TheNetworkEdge
The NF Network presents A quarterly research review
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The Network Edge **brings you quarterly updates on the latest neurofibromatosis (NF) research and clinical trial advances from recent scientific publications. The newsletter is organized into "bite-sized" pieces by specific subtopic, so you can focus in 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 from that section.

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Highlights from Volume 5 of *The Network Edge*:

- **Social challenges for those with NF1 and NF2**
- **A new look at life expectancy in NF1 and NF2**
- **Unique considerations of seizure and epilepsy management in NF1**
- **NF1 learning disabilities – clinical trials update; new modes of early detection; a possible link with sleep disorders**
- **Updates on monitoring for MPNSTs; developing targeted drugs for these tumors**
- **New NF2 candidate drug targets**
- **The search for NF1-related gene mutations beyond the *NF1* gene**
- **A definitive link between autism and NF1**

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1. NF1 Clinical Management

The Bottom Line: Improved care and treatments are improving lifespan for those with NF1; recent reports detail potential new clinical features of NF1; special requirements for managing NF1-related epilepsy and seizures are being examined.

Life Expectancy in NF1

Does NF1 impact lifespan? Past reports have suggested that an NF1 diagnosis can shorten life expectancy by fifteen to twenty years. **Evans and Ingham** FREE *(United Kingdom)* re-examine this question by reviewing previous publications. They suggest that, in fact, this figure may be negatively biased, as it includes NF1-related deaths occurring early in life due to malignancies. The majority of people with NF1 "live through" a "malignancy risk period," and once they do, go on to live fairly long lives. One of the challenges of studying NF1 life expectancy is accurate reporting in death records. In one of the previously published studies reviewed, only a third of persons who had NF1 actually had a listing of NF1 on their death certificate. It is anticipated that this data will become more accurate with the growth of expert NF care centers with patient registries that can track the individual throughout life and can also hopefully improve lifespan by providing better care and new treatments.

Lesser Known Clinical Features of NF1

The diagnostic criteria for NF1 are well established, but recent publications report additional clinical features that may be useful in diagnosis and monitoring of NF1.

Glomus tumors are benign growths found in glomus body, a structure within the skin of the hand that regulates temperature. Glomus tumors can occur in NF1 and cause pain, but they are not well studied and are not part of the established diagnostic criteria for NF1. **Harrison *et al.*** *(United States)* examined twenty-one persons with a glomus tumor removed from the hand between 2005 and 2010, and found that six also had a diagnosis of NF1. In a comparison group of two hundred persons with ganglionic cysts - another benign hand tumor - none had NF1. This small study supports a previously proposed link between NF1 and glomus tumors. The authors suggest hand surgeons should be alert to patients with glomus tumors who may not yet be diagnosed with NF1 but may have NF1.

Marque *et al.* *(France)* report an association between NF1 and the presence of nevus anemicus (NA) or "white" spots on the skin. Two hundred and ten persons with NF1 were examined for signs of NA and compared to a group of age-and sex-matched individuals from the general population/without NF1. The occurrence, size and locations of NA were logged for all participants. Seventy-seven (fifty-one percent) of the NF1 group had NA compared with six (two-percent) of the group without NF1. In the NF1 group, NA tended to be present in young persons (under seventeen years of age) and mainly localized to the upper front chest.

NF1 Seizures and Epilepsy

Seizures occur in around seven percent of persons with NF1 - about three times greater than in the general population. Previous studies of NF1-related seizures have looked at small groups of people, but **Ostendorf *et al.*** *(United States)* conducted a large study, reviewing the records of five hundred and thirty-six individuals with NF1. Fifty-one (nine percent) of them had a record of seizures, and thirty-five (six percent) had a record of epilepsy. Of those with a seizure history, the majority experienced the first seizure in childhood or adolescence. Half of those with a seizure history were "first in family" cases of NF1, the other half having inherited NF1. In inherited cases, those with a seizure history were more likely to have inherited NF1 from their mother than father.

Data from electroencephalography (EEG, a recording of electrical activity from the scalp/measure of brain activity) was available for a subgroup of those with seizure or epilepsy history. Around fifty percent had EEG abnormalities. Magnetic resonance imaging (MRI) revealed that a number of these persons also had T2-hyperintensities ("bright spots" in the brain), which may be indicators of a tendency to experience seizures.

For people in the general population/without NF1, seizures and epilepsy can frequently be managed with one drug. However, this has proven more challenging for persons with NF1 who are less responsive to anti-epileptic drugs, and in this study, the average NF1 seizure sufferer used two to three anti-epileptic medications. The authors comment that individuals with NF1-related seizures may be good candidates for epilepsy surgery, since those in this study group who had undergone surgery had a significantly reduced seizure burden.

This important study highlights the risk of seizures and epilepsy in NF1 and the potential need for management options that differ from those used in the general epilepsy population.

A. NF1 and the Eye: Optic Pathway Gliomas and Other Ocular Features

The Bottom Line: Approaches for monitoring changes in optic pathway glioma are reviewed.

The last volume of *The Network Edge* reported on controversies and different approaches for monitoring optic pathway glioma (OPG) growth in children with NF1. The three main approaches now used are ophthalmic exam/visual acuity measurement, magnetic resonance imaging (MRI) and measurement of visual evoked potential (VEP). Opthalmic exams are the cheapest and most readily available approach, but they also have low sensitivity and specificity in children. MRI is a more sensitive approach to use, but it is expensive and may require the child to be sedated. Additionally, clinicians often disagree on interpreting ocular MRI data and determining next clinical steps to take. Two recent papers look at this issue.

Pattern reversal VEP (pVEP) monitor responses to flashing light patterns. **Van Mierlo *et al.*** *(Belgium)* investigated whether pVEPs can be used to signal the presence of OPGs. They reviewed all pVEP publications between 1980 and 2012. On the positive side, they found that pVEPs have a high sensitivity for the diagnosis of OPGs and are safe and cost-effective. On the negative side, the technique has a low specificity, is not widely available, and can be tricky to use in children since it requires participant cooperation. (It can be done on children when anaesthetized, but this interferes with the integrity of the result recorded.)

Kelly and Weiss *(United States)* completed a retrospective study of fifty-four children with and without NF1, age 3 months to 13 years, who have been monitored for presence and progression of an OPG via MRI, VEP and visual acuity reading. The study concluded that visual acuity changes don't always correlate with tumor growth and are an unreliable measure: in a number of cases reviewed, there was decline in visual acuity without any tumor growth. Serial MRI capture can be a useful and important tumor-growth-monitoring technique. As reported above, VEPs were found to have sensitivity and specificity issues, and can't be used when there is pre-existing damage in the optic pathway. Together these studies conclude that MRI is the most sensitive tool for monitoring appearance and growth of OPGs, but it is expensive and not always available. Furthermore, there may be no meaningful link between tumor growth and vision deterioration (ophthalmic exam or VEP/pVEP measures). Overall, use of multiple methods where possible to monitor OPG growth may be the best approach.

Note: See Section 5 of this volume of *The Network Edge* for an update on the new REiNS Collaboration to develop standardized monitoring approaches for visual changes in clinical trials.

B. NF1 Bony Abnormalities

The Bottom Line: A new candidate drug treatment approach for fracture healing in NF1 is presented (includes a case study of NF1-related osteoarthritis management).

In persons with NF1, bone progenitor cells (cells that give rise to bone) don't develop normally, which likely contributes to later NF1-related bone abnormalities. The abnormal progenitor cell development is due in part to overactive signaling in the cell's Ras/mitogen-activated protein kinase (RAS/MAPK) pathway. This over-activity happens when the *NF1* gene is not functioning (e.g. in persons with NF1). In a new publication, **Sharma et al.** CDMRP *(United States)* demonstrate that overactive RAS/MAPK signaling is directly responsible for the weaknesses in bone healing seen in persons with NF1. This was demonstrated when various types of bone progenitor cells from people with NF1 skeletal abnormalities were grown in a dish. These cells were "rescued" (made normal) by genetically restoring *NF1* gene function in the cells. The cells were also rescued by treating with an experimental drug, called PD98059, which inhibits the overactive RAS/MAPK signaling pathway. The drug allowed the cells to develop into normal bone cells. PD98059 also improved bone fracture healing when it was given to mice that had genetically engineered NF1-related bone abnormalities. These findings suggest RAS/MAPK targeted drugs may have promise in the clinic for treating NF1-related bone defects, which might include applications in treating low bone mass or pseudarthrosis.

Patel *et al.* FREE *(United States)* report on a thirty-nine-year-old man with NF1-related osteoarthritis who had suffered from right knee instability, difficulty walking, pain and general ongoing disability since being diagnosed with NF1 at age nine. These disabilities were made worse by neurofibromas and lymphedema (lymphatic obstruction leading to tissue swelling) around the knee socket. The man received above-the-knee amputation and within six months had largely eliminated pain, was significantly more active, and was successfully using a prosthetic device.

The authors use this case to emphasize that if a person with NF1 presents with osteoarthritis, they should be examined for the presence of neurofibromas around the joints that might be contributing to the issue. If caught early, these may be removed and the limb spared. However, if amputation surgery is needed, this case also demonstrates that even in a relatively young person, amputation and a prosthetic limb can improve quality of life.

C. Heart and Blood Vessel Abnormalities in NF1

The Bottom Line: Children with NF1 and moyamoya have a compromised ability to heal wounds; potential exists to develop a marker to predict ability to heal after surgery.

Children with NF1 can develop moyamoya, in which the blood vessels that lie within the brain become twisted and torturous, resembling on imaging a "puff of smoke" (this is the Japanese translation of "moyamoya"). In NF1, the root cause of moyamoya is believed to be reduced function of the NF1 protein, neurofibromin, which helps maintain normal blood vessel growth and integrity. Moyamoya is treated by a surgery called pial synangiosis, which involves opening up the skull and brain and essentially creating a new blood supply to feed the brain. Moyamoya can occur in the general population as well as in NF1.

Golomb and Smith *(United States)* explore whether moyamoya is also associated with a reduced ability to heal wounds, a process which also relies on a healthy vascular system. They report on two

cases, nine-year-old and five-year-old girls each with NF1-related moyamoya. Both girls underwent pial synangiosis surgery, and both girls had difficulty in healing at the site of surgery. In contrast, thirty-three other patients with moyamoya but without NF1 who underwent pial synangiosis surgery in the same facility had no difficulties healing. The authors propose that this might suggest a reduced wound healing ability in the girls with NF1.

The authors plan to examine skin biopsies from children with NF1-related moyamoya to test whether there are also differences in the fine blood vessels of the skin. If this proves to be the case, these differences might be used to predict whether a child is likely to suffer from impaired wound healing following surgery. This research could also help to inform understanding of the biological basis of vascular abnormalities in NF1.

D. NF1 Malignant Peripheral Nerve Sheath Tumors

The Bottom Line: Imaging and monitoring techniques for MPNST detection are examined; NF1 may have age-related indicators of MPNST risk; PEDF halts MPNST tumor growth in cell and animal models; target therapies for MPNST are being developed.

A major concern in NF1 is that a benign plexiform neurofibroma will become malignant, as these tumors can be highly resistant to treatment. Early detection and intervention is therefore very important. However, monitoring for malignancies can be challenging.

Koethe *et al.* NIH *(United States)* report on successful imaging and biopsy of an NF1-related malignancy called an angiosarcoma in an eighteen-year-old female. This was done using positron-emission tomography (PET)-guided biopsy in conjunction with computed tomography (CT). Angiosarcomas can develop within a malignant peripheral nerve sheath tumor (MPNST) that has developed within a plexiform neurofibroma. Angiosarcomas are rare in NF1 and have a very poor prognosis. The female presented with pelvic pain at age seventeen, and a plexiform neurofibroma was identified in the lower back. Over the subsequent nine months, the pain progressed, and foot/leg weakness developed on one side, which is a "red flag" for a potential malignancy.

The angiosarcoma was imaged using fluorodeoxyglucose (FDG)-PET, which basically feeds the tumor fluorescently tagged sugar; this is taken up at greater rates in the malignant tissue that is growing fastest, so this region can be visualized. A region of tumor was identified as potentially malignant, and the female went into surgery where FDG-PET, CT and ultrasound were used in conjunction. A needle was used to take core biopsies, and the tip of the needle was visualized and monitored during surgery. This allowed the surgeons to collect samples of the suspected malignant area for analysis without damaging adjacent organs. Pathology revealed a high-grade angiosarcoma sitting within a benign plexiform neurofibroma. This technique could be useful for imaging and defining tumor regions within benign growths that are believed to be progressing to malignancy so that clinical intervention can be provided.

MPNSTs occur in a small percentage of NF1 cases, but persons with NF1 make up a third of all MPNST cases in the population. **Kamran *et al.*** NIH, FREE *(United States)* notes that there is a lack of published information on imaging of MPNSTs occurring within the chest (thorax, lungs or chest wall). The team did a retrospective analysis on a group of fifteen persons with chest MPNSTs, four with NF1, for whom both imaging and tumor tissue was available. Three of the individuals with NF1 had previously had the tumor treated with surgery and/or chemotherapy. The fourth person with NF1 had received no treatment. One person with NF1 had a malignant triton tumor; these account for less than 10% of all MPNSTs and have a poor outcome.

The authors concluded from their findings that differentiating between benign and malignant chest NF1-related tumors by imaging can be quite difficult. MPNST signs include bleeding, areas of tissue death visible on CT imaging, and rapidly increasing tumor size. The authors recommend that any tumors growing along major nerves in the chest should be closely examined to see if they are MPNSTs, and they note that chest MPNSTs are likely to be larger than MPNSTs elsewhere in the body.

Past research has suggested that a larger number of internal plexiform neurofibromas is a predictor for later developing MPNSTs. **Nguyen** *et al. (Canada, Germany and United States)* confirm this to be the case for persons younger than thirty years of age. However, the authors find that this correlation does not hold for persons over 30 years of age, in which there are a subset of persons who develop MPNSTs but had no pre-existing internal plexiform neurofibromas. From this study, the authors conclude that younger patients should be monitored for internal plexiform tumor growth, as this may be an indicator of future MPNSTs; they present a "risk scale" that can be used to evaluate patients, based on the size and rate of growth of internal tumors. However, for persons with NF1 older than 30, there is a risk of MPNSTs even when there has been no major internal plexiform burden. This should be kept in mind during clinical management. For this older group particularly, there is a need for new predictors of MPNST such as molecular markers.

Peacock *et al.* FREE *(United States)* explore a new strategy for developing MPNST treatments: molecular-guided therapy prediction. This approach is being developed for MPNSTs in the general population, but could be very useful for NF1 MPNSTs too. Software algorithms are used to analyze previously published microarray data from human MPNST samples and cell lines and from benign neurofibromas. This information is then used to "predict" what drugs might be effective in halting growth of these tumors or cell lines. This new technique predicted very different results for different human MPNST samples in terms of drug target and drug resistance pathways. For example, a subset of MPNST cells express a marker called ABCC1, which renders the cells unresponsive to the chemotherapy agent doxorubicin. This technique could hold promise in identifying the treatments most likely to work for individual cases of MPNST.

PEDF (pigment epithelium-derived factor) is a tumor suppressor protein that occurs naturally in the body. Purified PEDF has previously been shown to make tumor cells differentiate (to become less malignant), and to reduce growth of new blood vessels into tumors, cutting off the energy supply to the tumor thereby limiting its growth. **Demestre *et al.*** CDMRP *(Germany)* explore whether PEDF might have applications in treating MPNSTs. Human tumor cells were grown in a dish or implanted into mice and were treated with PEDF. The tumor cells showed signs of apoptosis (death), and the blood supply to the implanted tumors was reduced. This is the first evidence that PEDF may be effective in treating human MPNSTs. The authors plan to investigate whether PEDF may be developed as a drug therapy.

E. Other Clinical Features of NF1

The Bottom Line: Unique treatment considerations for NF1 gastrointestinal stromal tumors are revealed; links between NF1 and Charcot-Marie-Tooth syndrome and Cushing's Syndrome are examined; cases diagnosed as Jaffe–Campanacci Syndrome may actually be NF1.

Gastrointestinal Stromal Tumors (GIST)

Individuals with NF1 have a six percent lifetime risk of developing gastrointestinal stromal tumors (GISTs). **Doyle and Hornick** *(United States)* reviewed GISTs subtypes and their biology and show that NF1-associated GISTs appear at a younger age than GISTs do in the general population. NF1 GISTs

most commonly develop in the small intestine. There can be multiple primary tumors, which are often mistaken for metastases. It is more likely to find a GIST than a neurofibroma in the NF1 intestinal tract.

NF1-related GISTs are at risk of becoming malignant and need careful clinical management, but this is challenging because they possess unique molecular features that make them difficult to treat. In the general population, ninety percent of GISTs have mutations in the tyrosine kinase receptors *KIT* and *PDGFRA*; these tumors are responsive to Imatinib (Gleevec) treatment, which corrects these signaling pathways. However, NF1-related GISTs generally don't have these mutations and are therefore largely unresponsive to Imatinib. It can be difficult for doctors to determine how to treat NF1-related GISTs.

As an example case, **Hussey *et al.*** FREE *(Ireland)* report on a 65-year-old man with NF1 and presenting with iron-deficiency anemia and melaena (tarry stool). Bowel analyses revealed the presence of a number of tumors, and the small bowel was resected along with other tumors in adjacent parts of the intestines. A number of these tumors were confirmed as GISTs. The tumor cells did not appear to be dividing rapidly; and though there were a number of tumors, because of this low division rate, these were presumed to be multiple individual tumors, and the disease was thought not to be metastatic. Unfortunately, follow up a few months later revealed that the disease was in fact metastatic and had progressed in part of the bowel. The authors note that the fact that the GIST cells were dividing at a low rate seems to be a feature of NF1 GISTs compared to GISTs in the general population. It is important when making treatment decisions for NF1-related GISTs to fully evaluate whether multiple tumors are indeed individual or if they may actually represent metastases.

Links Between NF1 and Other Conditions

Jaffe–Campanacci Syndrome (JCS) is a condition that causes non-ossifying fibromas (abnormal growths) to occur within the long bones and giant cell granulomas within the jawbone, as well as café-au-lait marks on the skin, learning disabilities, precocious puberty, congenital blindness and curvature of the spine. Because many of these features also occur in NF1, it has been speculated (but never confirmed) that JCS is a form of NF1. Previously, only one person with clinical JCS had been found to have an *NF1* mutation.

Stewart *et al.* NIH *(United States)* examined past reports of JCS cases, and carried out mutational analysis on material from some of these past cases as well as from a number of patients who had presented with at least one non-ossifying fibroma. They found germline (suggesting inherited) NF1 mutations in thirteen of fourteen persons analyzed; these were individuals previously thought to have "classical" JCS. Furthermore, the non-ossifying fibromas associated with JCS were found to contain NF1 gene mutations. The group proposes that JCS is in fact, in most cases, actually NF1. There may still be a few "true" JCS cases, and these should be thoroughly evaluated to see if they may be either NF1 or other rare diseases.

Finally, **Rauen** NIH *(Belgium, Canada, The Netherlands, United States)* provides an updated review on the "RASopathies," a term that encompasses inheritable genetic disorders that affect signaling on the RAS cellular pathway and include NF1 and Legius Syndrome. The comparing and contrasting of the RASopathies is helping to shed new light on the biology of each condition and the crossover of drug therapies between these disorders.

2. NF1 Learning & Development

A. NF1 Learning Disabilities

The Bottom Line: Differences in findings of European and United States clinical trials of statin therapy for NF1 learning disabilities may be due to trial design; approaches for early detection of NF1-related learning disabilities are discussed; sleep disorders and learning disabilities in NF1 are investigated; new treatment strategies for NF1 behavioral differences are being developed.

Update on Lovastatin Clinical Trials for NF1 Learning Disabilities

Statin drugs are showing promise as treatments for learning disabilities in children with NF1. Clinical trials to test these drugs began with a 2005 report that Lovasatin improved learning and memory in mice with genetically engineered NF1 learning disabilities. Lovastatin acts by restoring long term potentiation (LTP), a type of brain signaling associated with learning and memory that is disrupted in people with NF1; Lovastatin improves brain function, specifically verbal and non-verbal memory. A national clinical trial for children with NF1 learning disabilities – called the STARS trial - is underway, managed by the Neurofibromatosis Clinical Trials Consortium (www.uab.edu/nfconsortium) CDMRP.

To better understand how Lovastatin works, **Mainberger *et al.*** FREE *(Germany)* used a technique called transcranial magnetic stimulation (TMS), which can monitor changes in LTP. This was measured in people with NF1, before and after a four-day course of Lovastatin or a placebo pill (no drug). The study was blinded, meaning the participants didn't know if they received a drug or a placebo. While LTP plasticity, inhibitory signals, and alertness were all abnormal in these persons before the trial, Lovastatin normalized these signals; the placebo had no effect. This study sheds more light on the mechanism of Lovastatin action.

While the U.S.-based studies of Lovastatin have shown promise in treating NF1 learning disabilities, a similar European trial reported a couple of years ago found no such effects for Simvastatin (a drug equivalent to Lovastatin). In a new study, **Van der Vaart *et al.*** *(Belgium and The Netherlands)* gave over forty children with NF1 between twenty and forty milligrams of Simvastatin, or placebo, daily for twelve months. The authors report that the drug had no effect on intelligence, attention or behavioral problems when compared to the placebo group.

The European group suggests that the positive effects of Lovastatin seen in the U.S. trials may have been a natural improvement of a child's abilities over the duration of time of the study or improvement of a child's ability over time to take the test used to measure learning ability.

To help shed light on the different findings between the European and U.S. trials, **Acosta** *(United States),* a leading expert in the NF1 learning disabilities field, points to the difference in trial design. The outcome measures used to determine whether or not there is a response are particularly important, and different measures were used for the U.S. and European trials. The U.S. trials, for example, used measuring tools developed to parallel the tests used in the original mouse studies; while the mouse was required to swim through a water maze to find a resting platform in the clinical trials, a computerized version of this maze was developed and used as a test for drug efficacy. Dr. Acosta also highlights the importance of international collaboration for clinical trial design and interpretation. Experts hope that what is learned from the statin trials will help pave the way for the future.

(Note: For news of the REiNS Collaboration, a new initiative to encourage collaboration for design of future NF clinical trials, see the Special Focus section in this volume of *The Network Edge.)*

At what age can NF1-related learning disabilities be detected in children? This is an important question, because early detection could allow for interventions to be provided sooner. **Lorenzo *et al.***

CDMRP *(Australia)* examined learning capacity in pre-school age children – around three years old – using an established test format that examined language, visual perception and executive function (the ability to organize information and forward plan). Forty-three children with NF1 and forty-three children from the general population/without NF1 were tested. The findings suggest that pre-school age children with NF1 have poorer intellectual function than children of the same age without NF1. These results were found even when the child's parents were of high IQ and provided an optimal socio-economic environment for learning and development.

These are important findings because they show that NF1-related learning disabilities may be identified before school age, that these are inherent rather than environment-dependent, and that very early educational intervention and special services for children with NF1 may offer the best chance of success to these children.

Learning and behavior can be affected by sleep disorders. This issue has not been well studied in NF1, though in one past report, children with NF1 were recognized to be at increased risk of sleepwalking and night terrors. **Licis *et al.*** NIH *(United States)* studied one hundred and twenty-nine children aged two to seventeen years with NF1 and a comparison group of eighty-nine of their siblings who did not have NF1. The children with NF1 and their siblings had to be sleeping in separate rooms so as not to disturb each other. Parents were asked to complete a questionnaire about their children's sleep habits.

Over half of the children with NF1 had sleep disturbances compared to about forty percent of their siblings. The children with NF1 had more problems going to sleep and maintaining sleep, as well as in waking from sleep, and overall they had more interruptions in sleep and less total sleep than their siblings. The children with NF1 did not have breathing issues during sleep or excessive drowsiness/napping at other times, though, as long as adequate sleep was achieved during the night. This study found small differences but not a solid link between sleep disorders and learning disabilities in the children with NF1. This area will benefit from a broader study of this important issue.

Individuals with NF1 can have an altered brain structure, and this may include an expanded amount of white matter. This is due to the presence of a greater-than-normal amount of myelin, the "insulation" that wraps around nerve fibers in the brain so that they are protected and can function normally. However, neither the biological basis nor the clinical significance of this is known. To address this, **Mayes *et al.*** *(United States)* NIH, CDMRP developed a mouse model in which *NF1* gene function is disrupted specifically in oligodendrocytes, the cells that make myelin in the brain and spinal cord. In this mouse, myelin organization and structure developed abnormally. The cells that make up the blood-brain barrier were also affected, even though the *NF1* gene was working normally in the blood-brain barrier cells. The cause of this was pinpointed to over-activity of enzymes in the white matter called nitric oxide synthases (NOS); when mice were treated with NOS inhibitor drugs, this restored a normal blood-brain barrier. This genetically engineered mouse was also hyperactive, and this behavior was corrected by NOS inhibitor drugs. This research has identified a new aspect of NF1 learning disabilities biology and highlighted NOS targeting as a new potential drug therapy pathway for behavioral abnormalities in NF1.

B. Special Focus: NF1 and Autism

The Bottom Line: The first clinical study to definitively show a link between NF1 and an increased occurrence of autism spectrum disorder has been published.

Autism spectrum disorder (ASD) is a clinical condition with onset in early childhood. Its features include impaired social interactions and communication and repetitive behaviors. ASD affects one to two percent of children in the general population, slightly more boys than girls.

A number of reports in the past few years have linked tumor suppressor gene mutations and ASD. For example, children with the rare disease Tuberous Sclerosis Complex (TSC) have a mutation in the *TSC* gene and can develop tumors as well as ASD. There has been speculation about a similar link between *NF1* gene mutations and ASD but no definitive clinical report.

Now **Garg *et al.*** *(United Kingdom)* report the results of the first population-based systematic analysis of ASD in NF1. The authors examined one hundred and nine persons with NF1 from their Genetic Register aged between four and sixteen years. This group was examined using standardized scales for assessing ASD. The authors report that twenty-five percent of the NF1 group has a diagnosis of ASD, with a further twenty percent having some features of ASD. This means that overall more than forty-five percent of their NF1 population had some features of ASD. There was a slight bias toward males, as would be seen in the general population.

This finding cannot be attributed to learning disabilities, as the testing scale used is very specific to ASD features. The authors suggest that in past clinical studies to look for ASD in NF1, symptoms that were actually representative of ASD were instead interpreted as being due to attention deficit and hyperactivity disorder (ADHD), which is more routinely screened for in NF1 than is ASD.

This is an important publication because it is the first to demonstrate an increased incidence of ASD in NF1 from a population study. The authors caution that this does not mean every child with NF1 needs to be tested for ASD, but they do suggest that clinicians keep ASD in mind as a consideration in NF1. The group suggests that, armed with this new information about ASD, it would be valuable to see if the occurrence of ASD in NF1 correlates with any physical manifestations of NF1 such as differences in brain structure. If so, this might be used to predict the likelihood of ASD so that clinical interventions may be provided.

3. What's New in NF1 Biology?

The Bottom Line: New evidence is presented for the molecular basis of muscle weakness in NF1.

A clinical feature of NF1 that is not well studied is reduced muscle size and strength. This can contribute to bone weakness, but the molecular basis of NF1-related muscle deficits is not understood.

Sullivan *et al.* *(Australia)* address this by studying mouse models in which *NF1* gene function was inactivated in all muscle tissue (called the *Nf1MyoD-/-* mouse). These mice live only a short time, but were found to have abnormal muscle metabolism. The authors then studied a mouse model in which *NF1* gene function was inhibited only in the limbs (called the *Nf1Prx1 -/-* mouse). This mouse had previously been shown to have muscle weakness. The authors showed that these mice also had changes in muscle metabolism, including alterations in fatty acid and lipids, and changes in the levels of the hormone leptin. These changes may contribute to muscle function changes and muscle weakness.

These early-stage findings shed light on the poorly understood area of molecular basis of muscle weakness in NF1. Further research and a search for similar changes in human muscle will hopefully identify any clinical significance of these observations.

4. Special Focus: Social Challenges in Neurofibromatosis

The Bottom Line: Women with NF1 and NF2 have increased social and physical self-consciousness; people with NF1 may have skewed perceptions of their social interactions; alterations in brain structure may offer clues to NF1 social challenges.

Adults with NF can face a range of health challenges, but they may also experience difficulties with social issues such as body image, self esteem and self-consciousness. Some recent publications focus on this under-studied area.

Smith *et al.* *(Canada and United States)* asked seventy nine women with NF1 and forty-two women with NF2 a series of questions about their appearance, self esteem, sexual/bodily and social self-consciousness, and experience with loneliness. For comparison, the survey was also completed by similarly-sized groups of women from the general population/without NF1 and of women who are breast cancer survivors (since these women too have lived with a significant life-impacting health challenge).

Eighty-five percent of women with either NF1 or NF2 reported concerns about their appearance. Women with NF1 or NF2 expressed similar levels of social self-consciousness, and this was greater than what was reported by either the general population or the breast cancer survivors. Increased social self-consciousness was linked to reports of a feeling of loneliness.

Women with NF1 reported a greater level of self-consciousness about sexual/bodily issues than did women with NF2. For the women with either NF1 or NF2, this was linked to reports of having low self-esteem.

When the women with either NF1 or NF2 were reorganized into those who were married/co-habiting and those who were not, the married/co-habiting group expressed a higher level of sexual/bodily self consciousness than those who are not married/co-habiting.

These findings highlight the social and body image challenges that can be faced by women with NF1 or NF2 and the importance of access to counseling and support services. The authors emphasize that this is a cross-sectional study that looks at a “snapshot” of each person’s experience. Future studies will revisit the same individuals over time; this should be informative since the health burden of NF changes over time; it will be interesting to see if social and bodily perceptions change too.

This topic was explored further by **Pride, Crawford *et al.*** *(Australia)*, again using a survey, completed by sixty-two adults with NF1 and one hundred adults from the general population/without NF1. The same survey was also completed by a family member/friend of each NF participant.

Almost half of adults with NF1 - men more so than women - were reported by their family member/friend to have a reduced level of “prosocial behavior” (defined as “taking positive action that benefits others”). Meanwhile, the participants with NF1 reported that their level of prosocial behavior was higher than that reported by their family member/friend. This is interesting because when the group without NF1 is surveyed, they tend to report themselves as being *less* prosocial than reported by their family member/friend. This finding suggests the persons with NF1 have a false perception of their interactions with others.

A subgroup of participants with NF1 was assessed in more depth for signs of learning disabilities or deficits in “social processing” (defined as “ability to read others’ faces and emotions”). Over half of

those with NF1 were found to have some learning disabilities and social processing deficits. They tended to be better at reading negative emotions in others than reading positive emotions in others. Previous studies of children with NF1 have suggested that there is a link between the severity of the NF1 manifestations and the level of social impairment, but no such link was seen in this adult study.

These are interesting findings because they shed light on how persons with NF1 perceive their behavior versus how the world perceives them. The authors of the study suggest that treatment for learning disabilities might also help to improve social behavior for adults with NF1.

Are there structural differences in the NF1 brain that might contribute to social deficits? **Pride, Kongaonkar *et al.*** *(Australia)* assessed a group of twenty-nine adults with NF1 and thirty adults from the general population/without NF1. They used a brain imaging technique called voxel-based morphometry, which helps visualize brain structure. The individuals with NF1 were found to have a smaller amount of gray matter volume in one region of the brain, called the right superior temporal gyrus, than those without NF1. Furthermore, when this structural difference was present, it correlated with a decreased "social processing ability," (defined as "recognizing emotions in others such as anger and sarcasm").

This study suggests a potential link between NF1-related social behavior impairments and brain structure. As this research develops further, examining brain structure might help predict whether someone with NF1 is likely to have social challenges, ensuring that appropriate clinical management may be provided.

5. NF2 Clinical Management

The Bottom Line: Studies in the United Kingdom come to a consensus on decision-making for auditory devices in NF2; improvements in NF2 lifespan are reported; NF2 diagnosis criteria and management are updated.

Three recent papers from the United Kingdom provide updates on a range of NF2 clinical management issues.

Auditory brainstem implants (ABIs) and cochlear implants (CIs) are offered to individuals with NF2 and sufficiently deteriorated hearing such that an implant should improve quality of life. However, for the person with NF2 and that person's clinical care team, the decision path can be complex. In **Tysome *et al.*** *(United Kingdom),* the leading NF2 clinical care units in England present a Consensus Statement that should help with this decision-making process. The Consensus participants included NF2 clinical and surgical team members who created an "algorithm" – essentially a map of questions - to help with this decision making. Algorithm components include audiometry and speech determination tests, analysis of vestibular schwannoma size and rate of growth, and status of cochlear nerve and facial nerve function. For example, if someone is having a tumor surgery and is considering a cochlear implant, then the surgery protocol should be designed to preserve the cochlear nerve. Personal choice is a major consideration for implant selection. Individuals with NF2 should be fully educated on ABI and CI technologies. If a device is selected and implanted, thorough post-operative training and ongoing management is needed. Annual reviews and data collection must be implemented to ensure the device is functioning optimally. The impact of the device on quality of life must be monitored.

This Consensus will augment NF2 clinical care practice in England and may be informative to clinicians and persons with NF2 living in other countries.

It has previously been reported that NF2 reduces life expectancy. In a new study, **Evans and Ingham** FREE *(United Kingdom*) examine this question by reviewing recently published reports. The

authors found that mortality in NF2 is closely linked to the growth of the hallmark NF2 tumors, vestibular schwannomas. Mortality risk is further increased when another NF2 tumor type, meningiomas, are present. Mortality risk is also increased when someone has specific types of genetic mutation, particularly truncating mutations.

Until recently, NF2 treatments were largely limited to surgery and radiotherapy; however, with the advent of targeted biological therapies such as Bevacizumab, NF2 life expectancy is improving. Patient registries that track individuals more closely are also helping to improve life expectancy by gathering useful information about the best approaches for NF2 clinical care and management.

Finally, **Lloyd and Evans** *(United Kingdom)* present a concise update on NF2 diagnosis and management. This includes a review of the current status of knowledge on tumor types and their clinical and drug therapy management, rehabilitation devices (ABIs and CIs, as discussed above), and the genetics of NF2.

6. What's New in NF2 Biology?

The Bottom Line: New candidate drug targets for NF2 treatment include LIMs and PAK; natural compounds could be used as therapies for NF2; the impact of NF2 gene mutations may lead to abnormalities in brain development; insights into how NF2 protein regulates the cell skeleton and the role of this in tumor growth are revealed.

A number of recent publications look at the function of the *NF2* gene and its protein, Merlin, and open potential new avenues for NF2 therapeutic development.

One challenge of developing NF2 drug therapies is identifying molecular targets that might respond to drugs. **Petrilli *et al.*** NIH *(United States)* explore one such target, the LIM domain kinases, LIMK1 and 2. The LIMs regulate the cell cycle; they also regulate the activity of actin filament, structural fibers in the cell which are disrupted in NF2 and believed to contribute to tumor formation. LIMKs are over-expressed in skin, breast, lung, liver and prostate tumors. Petrilli *et al.* found that mouse Schwann cells that lack Merlin have high levels of LIMK1/2; when *NF2* gene function is reintroduced into these cells, LIMK1/2 levels decline. When LIMK is inhibited by introducing the drug BMS-5, the cells start to die. The drug has no effect on normal mouse Schwann cells. BMS-5 seems to slow the cell cycle by decreasing levels of another signal, Aurora A.

Translating these findings to humans, Petrilli *et al.* found that LIMK1 levels are elevated in human schwannomas compared to normal human Schwann cells. Together these findings support the idea that LIMK1/2 hyperactivity may be a driving agent in NF2 tumors, and that targeting this signaling pathway with BMS-5 and similar drugs may be a potential approach for treating NF2 tumors.

It is known that cell signals called p21-activated kinases (PAK) promote tumor growth. The NF2 protein Merlin normally inhibits PAK activity; however, in NF2 tumors, Merlin does not function normally, and PAK is overactive. PAK has therefore been explored as a candidate drug target for NF2 tumor treatment.

Licciulli *et al.* NIH, FREE *(United States)* screened a library of small molecules and identified a molecule called FRAX597 that targets PAK. FRAX597 slows growth of mouse schwannoma cells (these lack a functional *NF2* gene) when these cells are implanted into the mouse sciatic nerve where they form a tumor. These results highlight the promise of PAK inhibitors for NF2 tumor treatment.

Spear *et al.* [NIH] *(United States)* report on two natural compounds that might represent treatments for NF2 tumors. These compounds, Cucurbitacin D and Goyazensolide, were first derived from medicinal plants and trees, and they can stop the growth of human meningioma and mouse schwannoma cells. Cucurbitacin D was isolated from the fruits and stem bark of Elaeocarpus chinensis (Elaeocarpaceae) collected in Vietnam; it is from a family of compounds known to induce cancer cell death and inhibit the JAK-STAT and MAPK signaling pathways. Goyazensolide is a sesquiterpene lactone from the plant Piptocoma rufescens (Asteraceae) collected in the Dominican Republic; it has been shown to have cytotoxic properties. These findings could provide a basis for developing new clinical therapeutics for NF2.

As the brain develops, cells called neural progenitor cells (NPCs) multiply and generate the neurons (nerve cells) and glia (supporting cells) that create the mature brain. It is very important that neurons and glia are generated at the correct rate; if too many are made, developmental abnormalities can arise in the fetus. However, the signals that regulate NPCs are not well understood.

In a mouse study, **Lavado *et al.*** [NIH] *(United States)* found that the *NF2* gene may play a role here, specifically in the area of the early brain that will give rise to the brain structure called the hippocampus (involved in memory formation). *NF2* seems to do this 1) by controlling cell positioning and 2) by determining whether NPCs keep replicating or turn into neurons or glia by regulating two further genes called *Yap* and *Taz*. When *Yap* is over-expressed in NPCs, it causes the hippocampus to develop abnormally as if the *NF2* gene were deleted; but when both *NF2* and *Yap* genes are inactivated, hippocampal development is normal.

These findings have uncovered a somewhat complicated but very important role for the *NF2* gene in early brain development. These findings could also provide avenues to a better understanding of why NF2-related tumors develop and how they may be prevented or treated.

Yin *et al.* [NIH, CDMRP] *(United States)* report new findings on how Merlin operates inside the cell. Recent evidence from *Drosophila* (flies) has suggested Merlin acts in part through another signal, called Hippo. Yin *et al.* show that this also happens in mice, working through a rather elegant mechanism that brings Merlin and Hippo together through the cell's actin cytoskeleton. In humans with NF2, the disruption of this interaction contributes to the formation of tumors.

Looking at Merlin from another perspective, **Qi *et al.*** [NIH] *(United States)* showed that in order to act as a tumor suppressor, Merlin protein has to be sumoylated, which means it has to be bound covalently by a molecule called a small ubiquitin-like modifier. Sumoylation is also important for positioning Merlin correctly in the cell membrane, further regulating its function.

7. Schwannomatosis Update

The Bottom Line: Experience with schwannomatosis in a Chinese clinic is retrospectively analyzed.

Chen *et al.* [FREE] *(China)* present a review of their clinic's experience with schwannomatosis. Of 180 persons who underwent operations for benign schwannomas from 2003 to 2012, four persons were clinically diagnosed with schwannomatosis and four others with suspected schwannomatosis. The group was unable to do genetic testing, so these diagnoses were based on the established clinical guidelines. The average age of diagnosis schwannomatosis was 40. One person had a sister with suspected NF1, but the rest had no family members with multiple tumors.

The schwannomas were well-defined, round or oval. All eight persons with confirmed or suspected schwannomas underwent surgery and were then monitored for between eight to 50 months. Pain disappeared in five persons and was reduced in one. One person had a tumor return over the observation period. Seven persons had no functional loss; one lost function in her ankles, which was attributed to a prior tumor removal surgery conducted by a less experienced clinic. The authors cautioned about the importance of understanding schwannomatosis and not mistaking a schwannoma for another tumor such as a lipoma.

8. NF Genetics Update

The Bottom Line: Scientists are searching for as-yet-unidentified genes that may be implicated in NF1.

Clinical NF1 occurs when someone has a mutation in the *NF1* gene, but there are a small number of people who present with clinical NF1 but have no *NF1* gene mutation. **Hamby *et al.*** FREE *(United Kingdom)* searched for mutations in other genes that may be implicated, focusing initially on genes whose normal role is to regulate *NF1* gene function. The authors sequenced genetic regions suspected to contain such "regulator genes" from 47 individuals who had clinical NF1 but no mutation in the *NF1* gene or in the *SPRED1* gene (the gene associated with NF1-Like Syndrome/Legius Syndrome). The analysis was done using a technique called "chromosome conformation capture." Five persons from the group were found to have variants (gene alterations) in a region called the "H3K27ac-enriched region." This is a very early finding, and the full significance of these variants has yet to be identified. Nevertheless, this paper highlights a new technique that can be used to identify regulatory mutations for NF1 in cases where there is no *NF1* gene mutation.

9. Special Focus: Recommendations from the REiNS Collaboration to Improve Outcome Measures for NF1, NF2 and Schwannomatosis Clinical Trials

The Bottom Line: A new initiative to facilitate international collaboration in designing clinical trial outcome measures provides updates.

As mentioned later in this volume of *The Network Edge,* U.S. clinical trials of statin drugs for treating NF1-related learning disabilities have yielded different results from similar trials done in Europe. This was attributed to likely differences in clinical trial designs, and it highlights a general need in the NF community for coordination of clinical trial design. This is now being addressed with the creation of the REiNS International Collaboration. REiNS stands for "Response Evaluation in Neurofibromatosis and Schwannomatosis," and the goal of the REiNS Collaboration is to develop standardized NF clinical trial design and endpoints that may be used for future trials and would allow direct comparison of trial results. The REiNS Collaboration has now published its first progress update in a series of papers. **Plotkin, Blakeley *et al.*** FREE *(United Kingdom, United States)* provide an overview of the REiNS Collaboration, which is structured into seven Working Groups focused on developing standards for imaging of tumor response; functional, visual, patient-reported, and neurocognitive outcomes; whole-body MRI; and disease biomarkers. Initial reports from these groups are as follows:

- ***Patient Reported Outcomes Group:*** This group's focus includes Quality of Life measures (QoL), and they have been evaluating existing measuring tools for patient-reported outcomes. **Wolters *et al.*** FREE *(United States)* report that the group first focused on evaluating existing tools for monitoring pain. From this analysis, they selected the Numerical Rating Scale-11 as the most optimal for NF clinical trials. This scale is reliable, simple and a can be effectively used in persons from age eight onward.

- ***Visual Outcomes Group:*** This group is exploring how to monitor response for optic pathway glioma (OPG) treatment. Progress to date is presented by **Fisher *et al.*** FREE *(Australia, United Kingdom, United States).* Monitoring options include visual acuity (ophthalmic exam), biomarkers of visual changes and quality of life changes relating to vision. The majority of OPG clinical trials will involve children since these tumors can develop in NF1 in early life. The group determined that visual acuity was the key primary measure to use when monitoring changes in tumor size. Visual acuity has the largest amount of supporting data available from past studies, it can be standardized, and it is reproducible. The group provides a recommended scale for measuring visual acuity changes, as well as some secondary endpoints that may be measured and used. Interestingly, the group decided against using visual evoked potentials (VEPs), which are further discussed later in this volume of *The Network Edge,* as this is still an emerging technique.

- ***Functional Outcomes Group:*** This group's work, as reported by **Plotkin, Ardern-Holmes *et al.*** FREE *(Australia, United Kingdom, United States)*, commenced with a focus on NF2 clinical trials and on the measures of hearing loss and facial weakness. Both are well-recognized markers of NF2 progression and are already used in clinical trials, but there is a lack of agreement in the clinical community on the measurement scales that should be used. For hearing endpoints, maximum word recognition score was selected as a primary endpoint. For facial nerve function, the scaled measurement of improvement in lip excursion (SMILE) system was selected.

- ***Imaging Tumor Response Group:*** This group has been tasked to identify the optimal tool for measuring growth changes in NF tumors. **Dombi *et al.*** NIH, FREE *(Australia, France, Germany, United Kingdom, United States)* report that magnetic resonance imaging (MRI) with volumetric analysis was selected as the best approach for sensitively and reproducibly evaluating changes in tumor size. A 20% volume change will determine a decrease or increase in tumor size. Looking ahead, this group will look for links between tumor size changes and patient-reported outcomes.

In concluding these REiNS updates, **Widemann *et al.*** NIH, FREE invite participation from all additional experts who wish to join the Collaboration. This initial work is very promising and suggests that this structured collaboration will be successful in standardizing NF research clinical trial design. One of the goals of REiNS is to engage with biotech and pharma partners, and with the Food and Drug Administration, to make REiNS protocols the gold standard for all future NF clinical trials. Ongoing REiNS Collaboration updates can be found on the initiative's website, www.reinscollaboration.org.

References

Acosta MT. (2013) Challenges of cognitive research in neurofibromatosis type 1. Lancet Neurol. 2013 12(11):1040-1. doi: 10.1016/S1474-4422(13)70179-0. Epub 2013 Oct 7.

Bano G, Mir F, Beharry N, Wilson P, Hodgson S, Schey S. (2013A Novel Medical Treatment of Cushing's Due to Ectopic ACTH in a Patient With Neurofibromatosis Type 1. Int J Endocrinol Metab. Winter;11(1):52-6. doi: 10.5812/ijem.6898. Epub 2012 Dec 21.

Chen SL, Liu C, Liu B, Yi CJ, Wang ZX, Rong YB, Zhu J, Ding Y, Tian GL. (2013) Schwannomatosis: a new member of neurofibromatosis family. Chin Med J (Engl). Jul;126(14):2656-60.

Demestre M, Terzi MY, Mautner V, Vajkoczy P, Kurtz A, Piña AL. (2013) Effects of pigment epithelium derived factor (PEDF) on malignant peripheral nerve sheath tumours (MPNSTs). J Neurooncol. Sep 28. [Epub ahead of print]

Dombi E, Ardern-Holmes SL, Babovic-Vuksanovic D, Barker FG, Connor S, Evans DG, Fisher MJ, Goutagny S, Harris GJ, Jaramillo D, Karajannis MA, Korf BR, Mautner V, Plotkin SR, Poussaint TY, Robertson K, Shih C-S, Widemann BC for the REiNS International Collaboration (2013) Recommendations for imaging tumor response in neurofibromatosis clinical trials. Neurology November 19, 2013 81:S33-S40

Doyle LA, Hornick JL. (2013) Gastrointestinal Stromal Tumors: From KIT to Succinate Dehydrogenase. Histopathology. Oct 3. doi: 10.1111/his.12302. [Epub ahead of print]

Evans DG, Ingham SL. (2013) Reduced life expectancy seen in hereditary diseases which predispose to early-onset tumors. Appl Clin Genet. Jul 24;6:53-61. doi: 10.2147/TACG.S35605. Print 2013.

Fisher, MJ, Avery, RA, Allen, JC, Ardern-Holmes, SL, Bilaniuk, LT, Ferner, RE, Gutmann, DH, Listernick, R, Martin, S, Nicole J. Ullrich, Grant T. Liu, for the REiNS International Collaboration (2013) Functional outcome measures for NF1-associated optic pathway glioma clinical trials. Neurology November 19, 2013 81:S15-S24

Garg S, Green J, Leadbitter K, Emsley R, Lehtonen A, Evans DG, Huson SM. (2013) Neurofibromatosis Type 1 and Autism Spectrum Disorder. Pediatrics. 2013 Nov 4. [Epub ahead of print]

Golomb MR, Smith JL. (2013) Poor Wound Healing After Pial Synangiosis in 2 Children With Moyamoya Vasculopathy Associated With Neurofibromatosis Type 1. J Child Neurol. Oct 18. [Epub ahead of print]

Hamby SE, Reviriego P, Cooper DN, Upadhyaya M, Chuzhanova N. (2013) Screening in silico predicted remotely acting NF1 gene regulatory elements for mutations in patients with neurofibromatosis type 1. Hum Genomics. Aug 15;7:18. doi: 10.1186/1479-7364-7-18.

Harrison B, Moore AM, Calfee R, Sammer DM. (2013) The association between glomus tumors and neurofibromatosis. J Hand Surg Am. 38(8):1571-4. doi: 10.1016/j.jhsa.2013.05.025. Epub 2013 Jul 9.

Hussey M, Holleran G, McNamara D. (2013) Rapid diagnosis of combined multifocal gastrointestinal stromal tumours and coeliac disease in a patient with type 1 neurofibromatosis. JRSM Short Rep. Jul 1;4(8):2042533313476687. doi: 10.1177/2042533313476687.

Kamran SC, Shinagare AB, Howard SA, Nishino M, Hornick JL, Krajewski KM, Ramaiya NH. (2013) Intrathoracic malignant peripheral nerve sheath tumors: imaging features and implications for management. Radiol Oncol. Jul 30;47(3):230-8. doi: 10.2478/raon-2013-0047.

Kashima TG, Gibbons MR, Whitwell D, Gibbons CL, Bradley KM, Ostlere SJ, Athanasou NA. (2013) Intraosseous schwannoma in schwannomatosis. Skeletal Radiol. Aug 31. [Epub ahead of print]

Kelly JP, Weiss AH. (2013) Detection of tumor progression in optic pathway glioma with and without neurofibromatosis type 1. Neuro Oncol. Oct 6. [Epub ahead of print]

Koethe Y, Widemann BC, Hajjar F, Wood BJ, Venkatesan AM. (2013) PET-guided biopsy with needle navigation facilitates diagnosis of angiosarcoma in neurofibromatosis type 1. Pediatr Blood Cancer. Aug 7. doi: 10.1002/pbc.24668. [Epub ahead of print]

Lavado A, He Y, Paré J, Neale G, Olson EN, Giovannini M, Cao X. (2013) Tumor suppressor Nf2 limits expansion of the neural progenitor pool by inhibiting Yap/Taz transcriptional coactivators. Development. Aug;140(16):3323-34. doi: 10.1242/dev.096537. Epub 2013 Jul 17.

Licciulli S, Maksimoska J, Zhou C, Troutman S, Kota S, Liu Q, Duron S, Campbell D, Chernoff J, Field J, Marmorstein R, Kissil JL. (2013) FRAX597, a small molecule inhibitor of the p21-activated kinases, inhibits tumorigenesis of NF2-associated schwannomas. J Biol Chem. Aug 19. [Epub ahead of print]

Licis AK, Vallorani A, Gao F, Chen C, Lenox J, Yamada KA, Duntley SP, Gutmann DH. (2013) Prevalence of Sleep Disturbances in Children With Neurofibromatosis Type 1. J Child Neurol. Sep 23. [Epub ahead of print]

Lloyd SK, Evans DG. (2013) Neurofibromatosis type 2 (NF2): diagnosis and management. Handb Clin Neurol. 115:957-67. doi: 10.1016/B978-0-444-52902-2.00054-0.

Lorenzo J, Barton B, Arnold SS, North KN. (2013) Cognitive Features that Distinguish Preschool-Age Children with Neurofibromatosis Type 1 from Their Peers: A Matched Case-Control Study. J Pediatr. Aug 1. pii: S0022-3476(13)00797-X. doi: 10.1016/j.jpeds.2013.06.038. [Epub ahead of print]

Mainberger F, Jung NH, Zenker M, Wahlländer U, Freudenberg L, Langer S, Berweck S, Winkler T, Straube A, Heinen F, Granström S, Mautner VF, Lidzba K, Mall V. (2013) Lovastatin improves impaired synaptic plasticity and phasic alertness in patients with neurofibromatosis type 1. BMC Neurol. 13(1):131. [Epub ahead of print]

Marque M, Roubertie A, Jaussent A, Carneiro M, Meunier L, Guillot B, Pinson L, Pinson S, Bessis D. (2013) Nevus anemicus in neurofibromatosis type 1: A potential new diagnostic criterion. J Am Acad Dermatol. 2013 Aug 20. pii: S0190-9622(13)00675-0. doi: 10.1016/j.jaad.2013.06.039. [Epub ahead of print]

Mayes DA, Rizvi TA, Titus-Mitchell H, Oberst R, Ciraolo GM, Vorhees CV, Robinson AP, Miller SD, Cancelas JA, Stemmer-Rachamimov AO, Ratner N. (2013) Nf1 Loss and Ras Hyperactivation in Oligodendrocytes Induce NOS-Driven Defects in Myelin and Vasculature. Cell Rep. 4(6):1197-212. doi: 10.1016/j.celrep.2013.08.011. Epub 2013 Sep 12.

Nguyen R, Jett K, Harris GJ, Cai W, Friedman JM, Mautner VF. (2013) Benign whole body tumor volume is a risk factor for malignant peripheral nerve sheath tumors in neurofibromatosis type 1. J Neurooncol. Oct 29. [Epub ahead of print]

Onu DO, Hunn AW, Peters-Willke J. (2013) Charcot-Marie-Tooth syndrome and neurofibromatosis type 1 with multiple neurofibromas of the entire spinal nerve roots. BMJ Case Rep. 2013 Jul 13. pii: bcr2013010078. doi: 10.1136/bcr-2013-010078.

Ostendorf AP, Gutmann DH, Weisenberg JL. (2013) Epilepsy in individuals with neurofibromatosis type 1. Epilepsia. Aug 29. doi: 10.1111/epi.12348. [Epub ahead of print]

Patel J, Whiting J, Jones D. (2013) Secondary Knee Osteoarthritis due to Neurofibromatosis Type 1 Treated with above the Knee Amputation: A Case Report. Case Rep Orthop. 2013:782106. doi: 10.1155/2013/782106. Epub 2013 Jul 7.

Peacock JD, Cherba D, Kampfschulte K, Smith MK, Monks NR, Webb CP, Steensma M. (2013) Molecular-guided therapy predictions reveal drug resistance phenotypes and treatment alternatives in malignant peripheral nerve sheath tumors. J Transl Med. 17;11(1):213. [Epub ahead of print]

Petrilli A, Copik A, Posadas M, Chang LS, Welling DB, Giovannini M, Fernández-Valle C. (2013) LIM domain kinases as potential therapeutic targets for neurofibromatosis type 2. Oncogene. Aug 12. doi: 10.1038/onc.2013.320. [Epub ahead of print]

Plotkin SR, Ardern-Holmes SL, Barker II FG, Blakeley JO, Evans DG, Ferner RE, Hadlock TA, Halpin C for the REiNS International Collaboration (2013) Hearing and facial function outcomes for neurofibromatosis 2 clinical trials. Neurology November 19, 2013 81:S25-S32

Plotkin SR, Blakeley JO, Dombi E, Fisher MJ, Hanemann CO, Walsh KS, Wolters PL, Widemann BC (2013) Achieving consensus for clinical trials: The REiNS International Collaboration. Neurology November 19, 2013 81:S1-S5

Pride NA, Crawford H, Payne JM, North KN. (2013) Social functioning in adults with neurofibromatosis type 1. Res Dev Disabil. Aug 1;34(10):3393-3399. doi: 10.1016/j.ridd.2013.07.011. [Epub ahead of print]

Pride NA, Korgaonkar MS, Barton B, Payne JM, Vucic S, North KN. (2013) The genetic and neuroanatomical basis of social dysfunction: Lessons from neurofibromatosis type 1. Hum Brain Mapp. Jul 24. doi: 10.1002/hbm.22334. [Epub ahead of print]

Qi Q, Liu X, Brat DJ, Ye K. (2013) Merlin sumoylation is required for its tumor suppressor activity. Oncogene. Oct 28. doi: 10.1038/onc.2013.438. [Epub ahead of print]
Rauen KA. (2013) The RASopathies. Annu Rev Genomics Hum Genet. Aug 31;14:355-69. doi: 10.1146/annurev-genom-091212-153523. Epub 2013 Jul 15.

Sharma R, Wu X, Rhodes SD, Chen S, He Y, Yuan J, Li J, Yang X, Li X, Jiang L, Kim ET, Stevenson DA, Viskochil D, Xu M, Yang FC. (2013) Hyperactive Ras/MAPK signaling is critical for tibial nonunion fracture in neurofibromin-deficient mice. Hum Mol Genet. Jul 24. [Epub ahead of print]

Smith KB, Wang DL, Plotkin SR, Park ER. (2013) Appearance concerns among women with neurofibromatosis: examining sexual/bodily and social self-consciousness. Psychooncology. Jul 19. doi: 10.1002/pon.3350. [Epub ahead of print]

Spear SA, Burns SS, Oblinger JL, Ren Y, Pan L, Kinghorn AD, Welling DB, Chang LS. (2013) Natural Compounds as Potential Treatments of NF2-Deficient Schwannoma and Meningioma: Cucurbitacin D and Goyazensolide. Otol Neurotol. Aug 7. [Epub ahead of print]

Stewart DR, Brems H, Gomes AG, Ruppert SL, Callens T, Williams J, Claes K, Bober MB, Hachen R, Kaban LB, Li H, Lin A, McDonald M, Melancon S, Ortenberg J, Radtke HB, Samson I, Saul RA, Shen J, Siqveland E, Toler TL, van Maarle M, Wallace M, Williams M, Legius E, Messiaen L Jaffe-Campanacci syndrome, revisited: detailed clinical and molecular analyses determine whether patients have neurofibromatosis type 1, coincidental manifestations, or a distinct disorder. Genet Med. Nov 14. doi: 10.1038/gim.2013.163. [Epub ahead of print].

Tysome JR, Axon PR, Donnelly NP, Evans DG, Ferner RE, O'Connor AF, Freeman SR, Gleeson M, Halliday D, Harris F, Jiang D, Kerr R, King A, Knight RD, Lloyd SK, Macfarlane R, Mannion R, Mawman D, O'Driscoll M, Parry A, Ramsden J, Ramsden R, Rutherford SA, Saeed SR, Thomas N, Vanat ZH. (2013) English Consensus Protocol Evaluating Candidacy for Auditory Brainstem and Cochlear Implantation in Neurofibromatosis Type 2. Otol Neurotol. Oct 16. [Epub ahead of print]

van der Vaart T, Plasschaert E, Rietman AB, Renard M, Oostenbrink R, Vogels A, de Wit MC, Descheemaeker MJ, Vergouwe Y, Catsman-Berrevoets CE, Legius E, Elgersma Y, Moll HA. (2013) Simvastatin for cognitive deficits and behavioural problems in patients with neurofibromatosis type 1 (NF1-SIMCODA): a randomised, placebo-controlled trial. Lancet Neurol. 12(11):1076-83. doi: 10.1016/S1474-4422(13)70227-8. Epub 2013 Oct 1.

Van Mierlo C, Spileers W, Legius E, Casteels I, Cassiman C. (2013) Role of visual evoked potentials in the assessment and management of optic pathway gliomas in children. Doc Ophthalmol. Jul 25. [Epub ahead of print]

Widemann BC, Blakeley JO, Dombi E, Fisher MJ, Hanemann CO, Walsh KS, Wolters PL, and Plotkin SR (2013) Conclusions and future directions for the REiNS International Collaboration. Neurology November 19, 2013 81:S41-S44

Wolters, PL, Martin, S, Merker, VL, Gardner, KL, Hingtgen, CM, Tonsgard, JH, Schorry, EK, Baldwin, A. for the REiNS International Collaboration (2013) Patient-reported outcomes in neurofibromatosis and schwannomatosis clinical trials. Neurology November 19, 2013 81:S6-S14.

Yin F, Yu J, Zheng Y, Chen Q, Zhang N, Pan D. (2013) Spatial Organization of Hippo Signaling at the Plasma Membrane Mediated by the Tumor Suppressor Merlin/NF2. Cell. Sep 4. pii: S0092-8674(13)01019-2. doi: 10.1016/j.cell.2013.08.025. [Epub ahead of print]

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