# TheNetworkEdge

The NF Network presents a periodic research review
by science writer, Vanessa L. Merker, PhD

## *The Network Edge* Volume 19: Spring, 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.

**- Federally-Funded Research**: All research identified as being either fully or partly funded by the Congressionally Directed Medical Research Neurofibromatosis Research Program (CDMRP NFRP) or the National Institutes of Health (NIH) is **tagged** CDMRP or NIH after the author name.

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

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

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

### Highlights from Volume 19 of *The Network Edge*:

- **NF1 Clinical Trials:** In Phase II clinical trials, both mirdametinib and cabozantinib shrunk plexiform neurofibromas in 42% of participants (all ages 16+) and seem to have improved participants' tumor-related pain.
- **NF1 Basic Science**: Disrupting *RAC1* gene function helps prevent plexiform neurofibromas from forming in mice, and treatment with mebendazole and celecoxib may help prevent malignant peripheral nerve sheath tumors (MPNSTs) from forming in mice.
- **Clinical Management of NF**: The COVID-19 pandemic delayed appointments and clinical trial enrollment in U.S. NF clinics, but also radically increased the use of telehealth for NF care.
- **NF2 Update:** Researchers determine safe dose of AR-42 (also called REC-2282) for use in future clinical trials; researchers review the signaling pathways affected by *NF2* mutations and how different drugs target these pathways.
- **Schwannomatosis Update:** People being diagnosed with schwannomatosis benefit from education, psychosocial support, and a collaborative relationship with their doctor. Researchers find molecular differences in schwannomas from people with and without schwannomatosis.
- **Quality of Life**: A brief psychosocial intervention delivered over the phone by other people with rare diseases may improve coping skills in adults with NF. Researchers develop a new measure of quality of life specifically for adults with plexiform neurofibromas.

## *The Network Edge*: Volume 19 – Contents

## 1. NF1 Clinical Trials

**The Bottom Line:** Both midrametinib and cabozantib show exciting promise for shrinking plexiform neurofibromas in adolescents and adults with NF1 (age 16 and up). In two Phase 2 clinical trials, both drugs were able to shrink 42% of tumors and also seemed to reduce participants' tumor-related pain.

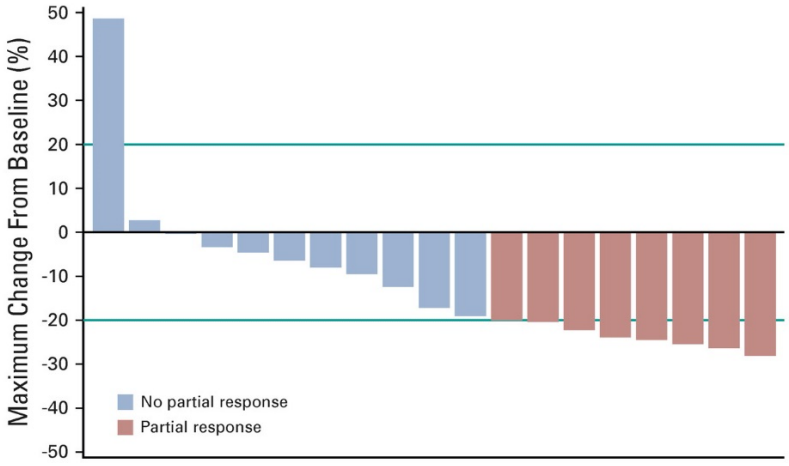
In Volume 19 of the Network Edge, we reported the positive results of a Phase 2 clinical trial of selumetinib (Koselugo) for the treatment of symptomatic plexiform neurofibromas in children with NF1. This trial led to the FDA approval of selumetinib for pediatric patients with NF1 in the U.S., and studies are currently underway to see if selumetinib is equally effective in adults. In parallel with investigations into selumetinib, the CDMRP-funded NF Clinical Trials Consortium has been conducting clinical trials to test whether other drugs can shrink plexiform neurofibromas in older adolescents and adults with NF1.

Here we report the results of two Phase 2 clinical trials for plexiform neurofibromas – one using mirdametinib (a newly developed drug) and one using cabozantinib (a drug that is currently FDA-approved for the treatment of medullary thyroid cancer and kidney cancer). Both clinical trials used very similar designs, eligibility criteria, and outcome measures, which makes it easier to compare their results. These results ended up being remarkably similar, despite the fact that each drug works on a different biological pathway. Mirdametinib is a MEK-inhibitor (just like selumetinib) and cabozantinib is an inhibitor of multiple receptor tyrosine kinases including DDR1, DDR2, AXL, MERTK, and MET.

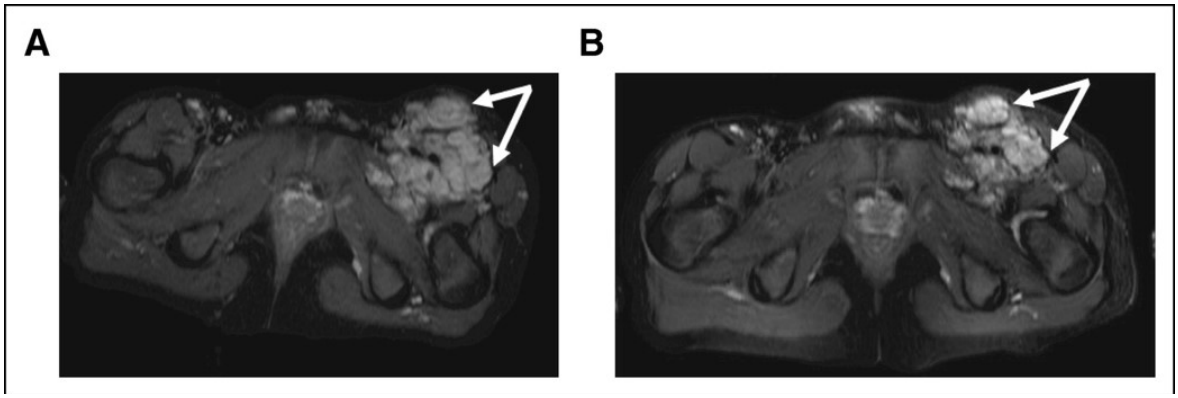
### *a. Clinical Trial of Mirdametinib for Plexiform Neurofibromas in Adults with NF1*

In this Phase 2 clinical trial, **Weiss et al.** [CDMRP] (United States) treated 19 people with NF1, ages 16-39, in the hopes of shrinking their symptomatic or rapidly growing plexiform neurofibromas. Mirdametinib was taken by mouth twice a day on a 3 weeks on, one week off schedule, for up to about 2 years. If a participant's tumor did not shrink by at least 15% in size after about 8 months, or by 20% in size after about 1 year, the participant stopped receiving the treatment at that point in time.

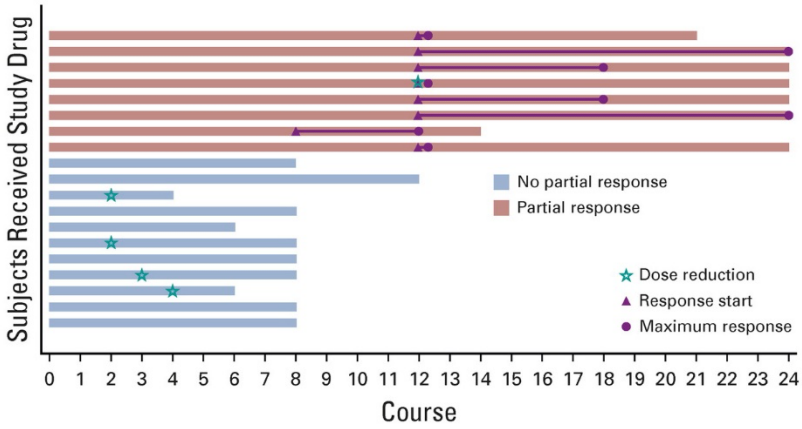
The bar graph below represents the most each person's tumor shrank during the trial. Overall, 8/19 participants (42%) had their tumors shrink by at least 20% in size (shown by the red bars). Ten participants (53%) had tumors that stayed roughly stable in size (9 people with tumors that shrunk less than 20% in size and one person with very minimal growth). One person's tumor grew significantly, by almost 50%, but this person had a rapidly growing tumor before the trial started.



To give an example of what 20% shrinkage in size looks like, the authors shared these MRI images from one of the participants in the trial. The image on the left shows this participant's thigh tumor at the beginning of the trial (when it was 593 mL in size), and the image on the right shows that same tumor after 12 months of treatment (when it was 473 mL in size).




Trial results indicated a slow, cumulative effect of mirdametinib treatment on plexiform neurofibromas. The graph below shows the timeline of treatment for each participant. The length of the bar indicates how long each participant took the study drug (with each course equivalent to roughly one month). The purple triangle shows at what time their tumor first shrunk by at least 20% percent, and the purple circle shows when the tumor was at its smallest size.




As you can see from this graph, most participants whose tumors shrunk by at least 20% needed a full year of treatment to reach this size threshold (shown by purple circles at course 12). This led the researchers to think that some of the participants who stopped treatment at 8 months because their tumor hadn't shrunk by at least 15% yet may have had more tumor shrinkage if they had been treated for a full year. The most anyone's tumor shrunk was 28%, but two people had tumors that were still shrinking at the end of the trial (shown by the purple circles at course 24). So, it is possible that if these two people had been treated for longer, their tumors might have gotten even smaller.

The trial results also suggest that treatment with mirdametinib might improve tumor-related pain. At the beginning of the trial, 16/19 (84%) of participants had tumor-related pain, which was rated on a scale of 0 to 10. The average pain across all participants significantly decreased in the first four months of treatment by 1.74 points, and in the 8 people who had tumors shrink by at least 20%, this decrease was even bigger over time (a decrease of 2.4 points by one year). This decrease in pain was

both statistically significant and has been described as a meaningful improvement by NF1 patients in the past. Patients whose tumors shrunk more than 20% also reported that pain interfered significantly less with their daily activities after one year.

Finally, treatment with mirdametinib was safe but did have some side effects. The most common were acneiform rash (18 participants, 95%), fatigue (11 participants, 58%) and nausea (10 participants, 53%). Four participants chose to stop taking the drug and withdraw from the trial early because of a persistent rash.

Based on the promising results of this trial, a larger Phase II trial of mirdametinib is currently underway for both children and adults with NF1, ages 2+. This trial will recruit 100 people with NF1 across the U.S. to try to confirm whether mirdametinib shrinks plexiform neurofibromas and reduces pain. This larger trial will also explore the effect of treatment on other plexiform neurofibroma symptoms like physical functioning, strength, and appearance. If you would like more information about this trial, please ask your doctor or visit https://www.clinicaltrials.gov/ct2/show/NCT03962543.

*Figures reprinted from "Weiss BD et al. NF106: A Neurofibromatosis Clinical Trials Consortium Phase II Trial of the MEK Inhibitor Mirdametinib (PD-0325901) in Adolescents and Adults With NF1-Related Plexiform Neurofibromas. Journal of Clinical Oncology. 2021. 39797-806." by CC BY 4.0 license.

## *b. Clinical Trial of Cabozantinib for Plexiform Neurofibromas in Adults with NF1*

In this Phase 2 clinical trial, **Fisher et al.** [NIH, CDMRP] (United States) treated 21 people with NF1, ages 16-34, in the hopes of shrinking symptomatic or rapidly growing plexiform neurofibromas. Participants took cabozantinib by mouth once a day. Similar to the mirdametinib trial above, participants could receive treatment for up to almost 2 years. If a participant's tumor did not shrink by at least 15% in size after about 8 months, or by 20% in size after about 1 year, they stopped receiving the treatment at that time.

Nineteen of the 21 participants received at least one month of treatment and were included in the main analysis of the drug's efficacy. Eight of these 19 participants (42%) had their tumors shrink by at least 20% in size. The remaining eleven participants (58%) had tumors that stayed roughly stable in size (7 people with tumors that shrunk less than 20% in size and three people with very minimal growth). Most participants whose tumors shrunk by at least 20% (7 out of 8 people) needed between eight months and a year of treatment to reach this reduced size. The most anyone's tumor shrunk was 38%, although two people still had tumors that were shrinking at the end of the trial, so it is possible if they had been treated for longer, their tumors might have gotten even smaller. Similar to the mirdrametinib trial, this seems to indicate a slow, cumulative effect of treatment for some people who respond to treatment.

It also seemed like treatment with cabozantinib improved tumor-related pain. At the beginning of the trial, 16/19 (84%) of participants had tumor-related pain, which was rated on a scale of 0 to 10. For people whose tumors shrunk by at least 20%, the average pain across the group members decreased by 2.7 points after 4 months on treatment. This decrease persisted over time, and by 12 months on treatment, the average pain across group members was down by 3 points from the beginning of the trial. This decrease in pain was both statistically significant and has been described as a meaningful improvement by NF1 patients in the past. Patients whose tumors shrunk more than 20% also reported that pain interfered significantly less with their daily activities after one year.

Treatment with cabozantinib was relatively safe but did have some bothersome side effects. In the 21 participants who received at least one dose of medication, the most common side effects were diarrhea (17 participants, 81%), asymptomatic hypothyroidism (15 participants, 71%), nausea (14 participants, 67%), fatigue (13 participants, 62%), and hand-foot syndrome (10 participants, 48%). Hand-foot syndrome is a painful condition where people get redness, swelling, and blisters on the palms of their hands and/or the soles of their feet. Two participants in the trial were removed from the trial early due to hand-foot syndrome, and six additional participants chose to stop taking the drug and withdraw from the trial early because of persistent side effects (including hand-foot syndrome, gastrointestinal symptoms, acneiform rash, and change in hair color.)

Based on these results, the NF Clinical Trials Consortium opened a pediatric arm of the trial for children ages 3 to 15 years. This trial enrolled up to 24 children with plexiform neurofibromas, and analysis of this data is currently ongoing. While it seems like cabozantinib was less well tolerated than mirdametinib, these results are still very exciting for highlighting new biological pathways that may be successful in treating symptomatic plexiform neurofibromas (beyond MEK inhibition, which both selumetinib and mirdametinib target).

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

**The Bottom Line:** Most low grade gliomas are benign pilocytic astrocytomas driven only by *NF1* mutations, but a subset of these tumors also have mutations in the *FGFR1* gene. Disrupting *RAC1* gene function helps prevent plexiform neurofibromas from forming in mice, and treatment with mebendazole and celecoxib may help prevent MPNSTs from forming in mice.

### *a. Molecular and Clinical Analysis of Low-Grade Brain Tumors*

Children with NF1 have a higher risk of developing brain tumors than children who don't have NF1. Most of these brain tumors are low-grade gliomas (less aggressive tumors that arise from the support cells that surround neurons in our brains). In people with NF1, most low-grade gliomas occur in the optic pathway and/or hypothalamus, but some occur in the brainstem or other places in the brain. Many of these tumors don't need active treatment, and are just observed carefully. Tumors that do need treatment are rarely surgically biopsied or removed due to the risks of these procedures (and people instead get chemotherapy or other treatments). Because so few people have surgery, there are very few samples of NF1-related low-grade gliomas for researchers to study. This has made it hard to understand the molecular features of these tumors and how they relate to clinical outcomes.

To address this issue, **Fisher, Jones et al.** [NIH] (United States, Germany, Russia, Italy, Sweden) brought together data from 25 medical centers across the world to perform the largest ever integrated analysis of clinical and molecular data for low-grade gliomas in kids with NF1. They collected tumor samples and clinical data from 70 children, ages 1 to 18, with NF1. Despite the fact that optic pathway gliomas are the most commonly occurring low-grade gliomas in NF1, these tumors represented only 27% of the study sample, likely because doctors are less likely to recommend a biopsy/surgery in the optic pathway area. The other gliomas were located in the cortex, cerebellum, brainstem or other locations of the brain.

The researchers confirmed that the vast majority of low-grade gliomas (>85%) were pilocytic astrocytomas, a generally very benign-acting tumor. However, some tumors (7 of 38 tumors that underwent extra molecular analyses) did have signs that could indicate more aggressive behavior. In particular, these tumors had mutations in additional genes beyond *NF1* and/or unusual methylation profiles – the patterns of genes were turned 'on' and 'off' in the tumor. These genetic and epigenetic changes occurred mostly in gliomas that were not in the optic pathway, and did not seem to be associated with participants' ages (so older kids were at no more risk for having these changes.) One of the most interesting changes was mutations in the *FGFR1* gene, which were seen in 3 of the 31 tumors with whole genome sequencing. The researchers did follow-up studies with the cells in the lab and in mice that suggest when both *NF1* and *FGFR1* are mutated, this can lead to increased tumor growth. The authors recommend doing more research in the future to see if drugs targeting *FGFR1* would be helpful for the subset of NF1 patients with these additional mutations.

## *b. Disrupting Genetic Signaling to Prevent Plexiform Neurofibroma Formation in Mice*

People with neurofibromatosis 1 have mutations in the *NF1* gene that lead to loss of the protein neurofibromin and hyperactive RAS signaling. While the excess RAS signaling is the primary driver of neurofibroma tumor formation, it is difficult to target RAS directly with drug treatments. So to indirectly target RAS, researchers are searching for proteins which interact with RAS and may also be more amenable to drug treatment. With this goal in mind, **Mund et al.** FREE, NIH (United States) did a systematic screen of signaling proteins and kinases (molecular switches inside your cells that help turn signaling pathways on or off) that interact with RAS.

The researchers found that the RAC1 protein interacted strongly with RAS. They then observed the function of the *RAC1* gene in human Schwann cells with NF1 mutations (these are the primary cell type that leads to neurofibroma formation). They found that by silencing the *RAC1* gene they could reduce Schwann cell growth. Further experiments in mice showed that deleting the *RAC1* gene could prevent plexiform neurofibromas from growing. A typical mouse with NF1 mutations used in these experiments developed an average of 20 plexiform neurofibromas, but the mice who had both *NF1* and *RAC1* mutations developed zero plexiform neurofibromas. Overall, this study provides proof-of-concept of the important role *RAC1* plays in the formation and growth of plexiform neurofibromas. While there are currently no clinically available drugs targeting RAC1, future research targeting this pathway may reveal an effective strategy to help prevent plexiform neurofibromas.

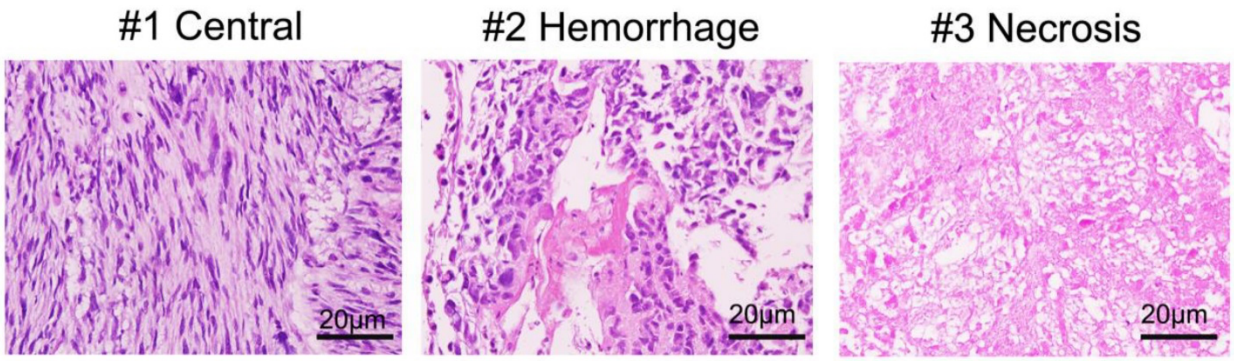
## *c. MPNST Genomics and Model Systems (Special Issue)*

The journal *Genes* published a special issue in November 2020 dedicated to NF1 called "Genomics and Models of Nerve Sheath Tumors." All 10 articles are available for free online at this address: https://www.mdpi.com/journal/genes/special_issues/Nerve_Sheath_Tumors These articles highlight recent advances in understanding the genetic drivers that lead some plexiform neurofibromas to transform into MPNSTs and in creating model systems to study MPNST biology. The introduction by **Hirbe, Dodd, and Pratilas** FREE (United States) outlines the topic of each article included in the special issue. Below, we briefly summarize a few of the included articles.

**Staedke et al.** FREE, NIH, CDMRP (United States) tested whether two drugs - mebendazole and celecoxib, both FDA-approved for non-NF related indications – could help prevent MPNSTs from forming in a mouse model of NF1. The researchers found that these drugs did help delay the formation of MPNSTs in mice at high risk of developing these tumors, thus increasing their overall survival (how long they lived). Interestingly, mebendazole had a greater benefit for male mice, while the combination of mebendazole and celecoxib had a greater benefit for female mice, leading the researchers to suggest future research on sex differences that may affect drug response. While more research is needed to validate whether these drugs would be effective in humans, the results are an exciting demonstration of the feasibility of 'chemoprevention' - using drug treatments to prevent MPNSTs from forming, rather than just treating them once they occur.

**Grit et al.** FREE (United States) studied how MPNSTs in three different genetically engineered mouse models develop resistance to three different drugs – two targeted therapies (the MET-inhibitor capmantinib and the MEK-inhibitor trametinib) and one classic cytotoxic chemotherapy (doxorubicin). The researchers found that activation of the AXL and NFkB pathways were associated with developing resistance to treatment (*i.e.,* when tumors that initially responded to treatment start growing again). This suggests that combining drugs that target these pathways with other treatments may lead to better long-term control of MPNSTs.

**Moon and Tompkins et al.** FREE (United States) performed a comprehensive genomic analysis of three separate areas within a single MPNST resected from a 40-year-old man with NF1. These areas represented a central area of typical solid tumor, a hemorrhagic area (with bleeding), and a necrotic area (where many cells have died). Each of these areas is shown under the microscope below:




The researchers showed that each tumor area had different genetic alterations. This research highlights that if researchers rely on just one tumor sample in their studies, their data might not accurately capture metabolic pathways that are more or less active in different areas of a tumor. Understanding this heterogeneity within tumors is necessary to better predict which tumors will respond to treatments that are targeted at each pathway.

*Figure reprinted from "Moon, C.-I. et al Unmasking Intra-Tumoral Heterogeneity and Clonal Evolution in NF1-MPNST. Genes 2020, 11, 499." by CC BY 4.0 license.

**Miller et al.** FREE (United States, Canada, United Kingdom, Japan) report on the development of the Genomics of MPNST (GeM) consortium, an international effort to perform the largest and most comprehensive analysis of MPNSTs to date. The researchers have collected 96 freshly frozen MPNSTs from 86 people with and without NF1, along with detailed clinical data from the patients, and plan to conduct detailed genetic analyses on each sample. In a subset of 9 people, the researchers will also analyze differences in samples taken from different spatial areas of the tumor and samples taken at different points in time to understand tumor evolution and heterogeneity (discussed by Moon et al. above). The consortium, which is funded by the NF Research Initiative at Boston Children's Hospital, plans to share all the data on a public website to facilitate more collaboration on MPNST research.

A summary of the Phase 1 analyses described above are also shown in the figure below, and include whole genome sequencing (WGS), whole exome sequencing (WES), RNA sequencing (RNA-seq), SNP arrays to analyze copy number variation, and epigenetic profiling (using the EPIC array and bisulfite sequencing) on MPNSTs, blood samples, and normal nerve (when available). The figure also shows Phase 2 analyses that will be performed on already collected samples of MPNSTs and other tumors stored in pathology department archives. In contrast to the freshly frozen tumors in Phase 1, these tumors are older and have been stored as formalin-fixed paraffin embedded samples (FFPE).

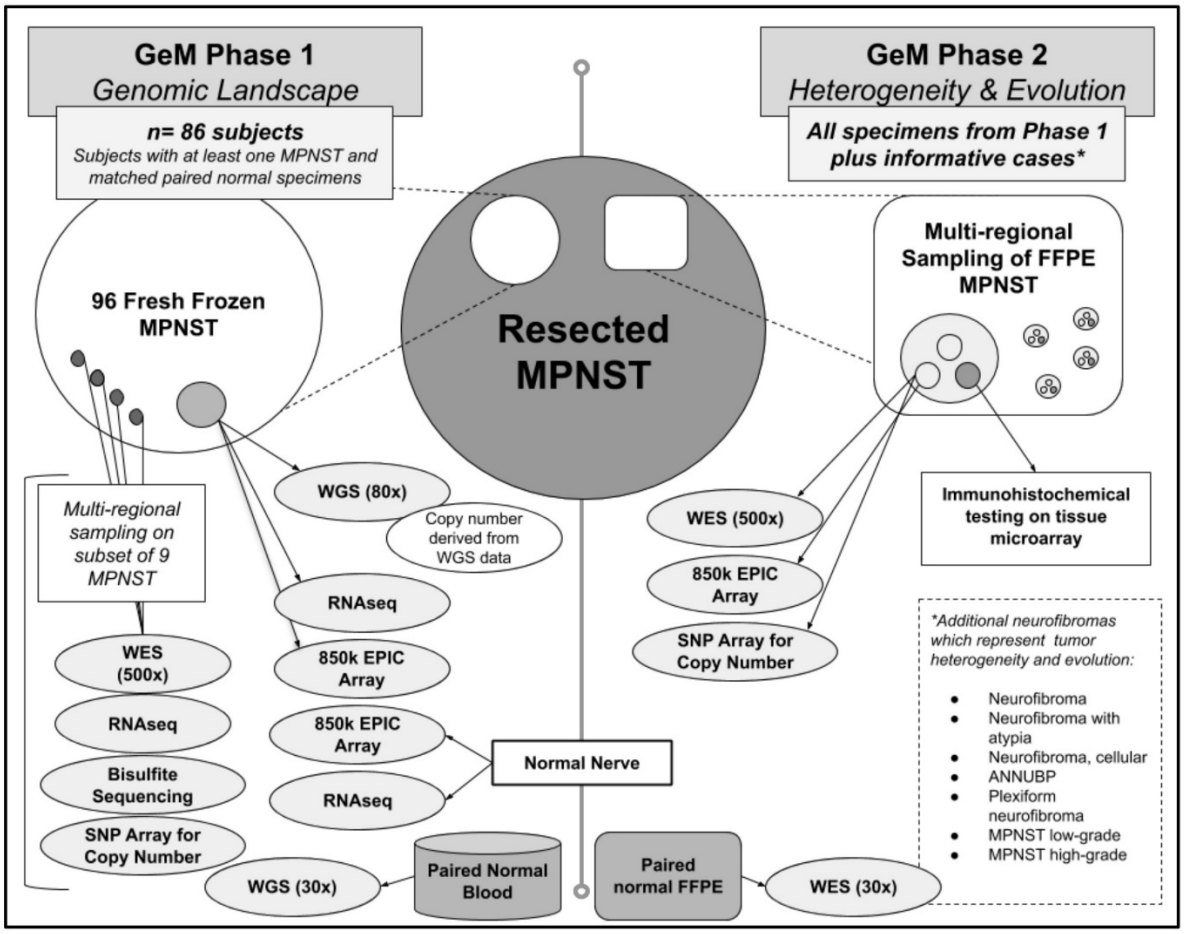



*Figure reprinted form "Miller, D.T. et al. on behalf of the Genomics of MPNST (GeM) Consortium; Genomics of MPNST (GeM) Consortium: Rationale and Study Design for Multi-Omic Characterization of NF1-Associated and Sporadic MPNSTs. Genes 2020, 11, 387." by CC BY 4.0 license.

## 3. Clinical Management of NF1, NF2, and Schwannomatosis

**The Bottom Line:** The COVID-19 pandemic delayed some U.S. NF patients' routine clinic visits, MRIs, and enrollment into clinical trials, but it also radically increased the use of telehealth for NF care. If legal and financial issues can be resolved, most NF clinics plan to continue offering telehealth even after the pandemic ends. We also link to a review of important topics in genetic counseling for NF.

### *a. Impact of the COVID-19 Pandemic on NF Clinics in the United States*

As the first wave of the COVID-19 pandemic hit the U.S. in March 2020, many states issued stay at home orders and many hospitals cancelled in-person appointments for routine or elective care. **Radtke et al.** FREE (United States) surveyed staff at NF clinics across the United States to understand the impact these initial stages of the COVID-19 pandemic had on clinical care for NF.

Clinicians at NF clinics were eligible to participate in this May 2020 survey; staff from 52 clinics responded. Clinics reported a drastic decrease in the estimated number of NF patient appointments in April 2020 compared to pre-pandemic averages. Thirty-four clinics (65%) reported that they saw less than half as many NF patients as usual, even counting any patients who were seen by telehealth instead of in-person. Fortunately, most clinics (92%) were able to see NF patients with urgent issues and could order urgent MRIs, so most of this decrease was in routine appointments.

Unfortunately, however, the COVID-19 pandemic may have delayed patients' access to new drugs and clinical trials. Selumetinib (Koselugo) received official FDA approval during the pandemic, in April 2020. Twelve percent of clinics had to postpone starting new patients on selumetinib until after pandemic restrictions eased. An additional 63% of clinics were waiting until patients' next appointments to discuss potential treatment with selumetinib (and many of these routine appointments were delayed, as noted above). Regarding clinical trials, 43% of clinics had to delay enrolling patients into existing clinical trials and 29% had to delay opening up new clinical trials.

The COVID-19 pandemic also had a major impact on the use of telehealth at NF clinics. Only one of the 52 clinics that responded to the survey had been using telehealth before the pandemic, but by May 2020, all but one NF clinic (51/52, 98%) had started offering telehealth appointments. By May 2020, 42 clinics (82%) were seeing the majority of their patients by telehealth instead of in-person. Sixty-three percent of the survey respondents said they were satisfied or very satisfied with telehealth capabilities. Clinicians were generally satisfied with how easy it was to use telehealth platforms, but many worried about the impact of not being able to do a physical exam with patients. Most NF clinics (84%) said they planned to continue to offer telehealth as an option for NF patients after the pandemic ends, if insurance continued covering it.

Legal regulations that normally limit clinicians' ability to provide care to patients in other states were temporarily eased during the pandemic; it remains to be seen if these restrictions will be permanently lifted in the U.S. If so, the increased access to telehealth spurred by the pandemic may be a silver lining for NF patients, especially those who can't travel to NF clinics in person due to geographic or financial barriers.

*Disclosure: The author of this newsletter is also a co-author of this paper.

### *b. Genetic Counseling Resource*

While not a research article, we at the Network Edge wanted to share a freely available publication by **Radtke et al.** FREE on genetic counseling for NF1, NF2, and schwannomatosis. Designed as a resource for genetic counselors and other healthcare professionals, this publication provides a brief recap of the genetic features of NF, the role of genetic testing in diagnosing NF, and information on reproductive considerations related to genetics. The paper also provides a list of resources for those seeking NF clinical care or patient support groups. Finally, the paper discusses various topics that may be of importance to families, including seeking educational support services, transitioning from pediatric to adult care, and disclosing you have NF to other people. We hope this is an informative article for people interested in what topics genetic counseling might address, and something you can pass on to your local doctors if they want more information about neurofibromatosis.

## 4. NF2 Update

**The Bottom Line:** Researchers determine safe dose of AR-42 (also called REC-2282) for use in future clinical trials; researchers review the signaling pathways affected by NF2 mutations and how different drugs target these pathways.

### *a. Clinical Trial to Establish a Safe Dose for AR-42 in People with NF2 and Other Tumors*

One of the main pathways driving tumor growth in people with NF2 is the PI3K/p-AKT/mTOR pathway, which becomes too active when merlin, the protein encoded by the NF2 gene, is not working correctly. Researchers at the Ohio State University developed a novel drug called AR-42 that helps correct this overactive signaling pathway by reducing p-AKT levels. Early research from **Bush et al.** FREE, NIH, CDMRP (United States) showed that AR-42 could potentially reduce the growth of vestibular schwannoma and meningioma cells in the lab, making it an attractive candidate for NF2 clinical trials. But before new drugs can be tested in large scale clinical trials to see if they are effective, they must go through smaller and shorter Phase 1 trials to make sure they are safe.

**Collier et al.** NIH (United States) designed a Phase 1 clinical trial to determine the maximum dose of AR-42 that was safe for people to take and document what side effects to expect from the medication. The trial enrolled 17 participants: 5 people had NF2, 2 people had non-NF2 related meningiomas, and the remaining participants had a variety of solid tumors, including breast cancer and lung cancer. The researchers gave participants increasing doses of the drug, which they took by mouth on an empty stomach, and then carefully monitored them for side effects. Based on their findings, the researchers recommended future trials use a dose of 60 mg, taken three times a week, on a cycle of three weeks on treatment and one week off treatment. Some of the most common treatment-related side effects were cytopenias - a decrease in the number of blood cells, including low platelets in 13 participants (77%) and low red blood cells in 10 participants (59%). Other common side effects were fatigue (11 participants, 65%) and nausea (10 participants, 59%).

Investigation into AR-42 for use in people with NF2 is still in progress. To better understand how AR-42 acts on tumors in people with NF2, the CDMRP funded a Phase 0 trial of AR-42. This ongoing multi-center clinical trial (NCT02282917) is examining the effects of AR-42 in NF2 patients who were already scheduled to have their vestibular schwannomas or meningiomas surgically removed. These patients take the drug for three weeks before surgery. Then after surgery, the scientists can test their

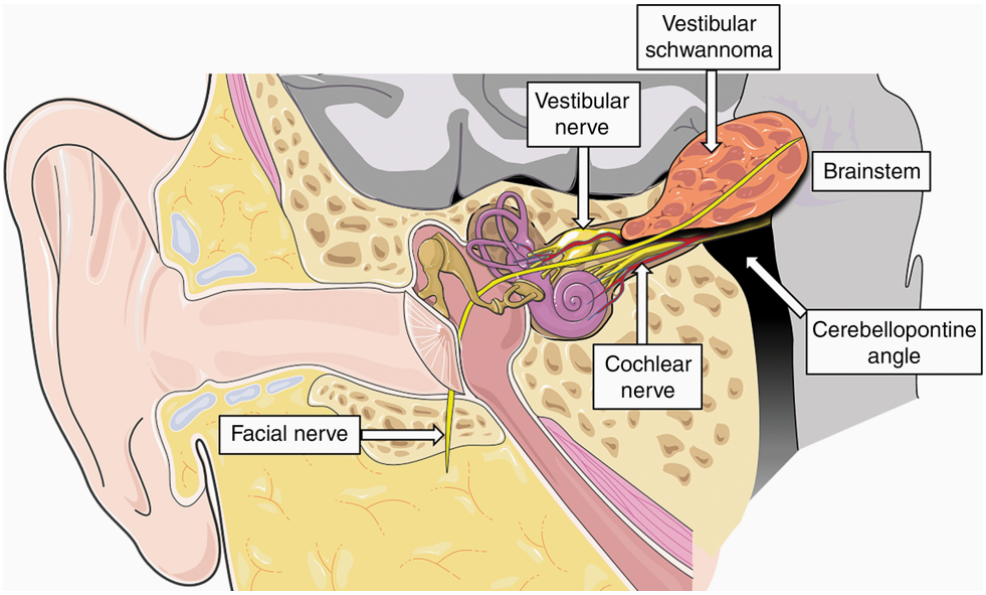
tumor samples to see what concentration of drug reached the tumors and whether it successfully reduced p-AKT levels (as expected based on mouse models).

After the launch of both of the clinical trials described here, AR-42 was licensed by Recursion Pharmaceuticals, and is being developed by its spin-off company, CereXis, as REC-2282. We look forward to future research on REC-2282 from the company, and will share results of the Phase 0 trial in the Network Edge as soon as they are published.

## *b. Reviewing Progress in Treating NF2 Vestibular Schwannoma*

**Ren et al**. FREE, NIH (United States) have published a free review article summarizing the clinical features of and treatment options for vestibular schwannomas in NF2, as well as some exciting ongoing areas of research. We encourage interested readers to check out the full article online, and have reproduced some key figures below.

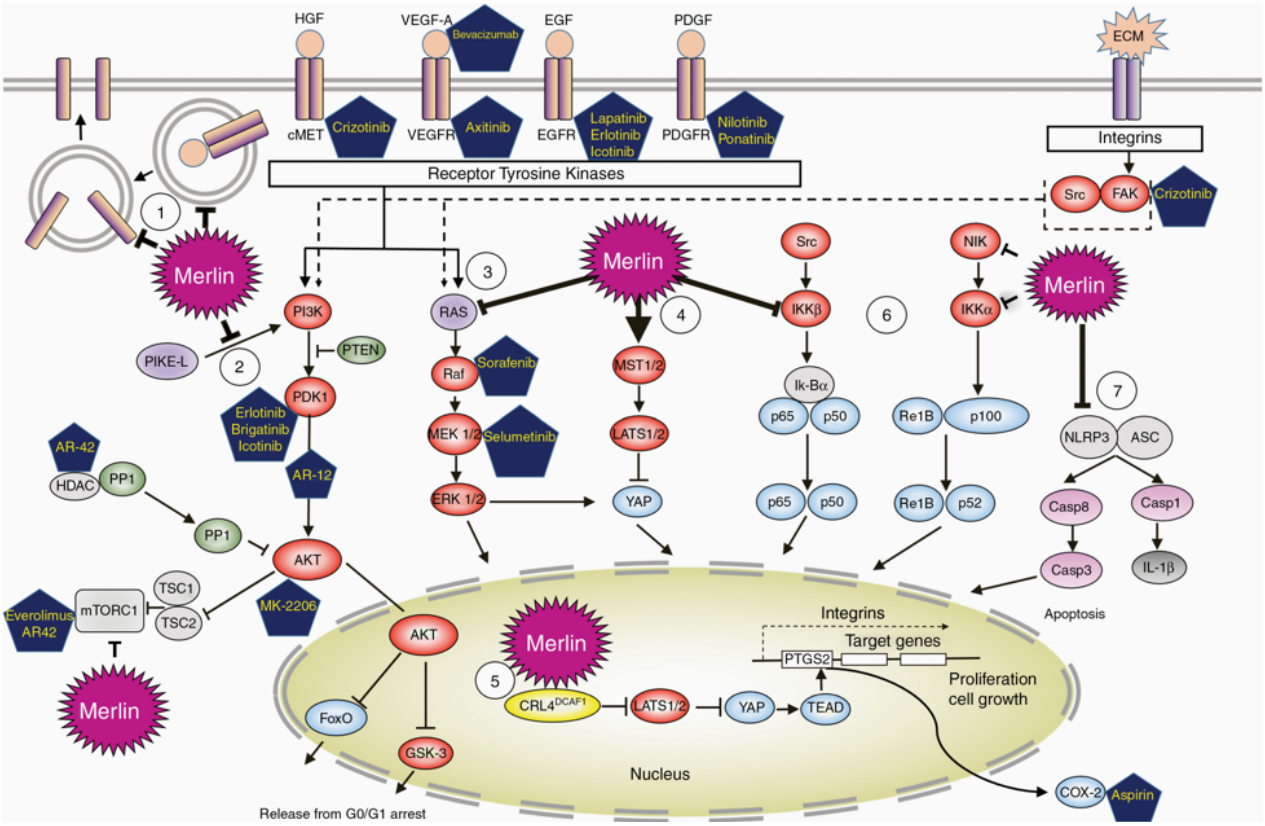
The hallmark tumor of NF2 is vestibular schwannomas, and most people with NF2 develop vestibular schwannomas on both their left and right sides. The following schematic illustrates a vestibular schwannoma arising from a vestibular nerve within the internal auditory canal. Also noted are important nearby nerves (the cochlear nerve that conducts sound and the facial nerve that controls facial movements like smiling) and areas of the brain (the brainstem and the cerebellopontine angle, the space between the cerebellum and the pons.)




These vestibular schwannomas and other NF2-related tumors are caused by mutations in the *NF2* gene, which lead to decreased levels of a protein called merlin. Merlin normally suppresses cell growth and proliferation, so when it is reduced or missing all together, tumors can grow unchecked. Merlin is involved in numerous signaling pathways in the body, including the Ras/Raf/MEK/ERK pathway, the PI3K/Akt/mTORC1 pathway, the NF-kB pathway, and Hippo signaling pathways.

These pathways are depicted in the diagram below. The yellow circle is the cell's nucleus and the double gray lines at the top are the cell wall. The cell wall is punctuated by various receptors (pinkish/lavender double rectangles) that attach to molecules circulating outside the cell (peach circles).

All of the drugs that have been tested to treat NF2-related vestibular schwannomas are shown inside blue pentagons, and some drugs are represented by multiple pentagons because they act on multiple pathways. For example, AR-42, the drug described in the previous article summary, is on the far left of the diagram. AR-42 is an HDAC inhibitor, which then in turn affects the function of PP1, AKT, TSC1 and TSC2, and mTORC1 – the molecule that was directly impacted by the loss of merlin.




As you can see from the diagram above, researchers have tried many different approaches to treat vestibular schwannomas. So far, bevacizumab, everolimus, and lapatinib have had successful clinical trials, but the search continues for drugs that will be effective in the widest range of people with the least side effects. (For a full list of ongoing and completed clinical trials for NF2-related vestibular schwannomas, please see Table 2 in the paper.) The authors also note that gene therapy and immunotherapy are both promising avenues for developing NF2 treatments in the future.

*Note: Both figures reprinted from "Ren Y. New developments in neurofibromatosis type 2 and vestibular schwannoma. Neuro-Oncology Advances, Volume 3, Issue 1, January-December 2021" via CC BY 4.0 license.

## 5. Schwannomatosis Update

**The Bottom Line:** People being diagnosed with schwannomatosis benefit from education, psychosocial support, and a trusting & collaborative relationship with their doctor. Comprehensive molecular analysis finds differences between schwannomas from people with and without schwannomatosis.

### *a. Learning How Doctors Can Better Communicate Schwannomatosis Diagnoses*

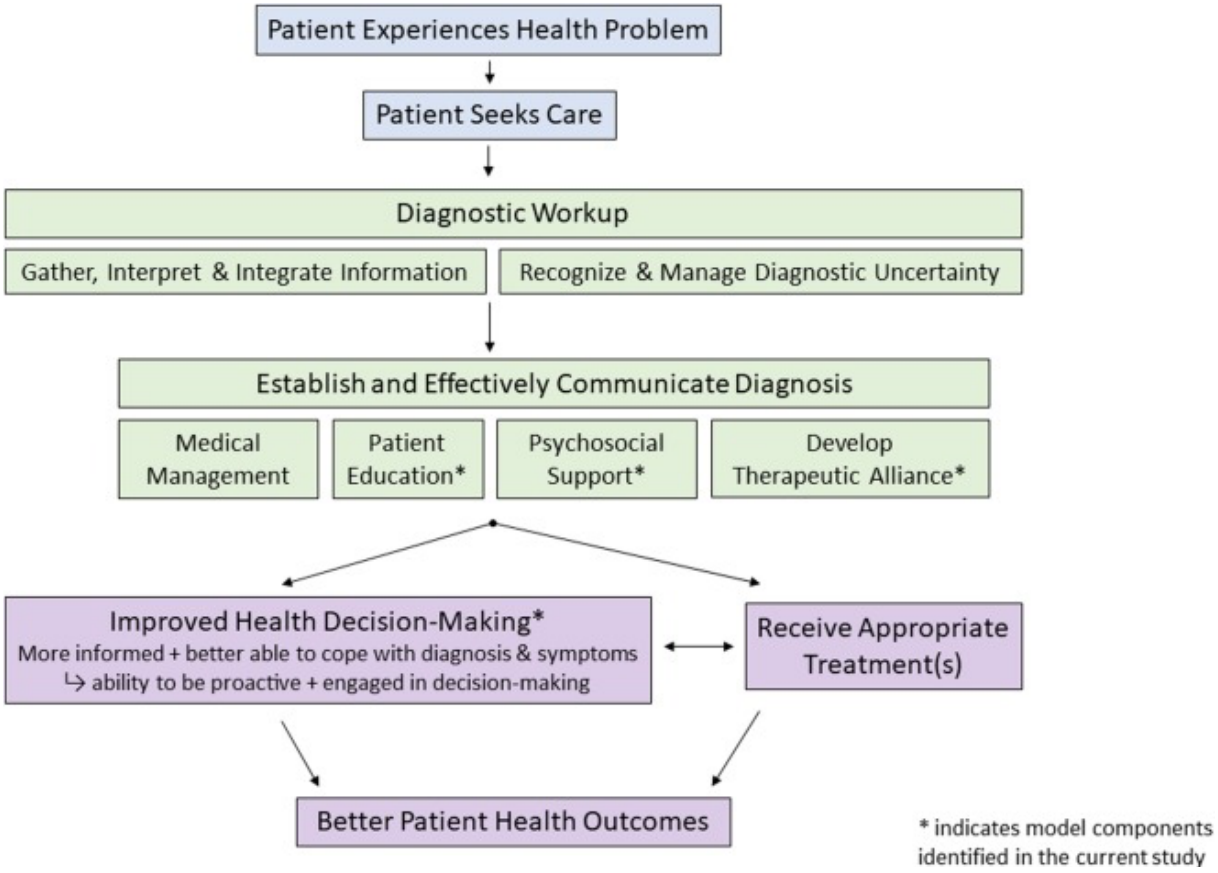
Getting correctly diagnosed can be a long and hard process for people with schwannomatosis, but no qualitative research had ever been done to systematically understand how patients describe their experiences. For this reason, **Merker et al**. FREE, NIH (United States) interviewed 18 people with schwannomatosis from across the United States to learn how clinicians can better work with patients to communicate their diagnosis. Participants in the study were recruited from the International Schwannomatosis Registry, a database of people who have an expert-verified diagnosis of schwannomatosis (http://sid2011.squarespace.com/)

When reflecting about how their doctors first told them about schwannomatosis, participants talked about three major things that were necessary for a good diagnosis experience. The first was in-depth and understandable information about schwannomatosis. This included a description of the symptoms of schwannomatosis and how they might progress over time, information on how schwannomatosis is different from other types of neurofibromatosis (especially if they had been misdiagnosed with NF1 or NF2 before), an explanation of the genetics of schwannomatosis, and an overview of potential treatment options. When this information was not provided, patients could understandably be very distressed and have a hard time figuring out what their next steps should be to monitor their tumors and treat their symptoms. Of particular note, many people were confused about genetics. Some participants didn't know that they could pass down schwannomatosis to their children or that genetic testing can sometimes identify whether their family members also have schwannomatosis. This highlights the need for better access to genetic counseling, both at the time of diagnosis and throughout follow-up when new genes that cause schwannomatosis are discovered.

The second element of a good diagnosis experience was psychosocial support, both in the way their doctor supported people during the clinical visit, and the referrals the doctor made to other sources of support (like psychologists or patient support groups). Some participants appreciated going to see psychologists who helped them adjust to being diagnosed with a chronic and often painful disease. Participants emphasized though that referrals to psychologists were only helpful if it was clear that the medical team didn't think their symptoms were "all in their head." In fact, clinicians who clearly articulated that they believed patients' pain was real and empathetically acknowledged past difficulties participants had with the medical system were highly valued, especially since multiple interviewees had been accused of exaggerating their pain, or stigmatized for their use of pain medications in the past.

The final element of a good diagnosis experience was whether patients had a sense of therapeutic alliance with their doctors – that is, a partnership founded on trust, positive rapport, and collaboration towards shared goals. Especially for patients who had difficult diagnostic journeys – due to difficulty finding care, misdiagnoses, or stigma – being able to trust one's new doctor was key to making all other efforts at education and psychosocial support succeed. And in the reverse, doctors who did the best at explaining information and supporting patients in their efforts to figuring out their next steps were the most able to establish a therapeutic alliance with their patients.

The role of these three elements of diagnosis are shown in the diagram below, which depicts the ideal diagnostic process for schwannomatosis. The actions patients take to seek care are shown in blue, the actions clinicians do to help figure out the correct diagnosis and tell it to their patients are shown in green, and the outcomes of these actions are shown in purple.




Overall, participants who experienced these positive communication attributes were more likely to feel informed and empowered, proactively engage in health decision-making, and feel better able to cope with their symptoms and new diagnosis of schwannomatosis. People with negative communication experiences could have significant psychological distress and potentially poorer health outcomes due to not knowing what monitoring or treatment they should pursue. These findings reinforce the importance of tailored, patient-centered communication strategies when discussing schwannomatosis, and any other rare, genetic, or commonly misdiagnosed disorders.

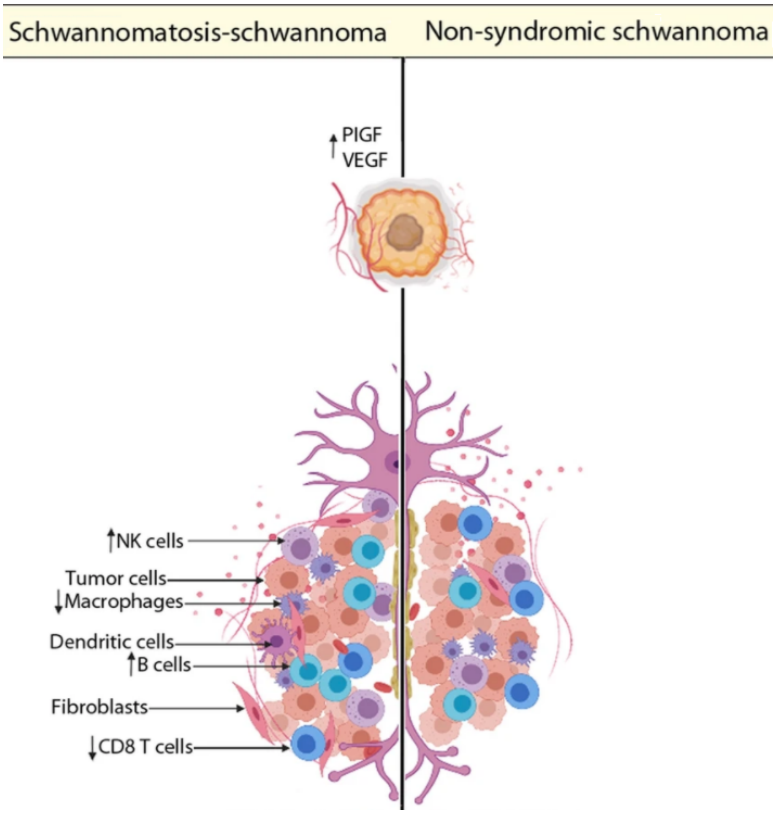
*Disclosure: The author of this newsletter is also the lead author of this paper.

*Note: Figure reprinted from "Merker et al. Effective provider-patient communication of a rare disease diagnosis: A qualitative study of people diagnosed with schwannomatosis. Patient Education and Counseling. 2021. 104(4):808-814." with permission from Elsevier [License 5040470901093].

## *b. Comprehensive Molecular Evaluation of Schwannomatosis-Related Schwannomas*

When viewed under a microscope, schwannomas from people with schwannomatosis, people with NF2, and people with no underlying genetic syndrome are nearly indistinguishable from another. But are they really biologically the same? We know that some people with schwannomatosis have germline genetic mutations in the *SMARCB1* or *LZTR1* gene – that is, mutations present in all the cells in their body. We also know that schwannomas from schwannomatosis patients often have somatic mutations in the *NF2* gene – that is, mutations present just in the tumor cells and not the rest of the person's body. But are there other molecular differences that might be driving tumor formation? And are these molecular features different between schwannomatosis-related schwannomas and other schwannomas?

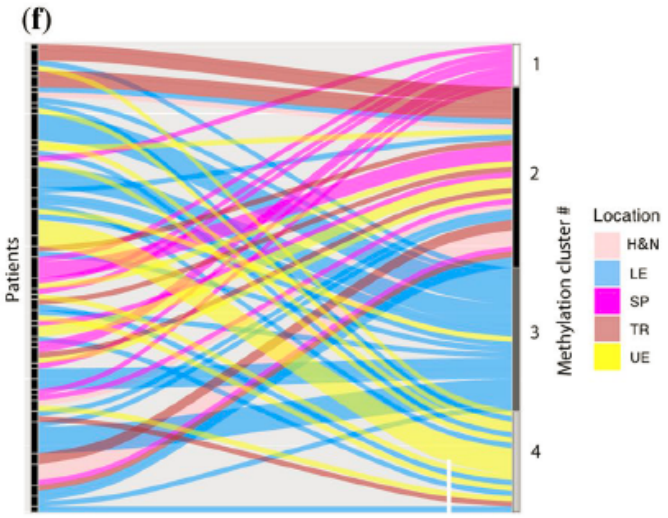
**Mansouri et al**. FREE (Canada, Italy, United States, Argentina) set out to answer this question by undertaking a comprehensive molecular evaluation of 165 schwannomas from 72 people with schwannomatosis. The researchers looked at the tumor cells' DNA (genomics), tags on top of DNA that turn genes on or off (epigenomics), and what DNA is transcribed into RNA (transcriptomics). They compared this data to schwannomas from people without an underlying genetic syndrome, schwannomas from people with NF2, and neurofibromas from people with NF1.




After doing many detailed analyses, the researchers found that schwannomatosis-related schwannomas are indeed very different from other schwannomas. The figure above shows just a few of the changes in schwannomatosis-related schwannomas on the left compared to non-syndromic schwannomas on the right (schwannomas from people without NF2 or schwannomatosis).

Schwannomatosis schwannomas have increased signaling in PIGF and VEGF (which affect the blood supply to the tumor) as well as different numbers of cell types within the tumor (more NK cells and B cells, but fewer macrophages and CD8 T cells). Not shown in this figure are other genetic changes, such as portions of DNA that were deleted, rearranged, or fused together in multiple schwannomatosis-related schwannomas.

Within the schwannomatosis-related samples, the researchers also discovered four distinct subtypes of schwannomas that had unique epigenomic and transcriptomic profiles. Even if multiple tumors were taken from the same person and had very similar DNA (genomics), these tumors had genes that were being "turned on" and transcribed into RNA at different rates. The four tumor subtypes were strongly related to the location in the body from which the tumor came, as depicted in the figure below. Each tumor, arranged in order of the patient it came from, is on the left, and is connected with a colored bar to the subtype of tumors it belongs to. As you can see below, all the tumors in group 1 came from the spine (SP, pink), almost all of the tumors in group 3 came from the lower extremities (LE, blue), and most of the tumors in group 4 came from the upper extremities (UE, yellow). While group 2 was more mixed, almost all of the tumors from the head and neck tumors (H&N, beige) or trunk (TR, brown) are in this group. This suggests that tumors in the different areas of the body may behave differently, and that in the future, we might be able to target treatments to the specific epigenetic subgroup a tumor is in.




Finally, the researchers looked at painful vs. non-painful schwannomas in schwannomatosis patients. They found that painful tumors had higher activation of multiple metabolic pathways - including PIGF, VEGF, MEK, and MTOR – and more mast cells infiltrating the tumor. Mast cells are immune cells living in our connective tissue that are known to be related to pain (see for example, **Chatterjea and Martinov** FREE, NIH). The researchers hope that this information is helpful in identifying effective treatments for schwannomatosis-related pain.

*Note: Figures are adapted from Mansouri, S., Suppiah, S., Mamatjan, Y. et al. Epigenomic, genomic, and transcriptomic landscape of schwannomatosis. Acta Neuropathol 141, 101–116 (2021) and reprinted via CC BY 4.0 license.

## 6. Quality of Life in NF1, NF2, and Schwannomatosis

**The Bottom Line:** A brief psychosocial intervention delivered over the phone by other individuals with NF may improve people's coping skills. Researchers develop a new measure of quality of life specifically for adults with plexiform neurofibromas.

### *a. Clinical Trial of a Peer-Delivered Self Management Intervention for People with NF1 and Other Rare Diseases*

Research has increasingly shown that people with many types of rare diseases face similar psychosocial challenges. For example, **Bogart and Irvin** FREE (United States) conducted a survey of 1218 people across the U.S. with any type of rare disease, and found that participants had worse quality of life on average than people with more common chronic conditions, perhaps due to challenges in getting properly diagnosed and accessing care. Additional analyses of this same survey published by **Bryson and Bogart** (United States) showed that having less stress, more companionship, and more emotional support was associated with being more satisfied with one's life.

Research like this demonstrates the potential of developing psychosocial interventions for people with multiple rare disorders that can be scaled up widely, rather than focusing on only one disorder at a time. It also highlights the potential benefits of programs where people with rare disorders can meet others like themselves for social support. **Depping et al.** (Germany) developed a brief, self-management intervention that accomplished both these goals, and tested it in a randomized controlled trial.

The intervention was six weeks long, and was delivered to people with four different rare diseases: neurofibromatosis type 1, Marfan syndrome, primary sclerosing cholangitis, and pulmonary arterial hypertension. Uniquely, this intervention was delivered by peer counselors – other people with rare diseases who had been hired and trained by the researchers to do counseling sessions with participants. Peer counselors went to a 2-day in-person training to learn the intervention content and practice counseling techniques. They also received written guidelines on what kinds of questions to ask during counseling sessions, and were supervised by a psychotherapist for the first session to make sure it went smoothly. If possible, participants in the trial were matched to a peer counselor with the same rare disease that they had.

The content of the intervention was based on Acceptance and Commitment Therapy - an approach that has been used before to help children and young adults with NF1 and painful plexiform neurofibromas. (See **Martin et al.** FREE, NIH in Volume 12 of the Network Edge for more information.) The intervention had six modules. The first module contained information specific to each rare disease so that patients could reflect on the impact the disease had on their lives. The other five modules were the same for everyone, and covered handling difficult emotions, accepting the things you can't change about your life, reflecting on your values, and setting goals that will help you serve your values. Participants would review one module per week, and then their peer counselor would call them for 30 minutes to discuss the content and provide counseling support. Telephone counseling was chosen instead of in-person to make it easier for people to participate, as both the counselors and the trial participants lived in different places across Germany.

For the clinical trial, 89 adults were randomized to either receive the intervention described above or to only receive their normal medical care. (People randomized to the usual care control group were all offered the chance to participate in the intervention after the clinical trial was completed.) Forty-five people received the intervention (10 of whom had NF1) and 44 people were in the control group (12 of whom had NF1). Overall, participants in the intervention group had higher acceptance of their condition six months after the trial ended compared to those in the control group. The intervention group also scored higher than the control group on measures of their ability to engage in productive coping mechanisms to deal with their disorder, social support, and overall mental health.

Based on these results, it seems that performing brief psychosocial interventions remotely with the support of peer counselors is a useful approach to improving psychosocial outcomes for people with NF and other rare disorders. Hopefully, more interventions with this innovative format will be translated, tested, and scaled up in other countries in the future.

## *b. Development of the PlexiQoL Measure to Assess Quality of Life in Adults with Plexiform Neurofibromas*

Researchers have attempted to measure quality of life in multiple ways. Some measures of health-related quality of life focus on patients' symptoms and functional limitations. For example, in Volume 14 of the Network Edge, we shared the development of two such measures for NF1 – the Pediatric Quality of Life Inventory (PedsQL) NF1 module developed by **Nutakki et al.** (United States), and the Impact of NF1 on Quality of Life (INF1-QOL) developed by **Ferner et al.** FREE (United Kingdom). But other quality of life measures focus on the broader physical, mental, emotional, and social wellbeing of patients. These measures may be influenced by a person's symptoms and functional ability, but expand beyond those concepts to cover people's overall ability to meet their basic human needs. **Heaney et al.** FREE (United Kingdom, United States) recently developed this type of quality of life measure, called the PlexiQoL, to assess the impact of plexiform neurofibromas on adults with NF1.

To develop this measure, the research team conducted interviews with 42 people with NF1 from the U.S. and the U.K. about how plexiform neurofibromas affected their everyday lives. Researchers analyzed what participants said, and came up with 42 questions that corresponded to their concerns. Then, they tested these questions with a separate group of 31 people to ensure that they were clear and easy to understand, and edited the questions as necessary. Finally, the researchers gave the questions in a written survey to 273 people with NF1 in the U.S. and the U.K. and analyzed their responses to see which questions had sufficiently good statistical properties to keep in the final measure.

The final PlexiQol has 18 questions on topics like relationships, independence, ability to fulfill social roles, and ability to enjoy oneself in life. For each question, respondents rate whether a statement is "True" or "Not True" of themselves - for example "I feel I have no control over my illness" or "I am reluctant to leave the house." Overall, the scale was reliable and moderately correlated with other established measures (showing that they all tap into quality of life, while still covering distinct domains). The Plexi-Qol could also successfully distinguish between people with different self-reported levels of general health and people with more or less severe plexiform neurofibromas, and between people who were or weren't taking pain medication. Future research will be needed to see if people's scores change over time when they receive treatment for their plexiform neurofibromas. If it does, this could potentially be used as an outcome measure in NF1 clinical trials to see how treatments impact patients' overall quality of life.

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| NF2 Clinical Trials | X | | X | | | X | X | | X | X | | x | | | | X | | X |
| NF2 Clinical Management | X | X | X | X | X | X | X | X | | X | X | | X | X | X | | X | X |
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