS International Collaboration. Validating Techniques for Measurement of Cutaneous Neurofibromas: Recommendations for Clinical Trials. Neurology. 2021 Aug 17;97(7 Suppl 1):S32-S41.

Thompson HL, Blanton A, Franklin B, Merker VL, Franck KH, Welling DB; REiNS International Collaboration. Patient Report of Hearing in Neurofibromatosis Type 2: Recommendations for Clinical Trials. Neurology. 2021 Aug 17;97(7 Suppl 1):S64-S72.

Vasiljevski ER, Burns J, Bray P, Donlevy G, Mudge AJ, Jones KJ, Summers MA, Biggin A, Munns CF, McKay MJ, Baldwin JN, Little DG, Schindeler A. L-carnitine supplementation for muscle weakness and fatigue in children with neurofibromatosis type 1: A Phase 2a clinical trial. Am J Med Genet A. 2021 Oct;185(10):2976-2985.

Vasiljevski ER, Houweling PJ, Rupasinghe T, Kaur T, Summers MA, Roessner U, Little DG, Schindeler A. Evaluating modified diets and dietary supplement therapies for reducing muscle lipid accumulation and improving muscle function in neurofibromatosis type 1 (NF1). PLoS One. 2020 Aug 10;15(8):e0237097

Wallis D, Stemmer-Rachamimov A, Adsit S, Korf B, Pichard D, Blakeley J, Sarin KY; REiNS International Collaboration. Status and Recommendations for Incorporating Biomarkers for Cutaneous Neurofibromas Into Clinical Research. Neurology. 2021 Aug 17;97(7 Suppl 1):S42-S49.

Walsh KS, Wolters PL, Widemann BC, Del Castillo A, Sady MD, Inker T, Roderick MC, Martin S, Toledo-Tamula MA, Struemph K, Paltin I, Collier V, Mullin K, Fisher MJ, Packer RJ. Impact of MEK Inhibitor Therapy on Neurocognitive Functioning in NF1. Neurol Genet. 2021 Aug 6;7(5):e616.

Weber SM, Brossier NM, Prechtl A, Barnes S, Wilson LS, Brosius SN, Longo JF, Carroll SL. R-Ras subfamily proteins elicit distinct physiologic effects and phosphoproteome alterations in neurofibromin-null MPNST cells. Cell Commun Signal. 2021 Sep 16;19(1):95.

Well L, Careddu A, Stark M, Farschtschi S, Bannas P, Adam G, Mautner VF, Salamon J. Phenotyping spinal abnormalities in patients with Neurofibromatosis type 1 using whole-body MRI. Sci Rep. 2021 Aug 19;11(1):16889.

Wolters PL, Reda S, Martin S, Al Ghriwati N, Baker M, Berg D, Erickson G, Franklin B, Merker VL, Oberlander B, Reeve S, Rohl C, Rosser T, Toledo-Tamula MA, Vranceanu AM. Impact of the coronavirus pandemic on mental health and health care in adults with neurofibromatosis: Patient perspectives from an online survey. Am J Med Genet A. 2021 Sep 18. Online ahead of print.

Wolters PL, Vranceanu AM, Thompson HL, Martin S, Merker VL, Baldwin A, Barnett C, Koetsier KS, Hingtgen CM, Funes CJ, Tonsgard JH, Schorry EK, Allen T, Smith T, Franklin B, Reeve S; REiNS International Collaboration. Current Recommendations for Patient-Reported Outcome Measures Assessing Domains of Quality of Life in Neurofibromatosis Clinical Trials. Neurology. 2021 Aug 17;97(7 Suppl 1):S50-S63.

Wu L, Vasilijic S, Sun Y, Chen J, Landegger LD, Zhang Y, Zhou W, Ren J, Early S, Yin Z, Ho WW, Zhang N, Gao X, Lee GY, Datta M, Sagers JE, Brown A, Muzikansky A, Stemmer-Rachamimov A, Zhang L, Plotkin SR, Jain RK, Stankovic KM, Xu L. Losartan prevents tumor-induced hearing loss and augments radiation efficacy in NF2 schwannoma rodent models. Sci Transl Med. 2021 Jul 14;13(602):eabd4816.