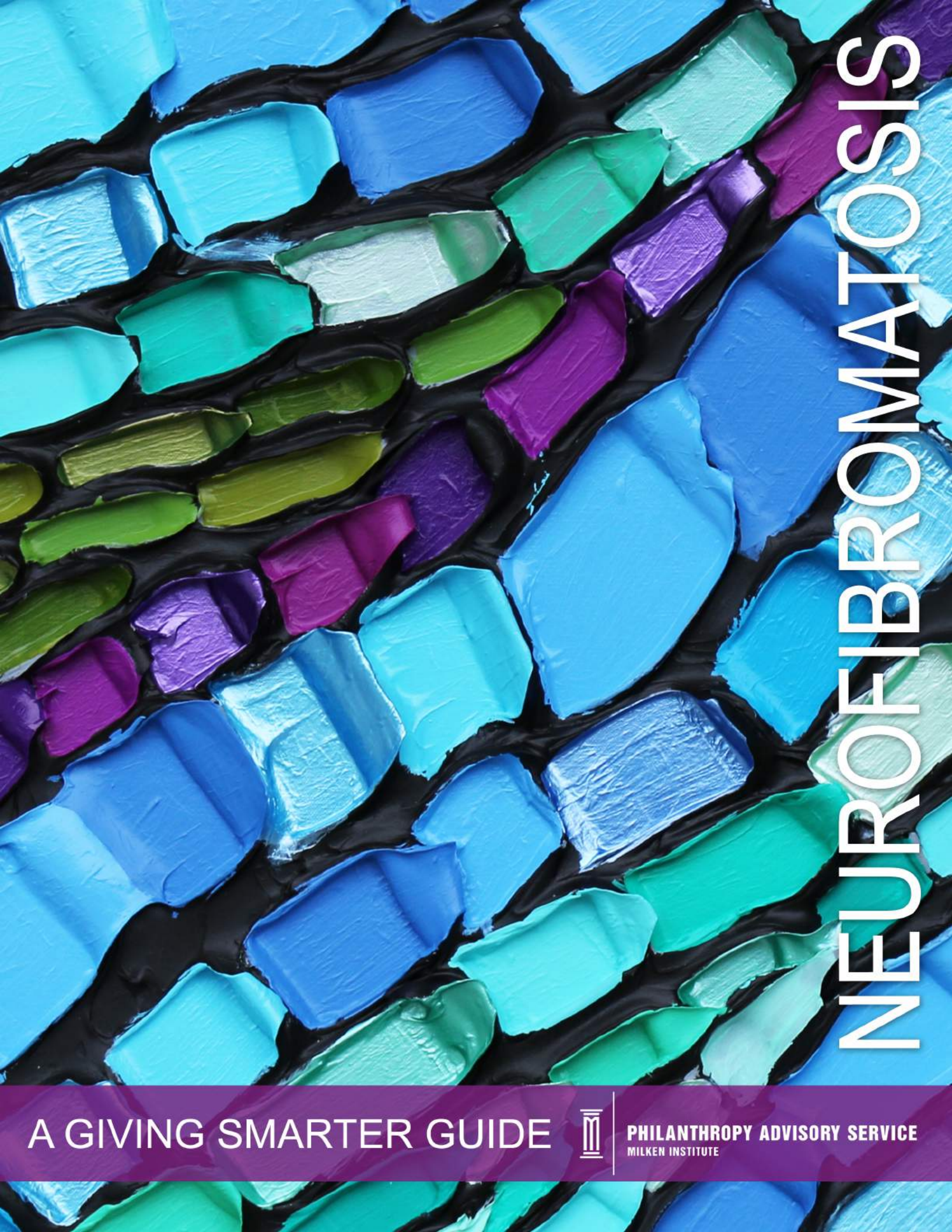

NEUROFIBROMATOSIS

A GIVING SMARTER GUIDE

PHILANTHROPY ADVISORY SERVICE
MILKEN INSTITUTE

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In 2015, the Milken Institute Philanthropy Advisory Service convened 35 world-renowned experts from the neurofibromatosis (NF) research community, various biomedical disciplines, patient foundations, the pharmaceutical industry, and the National Institutes of Health to discuss the state-of-the-science of NF and the barriers to research progress. We graciously thank the retreat participants for their contributions to our efforts in NF, including this Giving Smarter Guide. The informative discussions before, during, and after the retreat were critical to identifying the key unmet needs and philanthropic opportunities to advance NF research and patient outcomes.

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CONTENTS

EXECUTIVE SUMMARY

Neurofibromatosis type 1 (NF1) is a genetic disease that can cause a broad range of abnormalities throughout the body. A hallmark feature of the disease is the growth of tumors on nerves, which vary in size and number. Depending on their location in the body, the tumors can compromise essential functions such as vision. As a developmental disorder, NF1 can also cause cognitive disability, skeletal deformities, and cardiovascular malfunction. While symptoms appear early in life, they may get worse over time or new ones may arise. *The course of the disease is both unpredictable and variable among individuals.*

In the United States, approximately 100,000 individuals are living with the disease. Though it is classified as a rare disease, *NF1 is more prevalent than cystic fibrosis, Duchenne muscular dystrophy, and Huntington's disease combined.* It equally affects all genders, races, and ethnicities.

To date, there are no effective therapies to reverse disease symptoms or to prevent new ones from arising. There is no cure for NF1. Research and development in the field is hampered by several challenges, including:

- A highly-variable clinical care setting
- Limited access to patient tissue samples for clinical research
- Lack of biomarker discovery and development efforts
- Limited understanding of the underlying disease biology

The Milken Institute Philanthropy Advisory Service has developed this Giving Smarter Guide for NF1 to help patients, supporters, and other stakeholders understand the state of the science and make informed decisions when directing their philanthropic investments. Readers will be able to use this guide to pinpoint research solutions aligned with their interests. This guide will help answer the following questions:

- *What are key facts about NF1?*
- *What is the current state of care?*
- *What is the current state of research?*
- *What are major barriers to progress?*
- *Why should I invest in NF1 research?*
- *How can philanthropy advance new therapies for NF1?*

*__Bolded__ terms throughout the guide are defined in the glossary (page 25).

INTRODUCTION

Neurofibromatosis type 1 (NF1) is a genetic disease that causes tumors in the nervous system. Depending on their location in the body, the tumors can compromise essential functions such as vision or can result in physical disfigurement. Although the tumors are usually **benign** (noncancerous), they occasionally become **malignant** (cancerous); individuals with NF1 are thus predisposed to cancer. NF1 is also a developmental disorder. It often disrupts normal development of the brain, resulting in learning problems and behavioral dysfunction, and of bones, leading to disfigurement and disability.

NF1 is a progressive disease, so while symptoms arise early in life, they may get worse over time or new ones may arise. The course of the disease is both unpredictable and variable among individuals. Even within the same family, patients may experience different symptoms at varying degrees of severity.

IMPERATIVE TO ADVANCE NF1 RESEARCH

Approximately 1 in 3,000 individuals are born with NF1, regardless of gender, race, and ethnicity. Of the more than 6,800 **rare diseases**, NF1 is one of the most common, affecting approximately 100,000 individuals in the United States. *It is more prevalent than cystic fibrosis, Duchenne muscular dystrophy, and Huntington's disease combined.*

Despite the impact of NF1, no therapies have been developed to effectively modify the progression of the disease. Current treatments are not specific to NF1 and aim to eliminate existing tumors or alleviate other symptoms to improve quality of life. There are no effective means to reverse incurred damage or to prevent new tumors and symptoms. There is no cure for NF1.

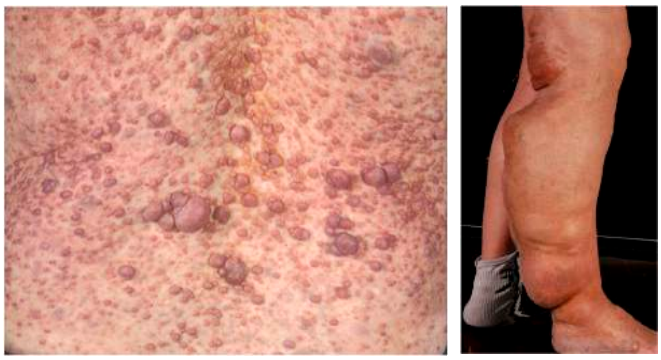
Unlike most diseases, the NF1 patient population is highly **heterogeneous**. This is due to the variable and unpredictable nature of the disease, which, in addition to a small population that is widely disbursed throughout the nation, makes studying NF1 particularly challenging. Furthermore, because NF1 is relatively rare and typically not life-threatening, it has not been highly prioritized for resources to educate the public and to advance medical research. However, the larger medical research community is increasingly realizing the potential value of NF1 studies in understanding other diseases, especially cancer. ***Now, we must mobilize the patient community at large and commit focused resources to raise awareness, establish a sense of urgency, and support NF1 research to tackle the disease.***

CLINICAL MANIFESTATIONS

NF1 entails a broad range of signs and symptoms, or **clinical manifestations**. Although manifestations usually arise during childhood, the disease is progressive with symptoms often becoming more pronounced during puberty and pregnancy. The types and severity of manifestations vary tremendously among affected individuals and the rate of disease progression is unpredictable.

TUMORS

Tumor growth on nerves is a hallmark feature of NF1. The most common type of NF1-associated tumor, **neurofibroma**, forms in the peripheral nervous system. Although neurofibromas are benign tumors, they can cause pain and debilitation and can grow large enough to encompass an entire region of the body. Figure 1 displays the two main types of neurofibromas. **Cutaneous neurofibromas** grow on single nerves in the skin, forming bumps of varying sizes. Although cutaneous neurofibromas may be painful, itchy, or disfiguring, they do not become malignant. In contrast, **plexiform neurofibromas** grow diffusely on networks of nerves anywhere in the body. They may cause pain, numbness, weakness, and major disfigurement. Approximately 10 to 15 percent of plexiform neurofibromas transform into cancer called **malignant peripheral nerve sheath tumor (MPNST)**, which is a major cause of NF1-related deaths. The number and location of neurofibromas differ among individuals and the course of their development is unpredictable, with periods of rapid growth and quiescence.



(a) (b)

Figure 1: Neurofibromas.
(a) Multiple cutaneous neurofibromas on the back. (b) Plexiform neurofibroma in the right leg.
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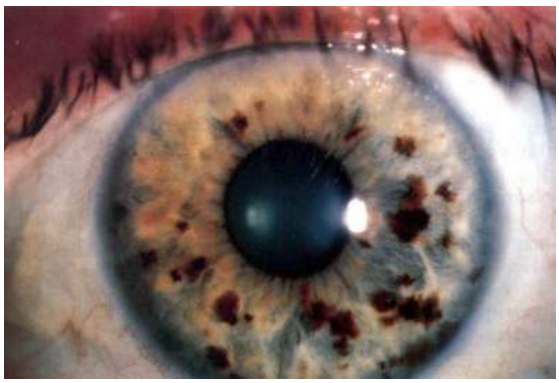
Additionally, brain tumors called **gliomas** develop in 15 to 20 percent of NF1 patients. These tumors are usually slow-growing, benign, and along the optic nerve, which connects the eye to the brain. Although most **optic nerve gliomas (ONGs)** are not problematic, some result in partial or complete blindness. ONGs may also cause eyeball protrusion as well as hormonal complications such as abnormal growth, appetite, and sleep regulation. Another eye-related manifestation is **Lisch nodules**, benign tumors that emerge as clumps of pigment in the iris (Figure 2). These clear yellow-brown bumps usually appear around puberty and do not cause medical problems or affect vision. Lisch nodules are unique to NF1 and therefore are useful for diagnosis.



Other tumors associated with NF1 include gastrointestinal stromal tumors, rhabdomyosarcoma, pheochromocytoma, leukemia, and breast cancer.

Figure 2: Lisch Nodules.
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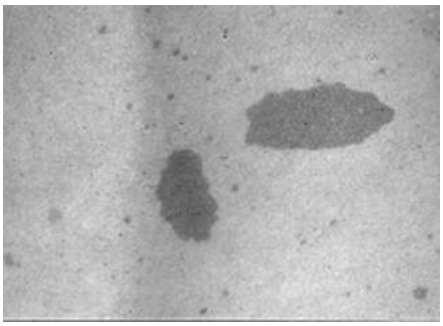
NON-TUMOR MANIFESTATIONS

As a developmental disorder, NF1 disrupts the normal formation of many tissues and organs in the body. Consequently, there are various manifestations of the disease besides tumor growth.

SKIN MANIFESTATIONS

In addition to cutaneous neurofibromas, two heralding skin features of NF1 are **café-au-lait macules** and freckles in areas of skin folds such as the armpits and groin. Café-au-lait macules are hyperpigmented, oval or circular, flat spots that can appear anywhere on the body (Figure 3). Virtually all NF1 patients have café-au-lait macules, and many of such patients are born with this manifestation. During the first several years of life, the spots increase in size and number.



Most individuals with NF1 also develop freckles in the armpits (**axillary freckling**) or groin (**inguinal freckling**). These freckles are helpful in the diagnosis of the disease since they develop in areas where freckles do not usually appear. This skin manifestation often appears after café-au-lait macules but before the development of neurofibromas.

Figure 3: Café-au-lait Macules.
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COGNITIVE IMPAIRMENT

More than one-half of individuals with NF1 have learning and behavioral difficulties. The exact form and severity of learning difficulty varies by individual and can involve any combination of visual, spatial, speech, language, reading, and math skills. However, visual spatial impairment and attention deficit are among the most common. Mental retardation occurs in 4 to 8 percent of the patients.

SKELETAL MANIFESTATIONS

Skeletal abnormalities occur in up to 50 percent of NF1 patients, with most defects evident at birth or by early childhood. Children may display short stature and enlargement of the head. Other skeletal complications include loss of bone mass (**osteoporosis**), spinal malformations such as **scoliosis**, deformities in the boney structures around the eye (**orbital dysplasia**), excessive bowing of the lower legs (**tibial dysplasia**), and non-union fractures (**pseudarthrosis**) in the tibia and the forearm.

CARDIOVASCULAR COMPLICATIONS

Cardiovascular disease is a common cause of NF1-associated perinatal death and individuals born with NF1 are more likely to have congenital heart and blood vessel defects. Potential cardiovascular manifestations include hypertension, vascular stenosis, and brain aneurysms.

DEVELOPMENTAL WINDOWS

Each of the individual manifestations tend to arise during specific times throughout life (Figure 4). The earliest manifestations are present at birth or develop within the first decade of life. They include café-au-lait macules, plexiform neurofibromas, optic nerve gliomas, and bone abnormalities. If these features do not develop during this early timeframe, then they will not develop later in life. Later in childhood, cognitive manifestations become increasingly evident as children with NF1 show difficulty developing specific skills. Cutaneous neurofibromas typically start emerging during puberty, becoming larger and more numerous with age. MPNSTs usually occur in adolescence or adulthood.

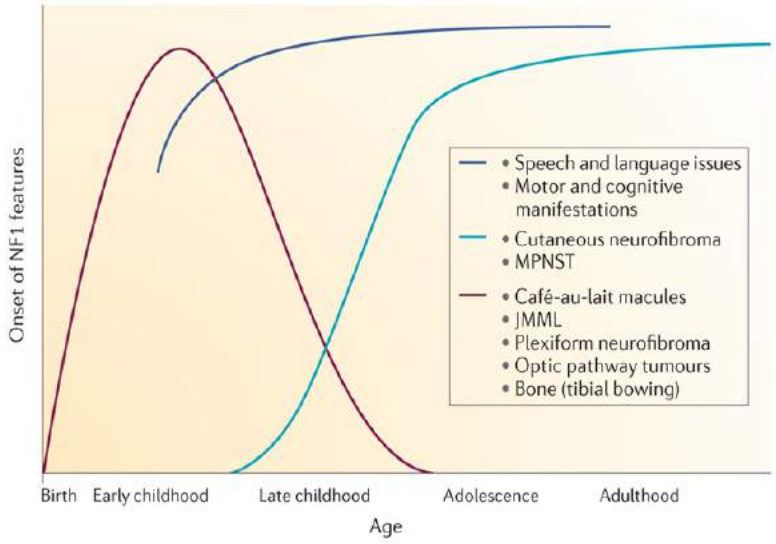

Figure 4: Epochs of Development of NF1 Manifestations.
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GENETICS

NF1 is caused by changes in the neurofibromin 1 gene (*Nf1* gene). These genetic changes, called **genetic mutations**, are inherited from a parent in one-half of NF1 cases. In other cases, they occur spontaneously in individuals with no family history of the disease. Once these spontaneous mutations have occurred, the mutant *Nf1* gene can be passed on to succeeding generations.

All humans have two copies, or **alleles**, of the *Nf1* gene. During reproduction, each parent passes one *Nf1* allele to each of child. Because one mutant *Nf1* allele is sufficient to cause the disease, an individual with NF1 has a 1 in 2 chance of passing on a mutant *NF1* gene, and therefore the disease, to each child, regardless of gender. Based on this pattern of inheritance, NF1 is an **autosomal dominant genetic disease**.

The *Nf1* gene is relatively large, which makes it particularly vulnerable to mutations. In fact, it has one of the highest mutation rates in humans, consistent with the fact that one-half of NF1 cases arise from spontaneous mutations in the gene. To date, more than 1,485 distinct mutations of the *Nf1* gene have been observed in patients.

PHENOTYPE IS DETERMINED BY VARIOUS FACTORS

Although the inheritance pattern of NF1 is well-defined, the physical expression of the disease, or **phenotype**, is highly variable and not solely dependent on the nature of a patient's *Nf1* gene mutations. Considerable phenotypic variation can occur within a given family. Furthermore, two individuals with the same type of *Nf1* gene mutations can experience different manifestations and disease severity. To date, researchers have discovered only a few correlations between specific types of *Nf1* gene mutations and particular clinical features.

Aside from the *Nf1* gene mutations themselves, the large phenotypic variability among NF1 patients is thought to be attributed to **modifier genes** and environmental factors. A modifier gene is any genetic sequence apart from the *Nf1* gene that influences one or more aspects of the disease phenotype. For example, a modifier gene may help suppress tumor growth; thus a NF1 patient who has two good alleles of this modifier gene may develop less neurofibromas than a patient who has only one good allele. Environmental factors that may influence a patient's phenotype include diet and exposure to harmful chemicals.

DISEASE BIOLOGY

The *Nf1* gene codes for **neurofibromin 1**, a protein involved in the regulation of cell growth and proliferation. Neurofibromin 1 is also necessary for embryonic development and is responsible for the proper differentiation and function of various types of cells. In NF1, **loss-of-function mutations** in the *Nf1* gene compromise the production of functional neurofibromin 1, leading to uncontrolled cell growth and tumor formation as well as abnormal development of cells and tissues throughout the body.

NEUROFIBROMIN 1 REGULATES RAS SIGNALING PATHWAYS

Neurofibromin 1 is involved in the regulation of many **cellular signaling pathways**, in which a signal is processed through a series of protein interactions within a cell, ultimately resulting in a cell response such as cell growth. In particular, neurofibromin 1 interacts with a protein called RAS by inactivating it and thereby turning off the **RAS/MAPK signaling pathway**. Figure 5 illustrates the individual proteins that are part of the RAS/MAPK signaling pathway. When RAS is activated, it interacts with and activates the RAF protein. In a process called **phosphorylation**, the activated RAF then adds phosphorous and oxygen molecules to the MEK protein, thereby activating it. The activated MEK then phosphorylates and activates the MAPK protein. Ultimately, this signaling cascade instructs the cell to grow and proliferate. Another pathway that is affected in NF1 is the **RAS/mTOR signaling pathway**, which also promotes cell proliferation. Because neurofibromin 1 controls these cell growth and proliferation signaling pathways, it is considered a tumor suppressor.

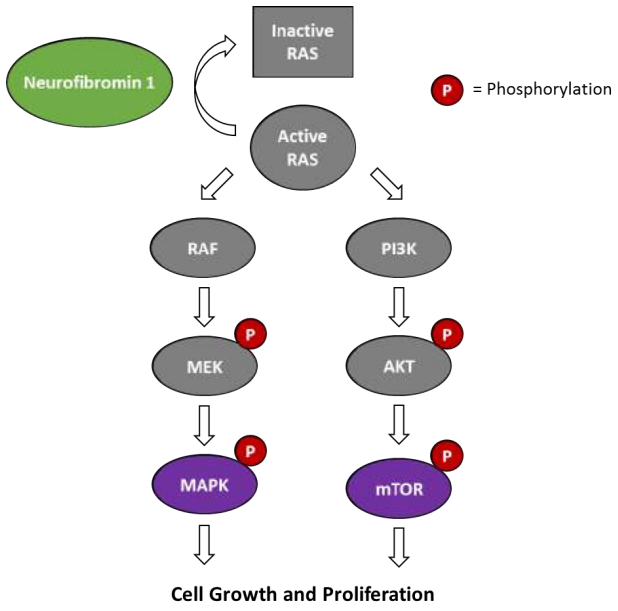

Figure 5: Neurofibromin 1 Regulates the RAS/MAPK and RAS/mTOR Cellular Signaling Pathways. The loss of neurofibromin 1 function via *NF1* gene mutations results in uncontrolled cell growth and proliferation, leading to tumor development.

In NF1, neurofibromin 1–deficient cells experience continuous activation of the RAS/MAPK or RAS/mTOR pathways. The overactive signaling pathways promote tumor development. Thus, many drugs in development for NF1-associated tumors target specific proteins within these RAS pathways (see *Investigational Therapies*, page 11).

Neurofibromin 1 regulation of the RAS pathways is also important for the proper development and function of various tissues throughout the body, and explains in part the wide range of non-tumor manifestations in NF1 patients. For example, overactive RAS/MAPK signaling in the skin's pigment-producing cells, **melanocytes**, disrupts the normal development and function of these cells. This leads to the abnormal distribution of pigment in the skin, manifest as café-au-lait macules and freckling. Likewise, unregulated RAS/MAPK signaling in **osteoclasts**, bone cells that break down bone tissue during growth and healing, stimulates the growth and survival of these cells. This in turn promotes bone degradation and may result in osteoporosis and other NF1-associated skeletal defects.

TUMORS DEVELOP WHEN BOTH *NF1* ALLELES ARE MUTANT

NF1 patients are born with one mutant *NF1* allele in every cell, which was inherited from a parent with NF1 or occurred spontaneously early in embryonic development. According to the prominent **two-hit hypothesis**, NF1-associated tumors develop only after specific cells incur loss-of-function mutations to both their *NF1* alleles. The second allele may undergo a spontaneous genetic mutation at any point in life. When both alleles are "hit," the cell loses the function of the neurofibromin 1 tumor suppressor.

In the case of neurofibromas, which consist of a mixture of cell types, only the **non-myelinating Schwann cells** have been found to have two mutant *NF1* alleles. Once a non-myelinating Schwann cell incurs mutations to both its *NF1* alleles, it proliferates rapidly. Researchers hypothesize that, during this time, the proliferating cells release chemicals that recruit other types of cells to support the neurofibroma formation. These other cells include **fibroblasts**, which provide structural support to cells and play a critical role in wound healing; **endothelial cells**, which support the structure and function of blood vessels; and **mast cells**, which are immune cells that also play an important role in the development of blood vessels.

Evidence suggests that the two-hit hypothesis likely applies to other NF1-associated tumors as well, including MPNSTs and optic gliomas. However, the applicability of the hypothesis to non-tumor NF1 manifestations is less apparent. For example, melanocytes from café-au-lait macules contain a functional *NF1* allele, suggesting that these lesions do not result directly from the "two-hit" mechanism.

DIAGNOSIS & PROGNOSIS

Most diagnoses are based on the observation of manifestations by physicians. A diagnosis requires that the individual has at least two of the following manifestations:

- Six or more café-au-lait macules over 5mm in diameter in pre-pubertal individuals and over 15mm in diameter in post-pubertal individuals
- Two or more neurofibromas of any type, or 1 plexiform neurofibroma
- Axillary or inguinal freckling
- Optic glioma
- Two or more Lisch nodules
- A distinctive bone lesion such as tibial pseudarthrosis
- A first-degree relative with NF1

Genetic tests for NF1 are also available and can be performed prenatally. However, the overall demand for genetic testing remains low, primarily because of its inability to predict the disease course and severity. There is a need to develop more rapid, informative, and cost-effective diagnostic tests for NF1.

Early diagnosis of the disease enables patients and their families to receive appropriate counseling and begin managing the disease. Because NF1 is a chronic and progressive disease, patients require lifelong monitoring for the appearance of new clinical manifestations and the worsening of existing ones. Although NF1 is typically not a life-threatening disease, early deaths can be caused by MPNSTs and cardiovascular complications. Accordingly, the median life expectancy of NF1 patients is 8 years lower than that of the general population.

CURRENT TREATMENTS

Because of the various disease manifestations, many patients require care from a multidisciplinary team of medical professionals, which may include geneticists, neurologists, oncologists, and ophthalmologists. Although there are no NF1-specific medications, there are drugs to address certain complications, such as pain, hypertension, or attention deficit.

Neurofibromas that are disfiguring or bothersome are typically removed surgically or with laser treatment. Treatment of other tumor types include surgery, chemotherapy, and radiotherapy. However, although these treatment options may reduce tumor size and prevent further growth, they do not necessarily restore the associated neurological deficits, such as vision loss from ONGs. For plexiform neurofibromas and MPNSTs, the only effective therapy is complete surgical resection; incomplete resections have a high incidence of recurrence, often necessitating multiple surgeries over a patient's lifetime.

To date, there is no cure for NF1 and there are limited options to address existing manifestations. Therapies that effectively treat existing manifestations and prevent future ones is the principal unmet need in NF1 treatment.

THERAPEUTIC DEVELOPMENT LANDSCAPE

CLINICAL TRIALS

Clinical trials are research studies with human subjects that evaluate the safety and efficacy of potential interventions, including drugs, vaccines, and medical devices. To obtain U.S. Food and Drug Administration (FDA) approval for use in human patients, a new treatment must undergo a series of clinical trials from a small-scale Phase I study on safety and dosage to a large-scale Phase III study on efficacy and adverse effects (Figure 6). After FDA approval, Phase IV studies are sometimes conducted to monitor effects of the treatment on the market.

Clinical trials are essential to the therapeutic development process but require substantial resources. On average, it takes $37 million and 5 to 7 years to complete the first three phases of clinical trials. Typical sponsors include pharmaceutical, biotechnology, and medical device companies as well as governmental organizations.

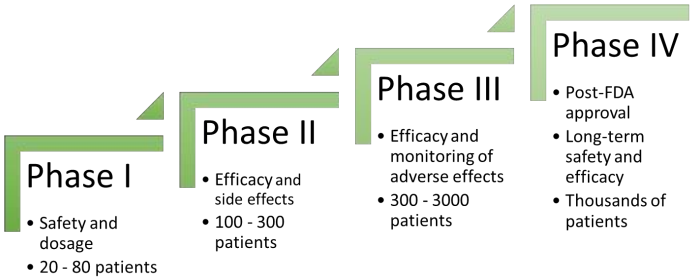

Figure 6: Phases of Clinical Trials.

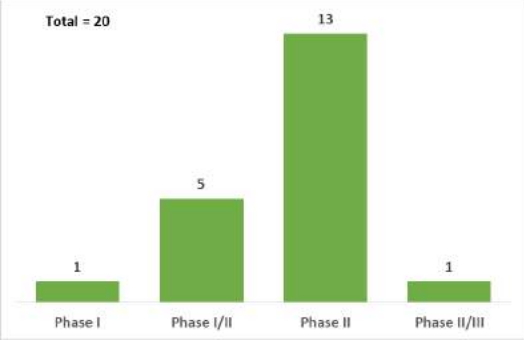

Figure 7: NF1 Clinical Trials (December 2015)
Created from data from clinicaltrials.gov

In December 2015, 20 active clinical trials were evaluating treatments for NF1 manifestations. Figure 7 illustrates the distribution of the NF1 clinical trials by phase of clinical development. The potential interventions include small molecule drugs, antibodies, nutraceuticals, medical devices, and combination therapies. Behavioral interventions, such as exercise, diet, and occupational therapy, are not included in the analysis.

INVESTIGATIONAL THERAPIES

Therapies that are currently being evaluated in clinical trials and thus have not been approved by the FDA are called investigational therapies. An investigational therapy can also be a treatment that is already FDA-approved but is now being studied for a different disease or condition. As of December 2015, the NF1 clinical pipeline consisted of eight distinct single agents and four drug combinations. These therapies aim to address different manifestations of the disease, described below.

CUTANEOUS NEUROFIBROMA

5-AMINOLEVULINIC ACID (ALA)
Photodynamic Therapy
Phase I

Photodynamic therapy (PDT) is a treatment that uses special drugs, called photosensitizing agents, along with light to kill tumor cells. Investigators are evaluating the safety and efficacy of ALA and 630 nanometer light in the treatment of benign

cutaneous neurofibromas. Light at the indicated wavelength causes the drug to react with oxygen, which forms a chemical that kills the cells. PDT might also help by destroying the blood vessels that feed the tumor cells and by alerting the immune system to attack the tumor.

EVEROLIMUS (AFINITOR®)
mTOR Inhibitor
Phase II

Everolimus is a cancer drug that is being evaluated for its efficacy in reducing the size of disfiguring cutaneous neurofibromas in NF1 patients. It is currently FDA approved for the treatment of advanced breast cancer in post-menopausal women, advanced kidney cell cancer, and advanced pancreatic neuroendocrine cancer. The drug acts by inhibiting the activity of the mTOR protein, which is abnormally high in neurofibromas. Because mTOR signals for cell proliferation, everolimus may stop tumor growth. Everolimus also reduces levels of certain cell growth factors involved in the development of new blood vessels that are required for tumor growth.

PLEXIFORM NEUROFIBROMA

PLX3397
Kinase Inhibitor
Phase I/II

PLX3397 is under investigation for the treatment of inoperable NF1-associated plexiform neurofibromas. The drug inhibits a specific pair of **kinases**¸ proteins that regulate cell signaling pathways by phosphorylating proteins. Phosphorylation of proteins in the RAS signaling pathway promote cell proliferation and tumor growth. PLX3397 also blocks the infiltration of immune cells called **macrophages** to tumors. Because macrophages support tumor progression, depleting them may shrink tumors or stop further growth.

IMATINIB MESYLATE (GLEEVEC)
Kinase Inhibitor
Phase I/II
Phase II

Imatinib mesylate is undergoing evaluation in two separate studies for its efficacy in reducing plexiform neurofibromas and/or stopping their progression in NF1 patients. The drug is currently FDA approved for the treatment of chronic myelogenous leukemia, gastrointestinal stromal tumors, and several other malignancies. Imatinib mesylate works as an anti-tumor agent by inhibiting specific kinases and their downstream cell proliferation signaling pathways.

SELUMETINIB
MEK Inhibitor
Phase I/II
Phase II

Selumetinib is being evaluated for the treatment of inoperable plexiform neurofibromas in two clinical trials. It inhibits MEK proteins in the RAS/MAPK pathway, thereby hampering the cell proliferation signaling cascade.

PD-0325901 MEK Inhibitor *Phase II*	As a MEK inhibitor, PD-0325901 decreases the overactive RAS/MAPK signaling in NF1. It is currently being evaluated for the treatment of inoperable plexiform neurofibromas that are symptomatic or progressing.
CABOZANTINIB Kinase Inhibitor *Phase II*	Cabozantinib binds to and inhibits a group of kinases called the **receptor tyrosine kinases (RTKs)**. Through various mechanisms, RTKs generally promote tumor growth and survival. By blocking the activity of RTKs, cabozantinib may help inhibit tumor growth and eventually lead to regression of plexiform neurofibromas.
SIROLIMUS mTOR Inhibitor *Phase II*	Sirolimus is a cancer drug that is currently FDA-approved for advanced kidney cancer. It works by blocking the RAS/mTOR signaling pathway that promotes tumor growth. It is currently being tested in children and adults with NF1 and inoperable plexiform neurofibromas that have the potential to cause significant morbidity.
METHOTREXATE + VINBLASTINE Chemotherapies *Phase II*	Both methotrexate and vinblastine are chemotherapy drugs that are FDA-approved for the treatment of various cancers. Each drugs works in different ways to stop tumor cells from proliferating. Investigators believe that combining these two drugs may be an effective treatment for progressive NF1-associated plexiform neurofibromas.
INTERFERON ALPHA-2B **+ CELECOXIB (CELEBREX)** **+ TEMOZOLOMIDE (TEMODAR)** **+ VINCRISTINE SULFATE (ONCOVIN)** *Phase II*	Interferon alpha-2b is a FDA-approved protein therapy that is used to treat hepatitis and numerous types of cancers. The protein has a wide range of biological activities, such as inhibiting cell proliferation signaling pathways and enhancing the immune system. A combination of interferon alpha-2b and different chemotherapy drugs is currently being evaluated as a potential treatment for plexiform neurofibromas that involve severe pain, physical disability, or organ dysfunction, or are life-threatening.

MPNST

SIROLIMUS + GANETESPIB mTOR Inhibitor + Hsp90 Inhibitor *Phase I/II*	Sirolimus is a cancer drug that works by blocking the RAS/mTOR proliferating signaling pathway. Ganetespib is an inhibitor of **heat shock protein 90 (Hsp90)**, a chaperone protein required for the stability and function of numerous signaling proteins that promote tumor growth and survival. Ganetespib has not yet been FDA-approved and is currently being investigated in a broad range of cancers. Based on strong preclinical rationale, researchers hypothesize that ganetespib in combination with

sirolimus will cause tumor regression in patients with refractory MPNSTs.

EVEROLIMUS + BEVACIZUMAB
mTOR Inhibitor + Anti-VEGF Antibody
Phase II

Bevacizumab is an antibody that selectively binds to and inhibits **vascular endothelial growth factor (VEGF)**, a signaling protein that promotes the growth and maintenance of tumor blood vessels. By blocking VEGF function, bevacizumab disrupts the blood vessels that supply oxygen to the tumor cells, ultimately causing the cells to starve and die. This drug is currently FDA-approved for the treatment of various cancers types, including those of the cervix, kidney, and brain. A combination therapy including bevacizumab and the mTOR inhibitor everolimus (page 12) is under investigation for the treatment of MPNST.

GLIOMA

SELUMETINIB
MEK Inhibitor
Phase I/II

(page 12)

EVEROLIMUS (AFINITOR®)
mTOR Inhibitor
Phase II

(page 12)

LENALIDOMIDE (REVLIMID®)
Phase II

Although lenalidomide's exact mechanism of action on cancer cells is unclear, it may act by inhibiting the growth of tumor blood vessels, thereby blocking blood flow to the tumors. Lenalidomide is FDA-approved for the treatment of multiple myeloma and mantle cell lymphoma. It is currently under investigation for the treatment of certain gliomas, including optic nerve gliomas that have come back (recurrent), have not responded to treatment (refractory), or are progressing.

COGNITION

LOVASTATIN (MEVACOR)
RAS/MAPK Signaling Pathway Inhibitor
Phase II

Lovastatin is a FDA-approved drug used to treat high cholesterol that has been shown to inhibit RAS/MAPK signaling in the brain in NF1 mouse models. By decreasing the over activity of the RAP/MAPK cascade, lovastatin reversed the NF1-associated learning and attention deficits in the mice. With this preclinical rationale, investigators are now evaluating the efficacy of lovastatin in improving visual spatial memory and/or sustained attention in children with NF1.

LAMOTRIGINE (LAMICTAL)

Brain cells of NF1 patients have attenuated function of the

HCN Agonist
Phase II/III

hyperpolarization-activated cyclic nucleotide-gated channel (HCN), a neuronal protein that is thought to play an important role in the NF1-associated cognitive deficits. As an HCN agonist, lamotrigine restored the function of HCN and improved the visual-spatial learning deficits in NF1 mice. Based on these preclinical studies, investigators are now evaluating lamotrigine for its efficacy in improving cognitive and neurophysiological deficits in NF1 patients. Lamotrigine is currently used as an anticonvulsant drug, FDA-approved for the treatment of epilepsy and bipolar disorder.

BONE DENSITY

CHOLECALCIFEROL
Vitamin D
Phase II

Cholecalciferol is a form of vitamin D, which is essential for the absorption and functioning of calcium in the body. As a dietary supplement, cholecalciferol is used to treat or prevent many conditions caused by a vitamin D deficiency, especially those of the skin and bones. In a Phase II study, the vitamin is under evaluation for the treatment of adults with NF1 who have insufficient vitamin D in their blood. The study aims to determine whether the vitamin D supplementation can ameliorate the usual loss of bone mineral density in these patients.

STRATEGIC PHILANTHROPIC OPPORTUNITIES

In 2015, the Milken Institute Philanthropy Advisory Service convened 20 world-renowned NF experts as well as 15 thought leaders from other biomedical disciplines, patient foundations, the pharmaceutical industry, and the National Institutes of Health to discuss the state-of-the-science of NF and the barriers to research progress. The mission of the retreat was to identify high-impact opportunities for strategic philanthropic investment. The experts prioritized the following unmet needs in NF research:

- Standardized clinical care
- Access to patient biospecimens
- Biomarkers
- Understanding of the disease biology
- Fresh research agendas
- Commercial development framework

This section outlines each of the key unmet needs along with potential solutions and corresponding philanthropic opportunities to address the issue and accelerate NF research. *The opportunities presented below are high-level representations and should be considered carefully with respect to your philanthropic goals and discussed in detail with a philanthropic advisor.*

STANDARDIZED CLINICAL CARE

Clinical care standards define the effective care that should be administered to all patients with a given disease. They are essential for the delivery of appropriate and consistent care across all treatment providers. In the absence of widely-implemented clinical care standards for NF, each medical center treats NF differently. The lack of clinical care standards, inadequate patient and physician education, as well as inequitable patient access to NF specialists generate a highly variable clinical care setting. This has led to vast differences in quality of care and healthcare outcomes and limits clinical research.

POTENTIAL SOLUTIONS

Care standards for NF would help mitigate variability in the NF clinical care setting, thus improving care quality and outcomes. The evidence-based guidelines would standardize care across the United States by informing general practitioners, NF specialists, and physicians of other specialties who are commonly seen by NF patients for their various manifestations. In addition to improving patient care, ***wide implementation*** of the guidelines would also grow the capacity to conduct high-quality clinical research on the disease***.***

STRATEGIC PHILANTHROPIC OPPORTUNITIES

- ❖ Development of evidence-based clinical practice guidelines that can be implemented at points of care throughout the United States.

- ❖ Development of a clinical care network to pioneer the implementation of the aforementioned guidelines and galvanize coordinated care among specialists who treat NF1 patients, e.g., geneticists, pediatricians, orthopedic physicians, ophthalmologists, oncologists, behavioral specialists. This infrastructure would also facilitate large-scale collection of standardized patient data into a central registry to support clinical research and drug development efforts.

ACCESS TO PATIENT BIOSPECIMENS

Despite their utility in studying disease and potential therapies, cellular and animal models do not represent all the intricacies of human biology, including the distinct and variable human genetic background in which NF develops. Although it is ideal to conduct research using human samples, called **biospecimens**, such studies require a critical mass of samples paired with comprehensive patient clinical data. To date, NF patient samples have not been collected in an organized, efficient manner. Because tissue collection is not a standard part of clinical practice, there is little incentive for surgeons to collect tissue or for clinicians to bank blood samples from NF patients. The limited amounts of biospecimens have been processed differently and are scattered throughout different institutions.

POTENTIAL SOLUTIONS

A ***centralized biobanking system*** based on ***standardized protocols*** for acquiring, processing, annotating, and storing biospecimens would facilitate large-scale collection of biospecimens from the NF patient population. Providing physicians with the tools and resources to conveniently procure patient samples will incentivize their participation. Centralizing biobanking operations across multiple institutions would help achieve the critical mass of high-quality biospecimens that researchers need to study the human disease and develop new therapies.

STRATEGIC PHILANTHROPIC OPPORTUNITIES

- Development of biobanking guidelines for NF patient samples that can be implemented at points of care throughout the United States.
- Development of a centralized biobanking system that is based on the aforementioned guidelines and includes multiple institutions across the United States. Biospecimens from each institution would be acquired, processed, and annotated in a uniform manner, and a portion of the samples would be shipped for storage at one or more central locations. Both the biospecimens and the data generated from the processed biospecimens, such as genomics data, would be available to qualified investigators for NF research.

BIOMARKERS

A **biomarker** is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or responses to a therapeutic intervention. Biomarkers are a clinical tool that could potentially be used to diagnose NF, characterize NF patients, predict disease course and severity, and track response to treatments. To date, few NF biomarkers have been reported, most of which are associated with MPNST or tumor burden, and none of which has been validated.

POTENTIAL SOLUTIONS

Reported NF biomarkers should be validated to ensure consistent and reproducible measurements. These ***validation studies*** as well as efforts to discover and develop new biomarkers for NF could be supported through a ***focused biomarker initiative*** that leverages the infrastructure and resources of the aforementioned clinical care and biobanking networks.

STRATEGIC PHILANTHROPIC OPPORTUNITIES

- ❖ Funding of studies to validate previously reported NF biomarkers.
- ❖ Development of a biomarker initiative that is focused exclusively on the discovery, development, and validation of NF biomarkers.

UNDERSTANDING OF THE DISEASE BIOLOGY

Despite many recent advances in NF research, significant knowledge gaps remain regarding the biological underpinnings of the disease, including the drivers of disease variability, and the role of the NF tumor microenvironment in the context of inflammation and immune response. Greater understanding of the NF disease biology is essential to discovering new and effective treatments for the disease.

POTENTIAL SOLUTIONS

At the retreat, NF experts identified major knowledge gaps that if addressed, would significantly accelerate progress in the field. As a group, they prioritized the corresponding research agendas:

- Basic biology and genetic studies of NF focused on understanding the natural history of the disease, tissue heterogeneity, and the variable progression of NF.
- In addition to human genomic analyses, development of simple model systems to identify modifier genes and determine the mechanisms responsible for variable phenotypes.
- Exploration of the NF microenvironment and tumor cell interaction as a strategy for activating immune pathways and identifying therapeutic targets.
- Launch natural history studies of etiology and the environment towards prevention strategies that minimize cognitive deficits and disfigurement.

STRATEGIC PHILANTHROPIC OPPORTUNITIES

- ❖ Development of focused research programs around the expert recommendations listed above.

FRESH RESEARCH AGENDAS

The complexity of NF1 has made drug development for the disease extremely challenging even with the continued advancement of traditional research tools. Despite the recent emergence of various novel technologies, there is a lack of exploration of these new tools in NF.

POTENTIAL SOLUTIONS

Because of their novelty in the clinical setting, gene therapy and stem cells are considered ***frontier science technologies***; and with a lot of unknowns left to be addressed, their research and development carry a high risk for stakeholders. These two technologies have been largely underexplored for NF. However, they provide alternatives to conventional therapeutic strategies that, to date, have not produced an effective treatment for NF. Successful applications of these frontier science technologies could provide disease-modifying treatments for NF, a key unmet need for the disease. Their immense potential impact on NF patients merits an aggressive pursuit.

STRATEGIC PHILANTHROPIC OPPORTUNITIES

- Development of high-risk, high-reward research programs around:
  - Gene therapy strategies as possible interventions, including gene replacement and gene editing
  - Stem cell therapy for optic nerve damage
  - Disease modeling with stem cells

COMMERCIAL DEVELOPMENT FRAMEWORK

While the NF research community continues to identify and evaluate potential therapies, there is no central discussion on what investors and pharmaceutical companies require for products that are ready for commercial development. This gap in the therapeutic development process between academia and industry is a roadblock to delivering new treatments to patients.

POTENTIAL SOLUTIONS

To maximize the likelihood of developing a marketable therapy that reaches NF patients, the research community needs to ***translate its scientific findings to pharmaceutical leads*** that are well-positioned for commercial development. This entails establishing a ***framework*** to inspire different industry partners to collaborate and develop NF therapies.

STRATEGIC PHILANTHROPIC OPPORTUNITIES

- Formation of management teams with business, legal, and industry expertise that could partner with NF researchers to shape their research findings into pharmaceutical compounds.
- Development of a central hub to facilitate material transfer agreements (MTAs) and negotiation terms around intellectual property between academic labs and industry partners.

KEY ORGANIZATIONS FOR NF RESEARCH

This section provides an overview of major non-profit organizations involved in NF research. Their involvement may be through directly funding research, advocacy, or conducting research themselves. Organizations that support NF research in multiple ways are categorized by their primary focus. This section only includes U.S.-based NF organizations that are active at the national level.

GRANTMAKING ORGANIZATIONS

Table 1 displays the major funders of NF research, each distributing more than $1 million of grants per year. These grantmaking organizations support research on all types of neurofibromatoses (NF1, NF2, and schwannomatosis), except the Neurofibromatosis Therapeutic Acceleration Program, which only funds research on NF1-associated plexiform neurofibromas. Descriptions of each organization follow Table 1.

Table 1. Top NF Research Grantmaking Organizations in FY 2014.

Organization	Sector	NF Research Grants ($)	% of Total Expenditure
Children's Tumor Foundation	**Nonprofit**	**4,964,065**	**34.2**
Neurofibromatosis Therapeutic Acceleration Program*	**Nonprofit**	**2,100,500**	**93.3**
National Institutes of Health	**Government**	**20,997,170**	**0.06**
National Cancer Institute		12,309,787	
National Institute of Neurological Disorders and Stroke		7,057,627	
National Institute on Deafness and Other Communication Disorders		936,691	
National Institute of Mental Health		474,857	
National Eye Institute		218,208	
U.S. Department of Defense Neurofibromatosis Research Program	**Government**	**13,487,422**	**89.9**

* NTAP funds are exclusively for plexiform neurofibroma research.

CHILDREN TUMOR'S FOUNDATION

The Children's Tumor Foundation (CTF) is a non-profit organization dedicated to finding effective treatments for NF and is the largest private funder of NF research. Its mission is to advance NF drug research and development; enhance support for NF patients and their families; establish best practices in clinical care; and expand public awareness of the disease. CTF's research programs include:

- NF Therapeutic Consortium (page 23)
- Synodos (page 24)
- Drug Discovery Initiative Awards
- Clinical Research Awards
- Young Investigator Awards
- Annual NF Conference

In addition, CTF supports a network for NF clinics as well as a patient registry to connect patients to clinical trials. The Foundation also includes programs for patient and caregiver support, public education, and advocacy. Founded in 1978 as the National Neurofibromatosis Foundation, it now comprises active chapters and affiliates in 37 states and is based in New York, NY.

NEUROFIBROMATOSIS THERAPEUTIC ACCELERATION PROGRAM

The Neurofibromatosis Therapeutic Acceleration Program (NTAP) is a non-profit organization dedicated to accelerating treatments for NF1-associated plexiform neurofibromas (pNFs). Through strategic research initiatives, NTAP provides grants to address specific knowledge gaps that were identified through discussions with patients, scientists, clinicians, industry leaders, investors, and government collaborators. Current research initiatives include:

- Cell models of pNF
- Drug screening in mouse models of pNF
- Patient-reported outcomes
- Natural history
- Biomarker development

In addition, NTAP supports investigators with independent research projects designed to accelerate the development of effective treatments for pNFs. It is also dedicated to attracting and fostering new talent in NF1 through its Francis S. Collins Scholars Program in Neurofibromatosis Clinical and Translational Research. The organization was founded in 2012 through a philanthropic gift to the Johns Hopkins University School of Medicine and does not seek donations from the public.

NATIONAL INSTITUTES OF HEALTH

The National Institutes of Health (NIH) is an agency of the U.S. government that is responsible for biomedical and health-related research. The NIH both conducts its own scientific research and provides research funding to non-NIH investigators in the nation. It comprises 21 separate institutes that conduct and fund research in different disciplines of biomedical science. Because NF affects multiple biological systems, NF research grants have been administered from various institutes of the NIH, including National Cancer Institute, National Institute of Neurological Disorders and Stroke, National Institute on Deafness and Other Communication Disorders, National Institute of Mental Health, and National Eye Institute. In Fiscal Year (FY) 2014, the NIH awarded approximately $21 million across 46 research grants for NF.

U.S. DEPARTMENT OF DEFENSE NEUROFIBROMATOSIS RESEARCH PROGRAM

The U.S. Department of Defense Neurofibromatosis Research Program (DOD NFRP) was established in FY 1996 through advocacy efforts. Since then, $288 million has been appropriated to the program, including $15 million in

FY 2015. The mission of the DOD NFRP is to promote research directed toward the understanding, diagnosis, and treatment of NF1, NF2, and schwannomatosis to enhance patient quality of life. It provides funding for basic, translational, and clinical trials. Areas of emphasis in FY 2015 were:

- Health services for NF
- Heterogeneity of neurofibromas and other NF-related tumors
- Manifestations of NF post-adolescence
- Mechanisms of pain
- Novel disease markers for NF using genomics, epigenetics, system biology, metabolomics, or other similar approaches
- Target identification and drug discovery for the treatment of NF
- Environmental, nutritional, and other modifiers of NF

ADVOCACY ORGANIZATIONS

NEUROFIBROMATOSIS NETWORK

Neurofibromatosis Network was founded in 1988 as a non-profit organization to join together several independent state and regional NF groups wishing to work together on national projects. Its mission is to find treatments and a cure for NF by promoting scientific research, improving clinical care, providing outreach through education and awareness, while offering hope and support to those affected by NF. The network is primarily focused on promoting federal funding of NF research through a grass roots advocacy program. It also provides funding for basic and clinical research as well as support for clinical care coordinators at NF research centers. In addition, NF network sponsors educational programs for NF patients and caregivers and assists in developing local NF groups.

RESEARCH INSTITUTES

GILBERT FAMILY NEUROFIBROMATOSIS INSTITUTE

The Gilbert Family Neurofibromatosis Institute at the Children's National Medical Center in Washington D.C. was established in 2007 through the philanthropic support of Jennifer and Dan Gilbert. The Institute consists of both basic and clinical research programs, and is primarily interested in translating its basic science research to inform innovative approaches to diagnosing and treating NF1. It focuses on NF1-associated gliomas, neurocognitive deficits, and plexiform neurofibromas. The Institute does not provide research grants to external investigators.

RESEARCH CONSORTIA

Consortia are temporary associations of stakeholders from various sectors—academia, industry, government, clinical care, nonprofits, and philanthropy—that share resources in order to achieve a common goal. According to *FasterCures*' Consortia-pedia, a database of biomedical research consortia, there are 5 active consortia for NF research and therapeutic development (http://consortiapedia.fastercures.org/). These research consortia are described below.

DEVELOPMENTAL AND HYPERACTIVE RAS TUMOR SPORE

The National Cancer Institute's Specialized Programs of Research Excellence (SPORE) are interdisciplinary translational research initiatives that aim to produce new approaches to the prevention, early detection, diagnosis, and treatment of human cancers. The Developmental and HyperActive Ras Tumor (DHART) SPORE is a 5-year, $12 million program led by the Indiana University School of Medicine and the University of California San Francisco. The overall goal of the consortia is to find effective targeted treatments for tumors caused by mutations in the *NF1* gene. It plans to repurpose drugs that are being developed to block the biochemical effects of RAS gene mutations.

Funded by: NIH, NCI

NEUROFIBROMATOSIS CLINICAL TRIALS CONSORTIUM

Neurofibromatosis Clinical Trials Consortium (NCTC) was established in 2005 by the DOD NFRP to facilitate NF clinical trials. The Consortium consists of 13 patient recruitment centers, 5 collaborating sites, and an Operations Center at the University of Alabama at Birmingham. Each site has a dedicated NF treatment and management team as well as an established patient population available for clinical trials. At present, the therapeutic focus of the NFTC includes NF1-associated plexiform neurofibromas, low-grade gliomas, neurocognitive difficulties, and tibial dysplasia.

Funded by: DOD NFRP

NEUROFIBROMATOSIS THERAPEUTIC CONSORTIUM

The Neurofibromatosis Therapeutic Consortium (NFTC) was developed by CTF to streamline and expedite the progression of promising NF therapies to clinical trials. This multi-center cooperative group integrates expertise and resources from philanthropic foundations, academia, and the pharmaceutical industry. Since its formation in 2008, the Consortium has tested 34 candidate drugs in mouse models of NF and has identified 16 drugs or drug combinations with promising efficacy. Some of these preclinical studies have directly informed the development of human clinical trials.

Funded by: CTF, NTAP

REiNS INTERNATIONAL COLLABORATION

The REiNS (Response Evaluation in Neurofibromatosis and Schwannomatosis) International Collaboration was established in 2010 to develop standardized criteria for the design and endpoints of NF clinical trials. The organization consists of 7 working groups that focus on:

- Functional outcomes
- Visual outcomes
- Patient reported outcomes
- Neurocognitive outcomes
- Imaging of tumor response
- Use of whole body MRI
- Role of biomarkers

The recommended criteria are continuously modified through experiences with NF clinical trials.

Funded by: CTF

SYNODOS

Synodos is a multi-institutional research consortium in which members have pledged to share tools, information, datasets, and results at every step in research development. The multidisciplinary team includes basic science, translational science, and clinical investigators. With the support of Sage Bionetworks, Synodos offers an open computational platform for research. The goals are to quickly disseminate data and knowledge gained by the group and to identify drugs for human clinical trials. Synodos for NF2 was started in 2014; Synodos for NF1 was started in 2015.

Funded by: CTF

GLOSSARY

Allele: one of two or more versions of a gene. An individual inherits two alleles for each gene, one from each parent.

Axillary freckling: freckles in the armpit; a skin manifestation of NF1.

Autosomal dominant genetic disease: hereditary disease in which an affected individual has a 50-50 chance of passing the mutant gene and therefore the disorder on to his/her child. It is indiscriminant of gender.

Benign: noncancerous.

Biomarker: a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.

Biospecimen: human tissue sample, often used for diagnostic tests or clinical research.

Café-au-lait macules: flat, hyperpigmented lesions on the skin that may vary in color from light brown to dark brown. The size and number of café-au-lait spots widely vary and are usually the earliest manifestations of neurofibromatosis.

Cellular signaling pathway: a series of protein interactions within a cell, through which a signal is transmitted, ultimately resulting in a cell response.

Clinical manifestations: signs or symptoms of a disease.

Clinical trials: research studies with human subjects that evaluate the safety and efficacy of potential interventions, including drugs, vaccines, and medical devices.

Cutaneous neurofibroma: benign tumors grow from nerves in or just under the skin and appear as small brown, pink, or skin-colored bumps. They typically start emerging around puberty and become more numerous with age.

Endothelial cell: type of cell that supports the structure and function of blood vessels; one of the cell types found in neurofibromas.

Fibroblast: type of cell that provides structural support to cells and play a critical role in wound healing; one of the cell types found in neurofibromas.

Genetic mutation: a permanent alteration in the DNA sequence that makes up a gene.

Glioma: tumor that arises from the supporting non-neuronal cells in the brain and spinal cord.

Heat shock protein 90 (Hsp90): a chaperone protein required for the stability and function of numerous signaling proteins that promote tumor growth and survival.

Heterogeneous: diverse in character, including types and severity of symptoms.

Hyperpolarization-activated cyclic nucleotide-gated channel (HCN): a neuronal protein that is thought to play an important role in the NF1-associated cognitive deficits.

Inguinal freckling: freckles in the groin; a skin manifestation of NF1.

Kinase: a type of protein that regulates cell signaling pathways by phosphorylating specific proteins.

Lisch nodules: yellow-brown clumps of pigment in the iris (colored part of the eye); an NF1-specific feature.

Loss-of-function mutation: a mutation that results in reduced or abolished protein function.

Macrophage: type of immune cell that engulfs cellular debris and foreign substances.

Malignant: cancerous.

Malignant peripheral nerve sheath tumor (MPNST): rare type of cancer that arise from the soft tissue that surrounds nerves.

Mast cell: type of immune cell that also plays an important role in the development of blood vessels; one of the cell types found in neurofibromas.

Melanocyte: pigment-producing cell in the skin.

Modifier gene: a gene that affects the phenotypic expression of another gene.

Neurofibroma: benign nerve sheath tumor that grows in the peripheral nervous system. They are usually found in most individuals with NF1.

Neurofibromin 1: protein that is predominantly expressed in neurons, Schwann cells, oligodendrocytes, and leukocytes. It functions in the RAS-mediated cell growth signaling pathway, helping regulate cell growth and proliferation. In NF1 patients, a loss of neurofibromin causes cells to grow uncontrolled, forming tumors.

Non-myelinating Schwann cells: cells that function to support and insulate neurons. These cells proliferate and initiate the growth of NF1-asscoiated tumors.

Optic nerve glioma (ONG): tumor that grows on the optic nerve.

Orbital dysplasia: deformity in the orbit, the bony wall behind the eye, and/or the bone behind it, the sphenoid; a skeletal manifestation of NF1.

Osteoclasts: bone cells that break down bone tissue during growth and healing.

Osteoporosis: condition in which bones become weak and brittle; a skeletal manifestation of NF1.

Phenotype: physical expression of a disease.

Phosphorylation: the addition of phosphorous and oxygen molecules to a protein, as a means to regulate the activity of that protein.

Plexiform neurofibroma (pNF): larger, more extensive tumors that grow from nerves anywhere in the body. Unlike cutaneous neurofibromas, plexiform neurofibromas are present at birth or become apparent in early childhood. They grow more diffusely than cutaneous neurofibromas and can have a higher risk for malignancy.

Pseudarthrosis: non-union after bone fracture. In pseudarthrosis, the body perceives bone fragments as separate bones and does not attempt to unite them; a skeletal manifestation of NF1.

Rare disease: In the United States, the Rare Diseases Act of 2002 defines rare disease strictly according to prevalence, specifically "any disease or condition that affects less than 200,000 people in the United States," or about 1 in 1,500 people.

RAS/MAPK signaling pathway: a signaling pathway that promotes cell proliferation.

RAS/mTOR signaling pathway: a signaling pathway that promotes cell proliferation.

Receptor tyrosine kinase (RTK): type of kinase that is involved in the regulation of various signaling pathways that promote tumor growth and survival.

Scoliosis: sideways curvature of the spine; a skeletal manifestation of NF1.

Tibial dysplasia: excessive bowing of the tibia (shin bone); a skeletal manifestation of NF1.

Two-hit hypothesis: a hypothesis that NF1 tumors form when both copies of the *NF1* gene in non-myelinating Schwann cells experience (are “hit” with) loss-of-function mutations. The first allele has a germline mutation (the mutation is inherited from a parent). The second allele undergoes a sporadic mutation.

Vascular endothelial growth factor (VEGF): a signaling protein that promotes the growth and maintenance of tumor blood vessels.

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Cover Art:

Jeffrey Owen Hanson (b:1993-) Overland Park, Kansas

Jeffrey Owen Hanson is an award winning, philanthropic artist on a mission to change the world through art. Visually impaired since childhood from neurofibromatosis, Jeffrey's acrylic on canvas works employ bold color and heavily sculptured texture to create a striking signature style. Jeffrey's commissioned paintings reside with art collectors around the globe, including Sir Elton John and Warren E. Buffett. While Jeffrey enjoys a very successful career as an artist, his philanthropic spirit has resulted in more than 150 nonprofit organizations such as Make-A-Wish® and the Children's Tumor Foundation benefitting from his auctioned works. Artwork gifted to charity has generated TWO MILLION dollars!

Jeffrey believes "Every act of kindness helps create kinder communities, more compassionate nations and a better world for all…even one painting at a time."

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