

Neurofibromatosis Research Program

Strategic Plan

INTRODUCTION

The Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas.

In 2015, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine was assembled to evaluate the CDMRP's two-tier review process and its coordination of research priorities with the National Institutes of Health (NIH) and the Department of Veterans Affairs (VA). As part of their final report,¹ the committee recommended that each CDMRP program "... develop a strategic plan that identifies and evaluates research foci, benchmarks for success, and investment opportunities for 3–5 years into the future," and that these strategic plans "should specify the mission of the program, coordination activities with other organizations, research priorities, how those priorities will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives."

In response to these recommendations, this document presents the current strategy for the CDMRP's Neurofibromatosis Research Program (NFRP). The NFRP Strategic Plan identifies the high-impact research goals most important to its stakeholders while providing a framework that is adaptable to changes in the medical research environment to address those goals. This plan has been formulated to provide greater clarity of the program's goals over time to the public and other stakeholders. Funding for the NFRP is Congressionally appropriated on an annual basis; therefore, there is no guarantee of future funding. The NFRP Strategic Plan will be reviewed during the program's annual Vision Setting meeting and updated as necessary.

NFRP BACKGROUND AND OVERVIEW

The NFRP was established in fiscal year 1996 (FY96), when the efforts of neurofibromatosis (NF) advocates led to a Congressional appropriation of \$8 million (M). Since that time, \$332.85M has been appropriated to the program, including \$15M in FY18. Over its 20-year history, the NFRP has invested in key initiatives to support the development of critical resources, sponsor multidisciplinary collaborations, bring talented investigators into the field, and promote the translation of promising ideas into the clinic.

Through the recommendations of the NFRP Programmatic Panel, the NFRP has developed the following vision and mission:

VISION: Decrease the clinical impact of neurofibromatosis

MISSION: Promote research directed toward the understanding, diagnosis, and treatment of NF1, NF2 and schwannomatosis to enhance the quality of life for persons with these disorders that impact Service members, Veterans, and the general public.



FUNDING HISTORY AND NUMBER OF AWARDS

As shown in **Figure 1**, NFRP funding from FY96 to FY18 totaled \$332.9M, resulting in 387 awards to researchers in academia, government, and industry.



Figure 1. NFRP Appropriations and Number* of Awarded Projects

* The number of awarded projects is anticipated for FY17, pending final negotiations, and is to be determined for FY18.

RESEARCH PORTFOLIO AND ACCOMPLISHMENTS

The program's research portfolio includes awards spanning basic, clinical, and population-based research. NFRP investments by scientific area of research are shown in **Figure 2** below. The NFRP has recently focused its efforts on developing therapies to help patients with NF, which is apparent from the increase in investments in clinical trials and clinical and experimental therapeutics in recent years.

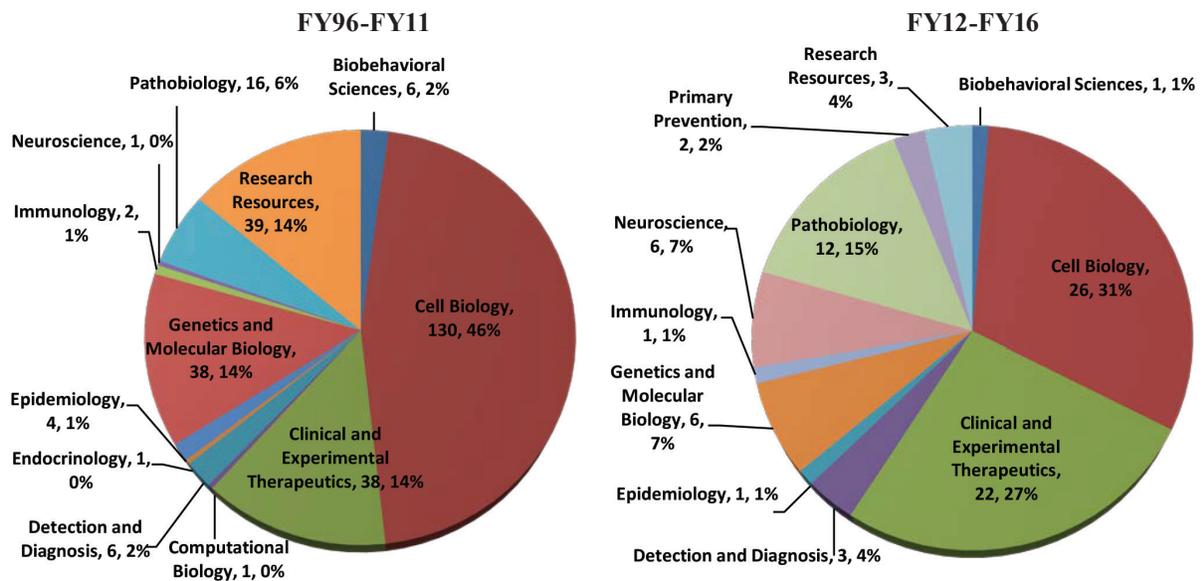


Figure 2. NFRP Investments by Scientific Area of Research

NF consists of three subtypes: neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis, each representing its own set of unique complexities. The NFRP supports research in treatment of all three subtypes. Historically, more funding has gone towards NF1 research, correlating with the state of the science and the number of applications submitted by investigators. However, as shown in **Figure 3**, an increasing number of NF2 projects was funded from FY10 to FY16, reflecting advances in our understanding of NF2 and interest from investigators.

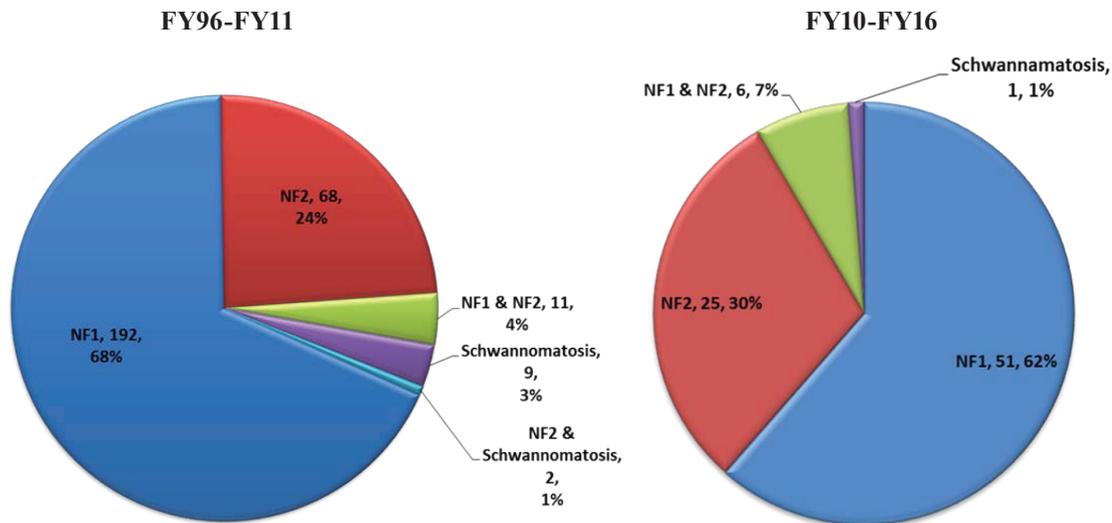


Figure 3. NFRP Investments in NF1, NF2, and Schwannomatosis

SUCCESSSES IN BASIC RESEARCH SUPPORTED BY NFRP

- Comparative Oncogenomics for Peripheral Nerve Sheath Cancer Gene Discovery.** Patients with NF1 often develop malignant peripheral nerve sheath tumors (MPNST). To fill the gap in understanding of MPNST pathogenesis, this project comprehensively characterizes alterations in the genomes and gene expression profiles of peripheral nerve sheath tumors arising in mouse models. The goal is to identify candidate driver genes mediating plexiform neurofibroma pathogenesis and MPNST progression, and thereby identify new therapeutic targets in the equivalent human tumors. Results from this study identified a number of candidate mutations that potentially promote MPNST pathogenesis and established that CD437 and polo-like kinase inhibitors are effective against MPNSTs. This transitional research will lead to refinement of molecular and cellular markers that will serve as new therapeutic targets.
- Exploiting Oncogene Addiction and Synthetic Lethal Phenotypes to Devise Novel Therapeutic Strategies for NF2.** Schwannomas, meningiomas, ependymomas, astrocytomas, gliomas, and other slow-growing tumors respond poorly to cancer therapies that target rapidly dividing cells. Understanding the Merlin (the gene whose mutations are associated with NF2) tumor suppressor functions and targets may lead to more effective therapeutic strategies for slow-growing tumors. This project aimed to identify Merlin downstream targets whose dysregulation is crucial to survival of Merlin mutant tissue and could therefore serve as drug targets. Novel downstream targets of Merlin were identified using a combination of *Drosophila* genetics and mammalian cultured cells. Several of these targets are important for the overgrowth and survival of Merlin mutant tissue and have provided insight on how Merlin regulates the cell cycle and other cellular processes. Understanding the mechanisms of these signaling pathways will have great impact on the field, potentially leading to the development of novel drug therapeutics.

CLINICAL TRIALS

A major focus of the NFRP in recent years has been clinical trials for treatment of NF manifestations. Over \$42M has been invested in 27 clinical trials through the Clinical Trial Award (17 trials), Clinical Consortium Award (9 trials), and New Investigator Award (1 trial) mechanisms. As indicated in **Figure 4**, the trials are spread out across the types of NF, as well as various symptoms of NF.

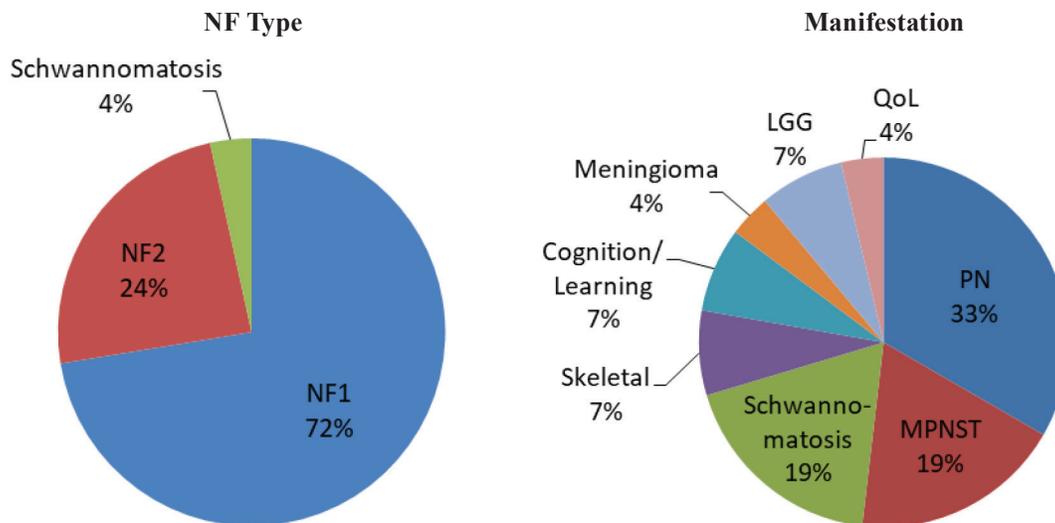


Figure 4. NFRP Investments in Clinical Trials for Treatment of NF1, NF2, and Schwannomatosis by Percentage

SUCCESSSES IN CLINICAL TRIALS

- **Mitogen-Activated Protein Kinase (MEK) Inhibitors.** MEK inhibitors have shown promise in treating various tumor types, including those that occur in NF patients. Multiple organizations, including the NFRP, NIH, Children’s Tumor Foundation (CTF), and industry, have established collaborations and contributed funding in an effort to streamline the development of therapeutics such as MEK inhibitors. The NFRP has supported development from basic science to clinical trials of 16 MEK inhibitors.
- **The NF Clinical Trial Consortium (NFCTC) (<http://www.uab.edu/nfconsortium>).** The NFRP established the NFCTC in FY07 to develop and perform clinical trials for the treatment of NF complications in children and adults. Currently, the consortium is composed of 15 clinical sites, 9 collaborating sites, and an Operations Center at the University of Alabama at Birmingham that provides administrative, data management, and statistical support to the NFCTC. Each of the clinical and collaborating sites has expertise in the treatment and management of NF and an established patient population that is available for clinical trials. The consortium has facilitated the launching of 11 clinical studies and contributed to 6 publications, 16 abstracts, and 26 invited presentations.
- **Other NFRP-Supported Clinical Trials.** The NFRP has supported several clinical trials of potential therapeutics for patients with NF1, NF2, and schwannomatosis including the following:
 - o Hsp90 + mTORi
 - Phase I/II study combines the Hsp90 inhibitor, ganetespib, with the mTOR inhibitor, sirolimus, in patients with sporadic and NF1-related unresectable or metastatic MPNST to assess toxicity, tolerability, and pharmacokinetics for drug combinations with potential uses for Ras-driven refractory tumors
 - o NIS-expressing Measles Virus
 - Phase I clinical trial of intratumoral administration of an NIS-expressing strain of the Measles Virus to patients with locally advanced, recurrent, or unresectable MPNST to develop a well-tolerated therapeutic option for prolonged survival and life expectancy for patients with non-operable MPNST
 - o Computerized Cognitive Training (Cogmed)
 - A multimodal interventional trial assessing the efficacy of a computerized cognitive training program, Cogmed, and stimulant medication for NF1 pediatric patients at high risk for neurocognitive deficits to facilitate treatment of a wider range of patients at an early timepoint, before cognitive deficits affect social and academic functioning



- o High-dose Vitamin D
 - Phase II trial on the effect of high-dose versus low-dose vitamin D supplementation on bone mass in adults with NF1
- o RAD 001
 - Phase II study to assess the safety and efficacy of single-agent Everolimus (RAD001), a novel derivative of rapamycin and an mTORC1 inhibitor, in patients with NF2-related vestibular schwannoma
- o AZD2014
 - Phase II clinical trial assesses the effectiveness and safety profile of a dual mTORC1/mTORC1 inhibitor, AZD2014, in NF2 patients with progressive or symptomatic meningiomas to confirm its ability to stop meningiomas from growing and to improve the quality of life

RESEARCH AND FUNDING ENVIRONMENT

STATE OF THE SCIENCE

Since its inception in FY96, the NFRP has been a critical funding source for NF researchers. These researchers are instrumental in advancing the research and basic understanding of the disease through preclinical and translational research, as well as clinical trials. Considered a rare disorder, NF is more common than cystic fibrosis, muscular dystrophy, Huntington’s disease, and Tay-Sachs disease combined. Due to the heterogeneous nature of the disorder and multitude of clinical manifestations, it is difficult to address all areas adequately.

RESEARCH FUNDING LANDSCAPE

In order to best utilize the funding appropriated annually by Congress, the NFRP Programmatic Panel has recommended funding strategies over the years to address gaps in research while complementing funding by other organizations. As shown in **Figure 5**, the NIH is the largest funder of research on neurological diseases. Other funding organizations include public and private partners, the CTF, and the Neurofibromatosis Therapeutic Acceleration Program (NTAP) at Johns Hopkins University. The funding distribution by the CTF is shown in **Figure 6**. Members of the Programmatic Panel include consumers, researchers, and clinicians, each representing the communities that they serve. Together, the Programmatic Panel recommends a strategy to address the varying needs of the NF community, while leveraging knowledge gathered through collaborations. The NFRP participates in planning and strategic meetings hosted by the NIH, CTF, and NTAP. Members from these organizations also serve on the NFRP Programmatic Panel to ensure appropriate collaboration and identification of research priorities.

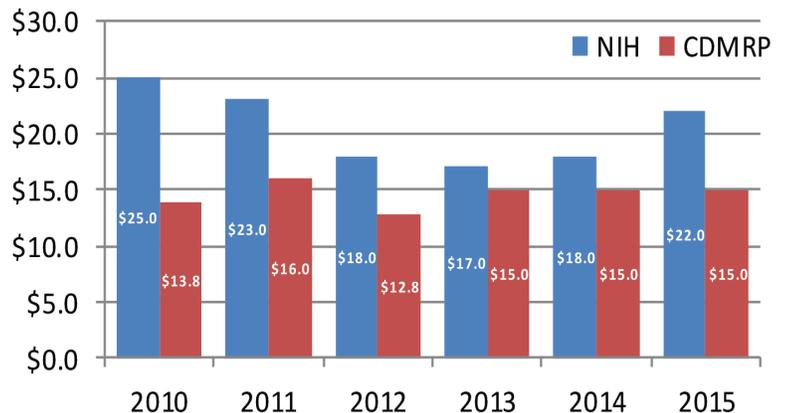


Figure 5. Comparison of NIH and NFRP Funding by Fiscal Year

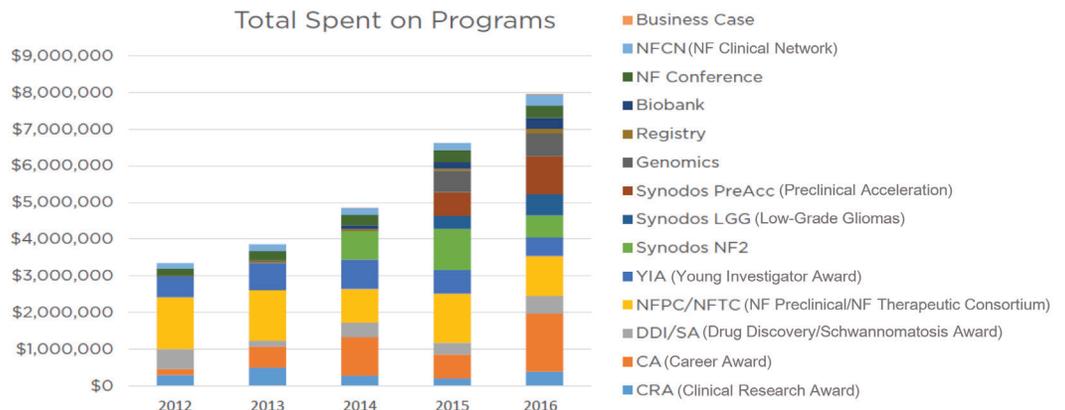


Figure 6. Children’s Tumor Foundation Funding

Graph provided by Children’s Tumor Foundation



RESEARCH GAPS

Each year, the NFRP Programmatic Panel identifies and recommends research gaps and research areas of particular importance to the program, and these are highlighted as Areas of Emphasis in the program announcements. To evaluate the distribution of NFRP funds across these topics, all recent (FY08-FY16) awards were categorized to the FY11-FY16 Areas of Emphasis. Clinical trials and animal model studies were mapped to the most appropriate manifestation (i.e., neoplasms, skeletal maladies, cognitive dysfunction).

The majority of NFRP FY08-FY16 funds were invested in target identification and drug discovery, as well as addressing the heterogeneity of neurofibromas and other NF-related tumors. Among the awards in the neoplasm category, four studies specifically addressed tumor heterogeneity. A large portion (\$14.6M) of the funds allocated to “other” research areas went to a \$9M FY11 NFRP Clinical Trials Consortium Award, as well as a \$5.6M FY16 NFRP Clinical Consortium Award that includes support for both clinical trials and consortium infrastructure.

For reference, the NFRP’s Areas of Emphasis through the years of the program are summarized in **Table 1** below.

NFRP Areas of Emphasis	FY08–FY16 Awards	FY08–FY16 Investment
Novel disease response & treatment biomarkers	15	\$9,001,021
Cerebrovascular abnormalities and cardiovascular disease	2	\$1,649,243
Clinical trial metrics, including standardization of imaging techniques and quality of life measures	1	\$ 107,956
Cognitive and social dysfunction, including learning disabilities	10	\$5,972,239
Target identification and drug discovery for NF	49	\$28,297,986
Effects of aging	0	\$0
Epigenetics in causation or progression of NF-associated abnormalities	4	\$1,822,180
Health services research for NF	2	\$2,622,432
Hormone-associated effects	0	\$0
Heterogeneity of neurofibromas and other NF related tumors	37	\$19,384,300
Nerve regeneration	1	\$755,164
Nutritional, environmental, and other modifiers of NF	1	\$681,586
Pain	6	\$2,543,023
Plexiform and dermal neurofibromas	4	\$3,109,560
Post-adolescence manifestations of NF	4	\$2,388,694
Skeletal maladies	5	\$3,411,084
Stress and inflammation	1	\$1,022,508
Wound repair	0	\$0
Other	15	\$22,777,896

Table 1. NFRP Areas of Emphasis FY08-FY16



STRATEGIC DIRECTION

The strategic direction for the NFRP is based on the current research gaps in the NF community. The following gaps have been discussed by the NFRP and the NF community and represent the most pressing research priorities, capability gaps, and NF community needs:

- Gaps in basic research
 - o Lack of support for the development of new concepts and ideas
 - o Lack of preclinical studies
 - o Lack of drug testing
- Lack of preclinical testing models mimicking the human condition
- Gaps in clinical trials infrastructure
- Small research community
- Lack of adequate support from biopharmaceutical companies

STRATEGIC GOALS

To better provide an overall perspective to the stakeholders, the NFRP has identified the following strategic goals to address the near- and long-term gaps and needs for the NF community of researchers, clinicians, and consumers.

1. Foster Basic and Exploratory Research

Increasing understanding of the underlying causes of NF1, NF2, and schwannomatosis is vital to identifying potential therapeutics. As such, the NFRP will continue supporting basic research that seeks to better understand the underlying mechanisms that lead to tumor formation and non-tumor manifestations.

2. Facilitate Rapid Testing of Potential Therapeutics

As basic research progresses toward better understanding of NF pathogenesis, potential therapeutic targets will be identified. Supporting the transition of findings through preclinical and clinical testing of promising interventions is needed.

3. Increase Research Capacity

As NF is considered a rare disorder, there are limited resources to support research, including an adequate number of investigators. In addition, investment from the biopharmaceutical industry in NF research is also limited due to the market size for potential therapeutics.

4. Encourage Research in Areas of Critical Interest to NF Patients

Each of the NF disorders (NF1, NF2, and schwannomatosis) is genetically and biologically distinct, resulting in a multitude of clinical manifestations that affect patients. Research in some areas is seen as more critical than others, while some areas remain underrepresented.

INVESTMENT STRATEGY

NEAR- TO LONG-TERM

• Fund innovation, new ideas, and generate preliminary data

The NFRP will provide funding to explore new ideas, pursue innovative ideas, and generate preliminary data that will form the basis of more hypothesis-driven research initiatives. Funding opportunities will be designed to encourage pursuing such research. The NFRP Investigator-Initiated Research Award and Exploration-Hypothesis Development Award were designed to provide opportunities for investigators to pursue innovative ideas based on sound scientific rationale. In the short term, such funding provides for development of preliminary data that can be utilized as the foundation of more robust, hypothesis-driven projects.

Basic laboratory research that is built on sound preliminary data and rigorous scientific methodology is essential to elucidating pathogenesis of the multiple NF manifestations. Although basic research may take years to achieve success, investments in such research are vital to forming the basis of ideas that have translational potential leading toward clinical interventions.



- **Support the transition of findings through preclinical and clinical testing of promising interventions**
The NFRP will help populate and improve the pipeline to clinical application by supporting preclinical studies of promising agents.
The NFCTC was established to rapidly develop and conduct clinical trials across an established network of NF clinical centers. The NFRP will continue monitoring and supporting the NFCTC's initiatives.
The NFRP will support independent clinical trials outside the NFCTC to encourage the design and conduct smaller-scale trials that do not typically require multiple sites or cross-disciplinary expertise.
- **Increase the number of NF investigators and resources**
The NFRP will support research conducted by promising early-stage investigators, recruit established investigators from other fields into NF research, and facilitate collaborations between academia and industry.
- **Develop areas of emphasis**
In order to address potential gaps in NF research, the NFRP will annually identify specific areas of emphasis to encourage investigations in these areas.

MEASURING PROGRESS

NEAR-TERM OUTCOMES (1 – 5 YEARS)

- Track the number of applications received in response to the Areas of Emphasis versus the number of applications funded
- Track the number outcomes from recruited investigators, such as the number of publications and patents in NF-related research
- Track the percentage of early-stage investigators conducting NF research 5 years after the end of their NFRP-supported award
- Track awards and collaborations supported by the NFRP between academia and industry

LONG-TERM OUTCOMES (6 – 10 YEARS)

- Track the number of applications received in response to the Areas of Emphasis versus the number of applications funded
- Track the number outcomes from recruited investigators, such as the number of publications and patents in NF-related research
- Track awards and collaborations supported by the NFRP between academia and industry
- Assess the investment in potential therapeutic targets, identify roadblocks, and track successes
- Assess the number of initiated clinical trials and new tools, integrating different activities from basic biology to the clinic
- Utilize an assessment of publications, patents, and follow-on awards to quantify a return on investment and contributions to advancing NF research

REFERENCES

1. *Evaluation of the Congressionally Directed Medical Research Programs Review Process*. 2016. The National Academies of Sciences, Engineering, and Medicine. The National Academies Press. Washington, DC.