Testimony Submitted to the House Appropriations Subcommittee on Defense
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Thank you, Mr. Chairman, for the opportunity to submit testimony to the Subcommittee on the importance of continued funding for Neurofibromatosis (NF), a terrible genetic disorder closely linked to many common diseases widespread among the American population.

On behalf of Neurofibromatosis, Inc., Northeast, a participant in a national coalition of NF advocacy groups, I speak on behalf of the 100,000 Americans who suffer from NF as well as approximately 175 million Americans who suffer from diseases linked to NF such as cancer, brain tumors, heart disease, memory loss and learning disabilities.

Mr. Chairman, I am requesting increased support, in the amount of **$20 million**, **to continue the Army's highly successful Neurofibromatosis Research Program (NFRP),** which is now conducting clinical trials at nation-wide clinical trials centers created by NFRP funding. These clinical trials involve drugs that have already succeeded in eliminating tumors in humans and rescuing learning deficits in mice. Administrators of the Army program have stated that the number of high-quality scientific applications justify a much larger program.

What is Neurofibromatosis (NF)?
NF is a genetic disorder involving the uncontrolled growth of tumors along the nervous system which can result in terrible disfigurement, deformity, deafness, blindness, brain tumors, cancer, and/or death. NF can also cause other abnormalities such as unsightly benign tumors across the entire body and bone deformities. In addition, approximately one-half of children with NF suffer from learning disabilities. While not all NF patients suffer from the most severe symptoms, all NF patients and their families live with the uncertainty of not knowing whether they will be seriously affected because NF is a highly variable and progressive disease.

NF is not rare. It is three times more common than Muscular Dystrophy and Cystic Fibrosis combined, but is not widely known because it has been poorly diagnosed for many years. Approximately 100,000 Americans have NF, and it appears in approximately one in every 2,500 births. It strikes worldwide, without regard to gender, race or ethnicity. Approximately 50 percent of new NF cases result from a spontaneous mutation in an individual's genes, and 50 percent are inherited. There are two types of NF: NF1, which is more common, and NF2, which primarily involves tumors causing deafness and balance problems. In addition, advances in NF research stand to benefit over 175 million Americans in this generation alone because NF, the most common neurological disorder caused by a single gene, is directly linked to many of the most common diseases affecting the general population.

NF's Connection to the Military
Research on NF stands to benefit the military because this disorder is closely linked to cancer, brain tumors, learning disabilities, brain tissue degeneration, nervous system degeneration, deafness, memory loss, and balance. Because NF manifests itself in the nervous system, findings generated by the Army-supported research on NF address peripheral nerve regeneration after injury from such things as missile wounds and chemical toxins, and is important to gaining a

better understanding of wound healing and war-related illnesses. In addition, NF research now includes important investigations into genetic mechanisms which involve not just the nervous system but also other cancers.

Link to Other Illnesses

Researchers have determined that NF is closely linked to cancer, heart disease, learning disabilities, memory loss, brain tumors, and other disorders including deafness, blindness and orthopedic disorders, primarily because NF regulates important pathways common to these other disorders such as the RAS, cAMP and PAK pathways. Research on NF therefore stands to benefit millions of Americans:

Cancer – NF is closely linked to many of the most common forms of human cancer, affecting approximately 65 million Americans, because of its tumor suppresser function. Research has demonstrated that NF's tumor suppressor protein, neurofibromin, inhibits RAS, one of the major malignancy causing growth proteins involved in 30 percent of all cancer. Accordingly, advances in NF research may well lead to treatments and cures not only for NF patients but for all those who suffer from cancer and tumor-related disorders. Similar studies have also linked epidermal growth factor receptor (EGF-R) to malignant peripheral nerve sheath tumors (MPNSTs), a form of cancer which disproportionately strikes NF patients.

Heart disease – Researchers have demonstrated that mice completely lacking in NF1 have congenital heart disease that involves the endocardial cushions which form in the valves of the heart. This is because the same *ras* involved in cancer also causes heart valves to close. Neurofibromin, the protein produced by a normal NF1 gene, suppresses *ras*, thus opening up the heart valve. Promising new research has also connected NF1 to cells lining the blood vessels of the heart, with implications for other vascular disorders including hypertension, which affects approximately 50 million Americans. Researchers believe that further understanding of how an NF1 deficiency leads to heart disease may help to unravel molecular pathways involved in genetic and environmental causes of heart disease.

Learning disabilities – Learning disabilities are the most common neurological complication in children with NF1. Research aimed at rescuing learning deficits in children with NF could open the door to treatments affecting 35 million Americans and 5 percent of the world's population who also suffer from learning disabilities. Leading researchers have already rescued learning deficits in both mice and fruit flies with NF1 with a number of drugs, and clinical trials have now been approved by the FDA. This NF research could potentially save federal, state, and local governments, as well as school districts billions of dollars annually in special education costs resulting from a treatment for learning disabilities. It also holds enormous implications for understanding and treating associated social and behavioral problems in children who suffer from learning disabilities.

Memory Loss – Researchers have also determined that NF is closely linked to memory loss and are now investigating conducting clinical trials with drugs that may not only cure NF's cognitive disorders but also result in treating memory loss as well with enormous implications for patients who suffer from Alzheimer's disease and other dementias. Indeed, one leading Army funded researcher is pursuing parallel research into both NF and Alzheimer's simultaneously.

Deafness – NF2 accounts for approximately 5 percent of genetic forms of deafness. It is also related to other types of tumors, including schwannomas and meningiomas, as well as being a major cause of balance problems.

The Army's Contribution to NF Research

Recognizing NF's importance to both the military and to the general population, Congress has given the Army's NF Research Program strong bipartisan support. After the initial three-year grants were successfully completed, Congress appropriated continued funding for the Army NF Research Program on an annual basis. From FY96 through FY10, this funding has amounted to $214.05 million, in addition to the original $8 million appropriation in FY92. In addition, between FY96 and FY09, 243 awards have been granted to researchers across the country.

The Army program funds innovative, groundbreaking research which would not otherwise have been pursued, and has produced major advances in NF research, including conducting clinical trials in a nation-wide clinical trials infrastructure created by NFRP funding, development of advanced animal models, and preclinical therapeutic experimentation. In addition, the program has brought new researchers into the field of NF. Unfortunately, despite this progress the number of awards has decreased over the last several years due to a decrease in funding levels, resulting in many highly qualified applications going unfunded. Army officials administering this program have indicated that they could easily fund more applications if funding were available because of the high quality of the research applications received.

In order to ensure maximum efficiency, the Army collaborates closely with other federal agencies that are involved in NF research, such as the National Institutes of Health (NIH). Senior program staff from the National Institute of Neurological Disorders and Stroke (NINDS), for example, sits on the Army's NF Research Program Integration Panel which sets the long-term vision and funding strategies for the program. This assures the highest scientific standard for research funding, efficiency and coordination while avoiding duplication or overlapping of research efforts.

Because of the enormous advances that have been made as a result of the Army's NF Research Program, research in NF has truly become one of the great success stories in the current revolution in molecular genetics. Accordingly, many medical researchers believe that NF should serve as a model to study all diseases. Indeed, since the discovery of the NF1 gene in 1990, researchers are now on the threshold of developing a treatment and cure for this terrible disease.

Thanks in large measure to this Subcommittee's support; scientists have made enormous progress since the discovery of the NF1 gene. Major advances in just the past few years have ushered in an exciting era of clinical and translational research in NF with broad implications for the general population. These recent advances have included:

- Phase II and Phase III clinical trials involving new drug therapies for both cancer and cognitive disorders;
- Creation of a National Clinical and Pre-Clinical Trials Infrastructure and NF Centers;
- Successfully eliminating tumors in NF1 and NF2 mice with the same drug;
- Developing advanced mouse models showing human symptoms;
- Rescuing learning deficits and eliminating tumors in mice with the same drug;

- Determining the biochemical, molecular function of the NF genes and gene products;
- Connecting NF to more and more diseases because of NF's impact on many body functions.

Future Directions
NF research has now advanced to the translational and clinical stages which hold incredible promise for NF patients, as well as for patients who suffer from many of the diseases linked to NF. This research is costly and will require an increased commitment on the federal level. Specifically, future investment in the following areas would continue to advance research on NF:

- Clinical trials;
- Funding of clinical trials network to connect patients with experimental therapies;
- DNA Analysis of NF tissues;
- Development of NF Centers, tissue banks, and patient registries;
- Development of new drug and genetic therapies;
- Further development of advanced animal models;
- Expansion of biochemical research on the functions of the NF gene and discovery of new targets for drug therapy; and
- Natural history studies and identification of modifier genes – studies are already underway to provide a baseline for testing potential therapies and differentiate among different phenotypes of NF.

Fiscal Year 2011 Request
Mr. Chairman, the Army's highly successful NF Research Program has shown tangible results and direct military application with broad implications for the general population. The program has now advanced to the translational and clinical research stages, which are the most promising, yet the most expensive direction that NF research has taken. The program has succeeded in its mission to bring new researchers and new approaches to research into the field. Therefore, increased funding is now needed to take advantage of promising avenues of investigation, to continue to build on the successes of this program, and to fund this promising research thereby continuing the enormous return on the taxpayers' investment.

I respectfully request an appropriation of $20 million in your FY11 Department of Defense Appropriations bill for the Army's Neurofibromatosis Research Program.

Mr. Chairman, in addition to providing a clear military benefit, the DOD's Neurofibromatosis Research Program also provides hope for the 100,000 Americans who suffer from NF, as well as the 175 million of Americans who suffer from NF's related diseases such as cancer, learning disabilities, memory loss, heart disease, and brain tumors. Leading researchers now believe that we are on the threshold of a treatment and a cure for this terrible disease. With this Subcommittee's continued support, we will prevail.

Thank you for your support of this program and I appreciate the opportunity to submit this testimony to the Subcommittee.