



NF Clinic Network (NFCN) Application Form*

Clinic Name:

MGH Neurofibromatosis Clinic

Affiliated Hospital:

Massachusetts General Hospital

Affiliated University or Institution:

N/A

Clinic Address:

MGH Neurofibromatosis Clinic
55 Fruit Street- Yawkey 9E
Boston, MA 02114

Clinic Director:

Scott Plotkin, MD, Ph.D.

Clinic Coordinator Name:

Marybeth Singh, NP

**Note: Some non-public information has been removed from this application form.*



The Neurofibromatosis Clinic Network (NFCN)

FORM PART A: Affiliate Clinic Application

1. ABOUT YOUR NF CLINIC

a. Is your NF Clinic:

- Freestanding
- Hospital based
- In an academic center
- Other (please describe)

b. Describe overall your NF Clinic, when it meets and how it functions.

The MGH Neurofibromatosis Clinic was established in 1982 by Dr. Robert Martuza, the current Chief of Neurosurgery. Since that time, the clinic has been dedicated to providing high quality, longitudinal care for patients with NF1, NF2, and schwannomatosis. The current director is Dr. Scott Plotkin, a board-certified neurologist with specialty training in neuro-oncology. He has clinic on Tuesdays. In the morning, he evaluates new patients who are suspected to have or have been

diagnosed with neurofibromatosis (broadly defined). On Tuesday afternoon, Dr. Plotkin sees established patients in clinic. On Friday morning, Dr. Plotkin has a traditional neuro-oncology clinic with a particular focus on NF-related tumors (e.g., schwannoma, meningioma, and neurofibromas) which occur in sporadic patients.

Marybeth Singh, NP, sees new patients and follow-up patients with Dr. Plotkin on Tuesday. In addition, she has her own clinic on Friday mornings where she sees established patients. Marybeth Singh's clinic was established to help NF patients gain easier access to clinic.

2. CLINIC DIRECTOR and STAFF EXPERTISE

a. CLINIC DIRECTOR: Please describe:

i. Your experience to date with NF care

Dr. Plotkin was recruited by Dr. Mia MacCollin to join the NF clinic in 2002, as he was completing his neuro-oncology fellowship. He joined the clinic as a staff member in 2003, and became director in 2005. Since 2002, he has cared for a large patient population at MGH, which includes patients with NF1, NF2, and schwannomatosis. At MGH, there is particular emphasis on patients with NF2 and schwannomatosis, as Dr. Plotkin has expertise in the comprehensive management of these patients.

ii. Your past and current association with NF clinical trials

Dr. Plotkin is actively involved in running clinical trials for NF. He is collaborating with the Mayo Clinic and the P2C consortium to enroll subjects in a clinical trial of AZD2171 in NF1 patients with progressive or symptomatic plexiform neurofibromas. To date, he has screened 3 patients for participation, has enrolled one, and is waiting to enroll a second. Dr. Plotkin has received an internal grant to study the effect of ranibizumab (Lucentis) for neurofibromas associated with neurofibromatosis. He is also Site PI of a clinical trial for meningioma, studying the effect of imatinib and hydroxyurea on progressive or recurrent lesions. This trial opened in June, 2007, at MGH and he expects to enroll NF2 patients with progressive meningioma.

iii. Your past and current association with other clinical trials e.g. oncology trials

Dr. Plotkin is an active member of the Neuro-oncology program at MGH. As such, he enrolls brain tumor patients on a variety (> 10) of clinical trials. He is site PI for the following studies: (1) phase II study of cellingitide for recurrent glioblastoma; (2) phase I study of cellingitide with concurrent and adjuvant chemoradiation for newly diagnosed glioblastoma; and (3) pilot study of sunitinib for recurrent glioblastoma.

b. CLINIC DIRECTOR: Please provide information on:

i. Present and past funding you have received for NF research. Include funding source, date received, amount and project description.

Ongoing Research Support

2006 [Plotkin] \$100,000 total 2006-2008
Pappas Center for Neuro-Oncology
Pilot study of ranibizumab (Lucentis) for neurofibromas associated with neurofibromatosis 1
The purpose of this grant is to determine the efficacy of anti-angiogenic therapy in the treatment of neurofibromas.
Role: P.I.

MC047F [Babovic] \$6300/subject 2006-2010
N.C.I.
A phase 2 study of AZD2171 in adult patients with neurofibromatosis type 1 and extensive plexiform and paraspinal neurofibromas
The major goal of this project is to determine the efficacy of AZD2171 in treating benign neurofibromas.
Role: Site P.I.

NF050202 [Plotkin] \$1,300,000 total 9/1/2006 - 8/31/2010
D.O.D.
Whole body MRI evaluation of subjects with NF1, NF2, and schwannomatosis
The major goal of this research is to evaluate the role of whole body MRI scanning in patients with neurofibromatosis.
Role: P.I.

DAMD17-03-1-0045 (MacCollin) 6/01/03-7/31/07
USAMRMC
Molecular Identification of the Schwannomatosis Locus
The major goal of this project is to identify the locus on chromosome 22 that is responsible for the neuro-genetic condition schwannomatosis.
Role: Co-Investigator

Completed Research Support

NF050131 [Plotkin] \$100,000 total 12/15/2005 - 12/14/2006
D.O.D.
Endothelial cell-smooth muscle cell interactions in a mouse model of NF1
The major goal of this project is to investigate the cellular basis of vasculopathy using an established mouse model of NF1.
Role: P.I.

NF000014 [Slattery] 1/1/2002 - 12/31/2005
D.O.D.
Neurofibromatosis type 2 natural history consortium
The major goal of this research was to establish the natural history of tumors associated with NF2.
Role: Investigator

NF030032 [Gusella] \$100,000 total 1/2/04-1/1/05
Department of Defense

A prospective, randomized clinical trial of celecoxib for the control of symptomatic plexiform neurofibroma in neurofibromatosis 1

Role: Co-Principal Investigator

- ii. Your NF-related clinical and scientific publications.
Include Journal, Citation and Title.

MacCollin M, Chiocca EA, Evans DG, Friedman JM, Horvitz R, Jaramillo D, Lev M, Mautner VF, Niimura M, Plotkin SR, Sang CN, Stemmer-Rachamimov A, Roach ES. Diagnostic criteria for schwannomatosis. *Neurology*. 2005;64(11):1838-45.

Mrugala MM, Batchelor TT, Plotkin SR. Peripheral and cranial nerve sheath tumors. *Curr Opin Neurol*. 2005;18(5):604-610.

Plotkin SR. Neurofibromatosis 2 and schwannomatosis. In: Ruggieri M, Pascual-Castroviejo I, and DiRocco C, editors. *Neurocutaneous Disorders*. Springer; 2007.

Farrell CJ and Plotkin SR. Genetic Causes of Brain Tumors: Neurofibromatosis, Tuberous Sclerosis, Von Hippel-Lindau, and Other Syndromes. In: Wen PY, Schiff D, editors. *Neurologic Clinics: brain tumors in adults*. 2007.

Chu-Shore C and Plotkin SR. The Phakomatoses. In: Rosenberg RN, DiMauro S, Paulson H, Ptacek L, Nestler E, editors. *The molecular and genetic basis of neurological and psychiatric disease*. Philadelphia (PA): Lippincott Williams & Wilkins;2007.

S.R. Plotkin. Phakomatoses: Neurofibromatosis II. In: *The New Encyclopedia of Neuroscience*. Elsevier; 2007.

- c. Who are the key staff in your NF clinic facility?

Provide Name; Title; Degree/Qualifications; Role in Clinic.

1. Scott Plotkin, MD PhD. Neuro-Oncologist. Director of the neurofibromatosis clinic.
2. Marybeth Singh MSN, NP/Research nurse. Provides care to patients in NF clinic. Sees NF1, NF2 and Schwannomatosis patients (adult & pediatrics). Provide education to patients and families. Provide emotional support to families. Work with patients and their insurance companies to cover certain tests and procedures. Research NP in the clinic. Enroll patients in research studies.
3. Caroline O' Donnell, BS. Clinical Research coordinator, database manager.
4. Marie Aste, BS. New patient service coordinator. Schedules new patient appointments.
5. Angelika Bartolomeo, patient service coordinator. Schedules existing patients in our clinic. Schedules follow-up appointments and imaging studies.

6. Barbara Bell, RN BSN. Intake nurse. Calls new patients to document past medical history etc, prior to scheduled appointment with Dr. Plotkin.

d. Who within this core staff currently coordinates NF patient services? Describe this individual's NF clinic related duties.

Marybeth Singh, NP, coordinates patient services, including referrals to specialists in other clinics. Ms. Singh assesses patient needs, orders necessary tests, and decides when patients will return to clinic. Marybeth returns calls to patients regarding tests and procedures that are needed prior to scheduled appointment.

e. Describe any areas of NF care in which your clinic has particular expertise (e.g. optic glioma, vestibular schwannoma, bone manifestations, learning disabilities etc.) and the clinic staff that provide this care.

- NF2— The MGH clinic has a long-term commitment to the care of patients with NF2 and related tumors (schwannoma, meningioma, ependymomas). We have a comprehensive neurosurgical team (Drs. Martuza, Frederick Barker, Jean Coumans), ENT team (Dr. Michael McKenna), radiation oncology (Dr. Jay Loeffler) and neurology team (Dr. Scott Plotkin).
- Schwannomatosis— Over the past 15 years, Dr. Mia MacCollin, the previous clinic director, was one of the key researchers to describe the clinical and genetic basis of this disorder. The MGH clinic has an active interest in managing these patients. Comprehensive pain care is provided by Dr. Christine Sang. The neurosurgical team (above) is experienced in resecting peripheral schwannomas and has just recruited a neurosurgeon with particular interest in peripheral nerve disease and NF (Dr. Ziv Williams).
- NF1 tumors— Dr. Plotkin is actively involved in designing clinical trials for NF1-related tumors. The surgical team (above) evaluates patients but more commonly they are managed conservatively at MGH. Current trials include AZD2171 for progressive plexiform neurofibroma. There is a comprehensive team to coordinate clinical trials at MGH that is based in the Pappas Center for Neuro-oncology. This includes a research nurse, clinical research coordinators, and clinical research associates.
- Learning disabilities— Marybeth Singh NP, helps patients with learning disabilities obtain the help they need in school. Marybeth works with pediatric patients and their parents to obtain services needed in school. Marybeth writes letters to schools to ask if services such as PT/OT & speech are needed as part of a child's individualized educational plan.

3. PATIENT SCHEDULING and REFERRALS

- a. Provide the details of the ‘typical’ timeframe in which patients receive a response to a request for scheduling, are actually scheduled for an appointment, how patients are prioritized, etc.

Patient calls are returned within two business days. Patients who are new to the NF clinic are scheduled within 2 months to see Dr. Plotkin. If a new patient needs to be seen urgently, or sooner than the wait time (e.g., concern for malignant peripheral nerve sheath tumor or progressive symptoms), the patient may be added on to Dr. Plotkin’s schedule. Urgent visits can also be scheduled with Marybeth Singh NP.

- b. Provide details of those specialists to whom (either within or outside our own clinic facility) your clinic refers NF patients for the following specialty care. **These should individuals familiar and experienced with consensus guidelines for care of individuals with NF** (Please provide information for PEDIATRIC CARE referrals in the first table and ADULT CARE in the second table).

PEDIATRIC CARE

SPECIALTY	DOCTOR	CLINIC ADDRESS	PHONE	EMAIL (if available)
Genetics	Dr. Lewis Holmes	MGH, Yawkey 4 & 6	617-726-6292	
Neurology	Dr. David Holtzman Dr. Kenneth Sassower	MGH, Yawkey 3 MGH, GRB	617-726-3402 617-724-7426	
Orthopedics	Dr. Kevin Raskin	MGH, Yawkey 3	617-724-3700	
Developmental pediatrics/learning disabilities	Dr. Florence Lai	MGH VBK 7 55 Fruit St Boston, MA 02114	617-726-2664	
Ophthalmology	Dr. Simmons Lessell	MEEI 243 Charles St Boston MA 02114	617-573-3202	
Neurosurgery	Dr. William Butler	MGH , WAC 03	617-726-3801	
Plastic surgery	Dr. Jay William Austen	POB 275 Cambridge St Boston, MA 02114	617-724-6026	
Neuro-Oncology	Dr. David Ebb Dr. Scott Plotkin	MGH, Yawkey 8 MGH, Yawkey 9E	617-726-2737 617-724-7856	
Medical Oncology/ Radiation Oncology	Dr. David Ebb Dr. Nancy Tarbell	MGH, Yawkey 8 MGH Francis H. Burr Proton Therapy Center	617-726-2737	
Endocrinology	Dr. Paul Boepple Dr. Park- Bennet	MGH, Wellman 05	617-726-2909	

Audiology/ENT	Dr. Michael McKenna	MEEI 243 Charles St Boston, MA 02114	617-523-7000	
Radiology/ Neuroradiology	Dr. Ellen Grant	MGH, Ellison 2 55 Fruit St Boston, MA	617-724-4207	
General Surgery/ Surgical Oncology	Dr. Sam Yoon	Professional office Building 243 Charles St Boston, MA	617-724-9922	
Dermatology	Dr. Pamela Norden	1 Washington St Suite 401 Wellesley Hills, MA	781-416-3500	
Cardiovascular Disease	Dr. Mary Etta King Dr. Ana Marie Rosales	MGH, Yawkey 6 MGH Yawkey 6	617-726-3826 617-726-3826	
Oral and Maxillofacial Surgery	Dr. Meredith August	MGH, WAC 2	617-726-2740	
Behavioral Issues	Dr. Florence Lai	MGH, VBK-7	617-726-2664	

ADULT CARE

SPECIALTY	DOCTOR	CLINIC ADDRESS	PHONE	EMAIL (if available)
Genetics	Dr. Lewis Holmes	MGH, Yawkey 4 & 6	617-726-6292	
Neurology	Dr. Scott Plotkin	Yawkey 9E	617-724-7856	
Orthopedics	Dr. Kevin Raskin	MGH, Yawkey 3	617-724-3700	
Developmental pediatrics/lear ning disabilities	Dr. Florence Lai	MGH VBK 7	617-726-2664	
Ophthalmology	Dr. Simmons Lessell	MEEI 243 Charles St Boston MA 02114	617-573-3202	
Neurosurgery	Dr. Robert Martuza Dr. Fred Barker Dr. Jean Coumans	MGH, WHT 502 MGH, Yawkey 9 MGH, WACC 0	617-726-8581 617-724-8772	
Plastic surgery	Dr. Jonathan Winograd Dr. Jay William Austen	MGH, WAC 4 POB 275 Cambridge St	617-523-7000 617-724-9922	

Neuro-Oncology	Dr. Scott Plotkin	MGH, Yawkey 9	617-726-8770	
Medical Oncology/ Radiation Oncology	Dr. David Harmon Dr. Jay Loeffler	MGH, Yawkey 7A MGH, Cox	617-724-4000 617-724-1548	
Endocrinology	Dr. Juan Pallais	50 Staniford St Boston, Ma 02114	617-726-8720	
Audiology/ENT	Dr. Michael McKenna	MEEI	617-523-7000	
Radiology/ Neuroradiology	Dr. Miriam Bredella Dr. Michael Lev	MGH, Yawkey 6 55 Fruit St Boston, Ma 02114	617-726-7717	
General Surgery/Surgical Oncology	Dr. Sam Yoon	MGH, Yawkey 7	617-726-4241	
Dermatology	Dr. Pamela Norden	1 Washington St Suite 401 Wellesley Hills, MA 02481	781-416-3500	
Cardiovascular Disease	Dr. Jagmeet Singh	MGH-Gray	617-726-4662	
Oral and Maxillofacial Surgery	Dr. Meredith August	MGH, WAC 2	617-726-2740	
Behavioral Issues	Dr. John Herman	MGH, Bul 03	617-726-2993	

4. NUMBER OF NF PATIENTS YOUR CLINIC SEES

- a. How many NF PATIENTS did you see in the past 12 months?
- b. How many of these were **NEW** patients to your clinic?

Insert numbers below

	NF1	NF2	SCHWANNOMATOSIS	OTHER
NUMBER OF PATIENTS SEEN IN PAST 12 MONTHS	223	105	28	80
NUMBER OF <u>NEW</u> PATIENTS SEEN IN PAST 12 MONTHS	92	22	9	320
TOTAL	315	127	37	400

3. Weekly vascular surgery conference including vascular neurosurgeons, interventional radiologists, and radiologists, in which NF1 patients with vascular disease are discussed.

7. CLINICAL TRIALS

Our clinic is willing and able to provide our NF patients with information on, and to facilitate their participation in, clinical trials for which NF patients are eligible (check box)

Yes No

If 'no', briefly describe why.

Do you currently refer patients to clinical trials?

Yes No

If 'yes', provide details of current clinical trial protocols in which you currently or have had patients involved in the past 5 years.

- AZD2171 in NF1 patients with progressive or symptomatic plexiform neurofibromas, in collaboration with the Mayo Clinic and the P2C consortium
- Ranibizumab (Lucentis) for neurofibromas associated with neurofibromatosis.
- Imatinib and hydroxyurea for progressive or recurrent meningioma (NF2 patients are eligible for enrollment)

8. PATIENT REGISTRY

Do you currently have an NF specific patient database/registry?

Yes No

If 'yes', please describe.

We have a clinical (ie., non-research) database that is current and lists the number of patients seen in the NF Clinic. NF1, NF2 and schwannomatosis patients are listed in the database according to diagnosis.

Would you be willing to transfer this data to a centralized CTF NF Database?

Yes No

If 'no', explain your limitations.

9. PUBLICATIONS and RESEARCH (IF APPLICABLE)

- a. Please list any relevant NF publications from your clinic in the past 5 years. Include Journal, Citation and Title.

MacCollin M, Chiocca EA, Evans DG, Friedman JM, Horvitz R, Jaramillo D, Lev M, Mautner VF, Niimura M, Plotkin SR, Sang CN, Stemmer-Rachamimov A, Roach ES. Diagnostic criteria for schwannomatosis. *Neurology*. 2005;64(11):1838-45.

Mrugala MM, Batchelor TT, Plotkin SR. Peripheral and cranial nerve sheath tumors. *Curr Opin Neurol*. 2005; 18(5): 604-610.

Plotkin SR. Neurofibromatosis 2 and schwannomatosis. In: Ruggieri M, Pascual-Castroviejo I, and DiRocco C, editors. *Neurocutaneous Disorders*. Springer; 2007.

Farrell CJ and Plotkin SR. Genetic Causes of Brain Tumors: Neurofibromatosis, Tuberous Sclerosis, Von Hippel-Lindau, and Other Syndromes. In: Wen PY, Schiff D, editors. *Neurologic Clinics: brain tumors in adults*. 2007.

Chu-Shore C and Plotkin SR. The Phakomatoses. In: Rosenberg RN, DiMauro S, Paulson H, Ptacek L, Nestler E, editors. *The molecular and genetic basis of neurological and psychiatric disease*. Philadelphia (PA): Lippincott Williams & Wilkins;2007.

S.R. Plotkin. Phakomatoses: Neurofibromatosis II. In: *The New Encyclopedia of Neuroscience*. Elsevier;2007.

McLaughlin ME, Pepin SM, Maccollin M, Choopong P, Lessell S. Ocular pathologic findings of neurofibromatosis type 2. *Arch Ophthalmol*. 2007 Mar;125(3):389-94.

Courtois-Cox S, Genter Williams SM, Reczek EE, Johnson BW, McGillicuddy LT, Johannessen CM, Hollstein PE, MacCollin M, Cichowski K. A negative feedback signaling network underlies oncogene-induced senescence. *Cancer Cell*. 2006 Dec;10(6):459-72.

Ahronowitz I, Xin W, Kiely R, Sims K, MacCollin M, Nunes FP. Mutational spectrum of the NF2 gene: a meta-analysis of 12 years of research and diagnostic laboratory findings. *Hum Mutat*. 2007 Jan;28(1):1-12.

Nakai Y, Zheng Y, MacCollin M, Ratner N. Temporal control of Rac in Schwann cell-axon interaction is disrupted in NF2-mutant schwannoma cells. *J Neurosci*. 2006 Mar 29;26(13):3390-5.

5: Lee JW, Houtchens M, Hochberg F, Price B, M L, Cunnane M, Pfannl R, MacCollin M. Glioblastoma multiforme presenting as bilateral internal auditory canal tumors. *J Neurol*. 2006 Apr;253(4):522-4. Epub 2006 Mar 20.

6: Aghi M, Kluwe L, Webster MT, Jacoby LB, Barker FG 2nd, Ojemann RG, Mautner VF, MacCollin M. Unilateral vestibular schwannoma with other neurofibromatosis type 2-related tumors: clinical and molecular study of a unique phenotype. *J Neurosurg*. 2006 Feb;104(2):201-7.

Nunes F, Shen Y, Niida Y, Beauchamp R, Stemmer-Rachamimov AO, Ramesh V, Gusella J, MacCollin M. Inactivation patterns of NF2 and DAL-1/4.1B (EPB41L3) in sporadic meningioma. *Cancer Genet Cytogenet*. 2005 Oct 15;162(2):135-9.

Eckstein O, Stemmer-Rachamimov A, Nunes F, Hoch D, Ojemann R, MacCollin M. Multiple meningiomas in brain and lung due to acquired mutation of the NF2 gene. *Neurology*. 2004 May 25;62(10):1904-5.

Stemmer-Rachamimov AO, Louis DN, Nielsen GP, Antonescu CR, Borowsky AD, Bronson RT, Burns DK, Cervera P, McLaughlin ME, Reifenberger G, Schmale MC, MacCollin M, Chao RC, Cichowski K, Kalamarides M, Messerli SM, McClatchey AI, Niwa-Kawakita M, Ratner N, Reilly KM, Zhu Y, Giovannini M. Comparative pathology of nerve sheath tumors in mouse models and humans. *Cancer Res*. 2004 May 15;64(10):3718-24.

Kaufman DL, Heinrich BS, Willett C, Perry A, Finseth F, Sobel RA, MacCollin M. Somatic instability of the NF2 gene in schwannomatosis. *Arch Neurol*. 2003 Sep;60(9):1317-20.

Nunes F, MacCollin M. Neurofibromatosis 2 in the pediatric population. *J Child Neurol*. 2003 Oct;18(10):718-24.

MacCollin M, Willett C, Heinrich B, Jacoby LB, Acierno JS Jr, Perry A, Louis DN. Familial schwannomatosis: exclusion of the NF2 locus as the germline event. *Neurology*. 2003 Jun 24;60(12):1968-74.
PMID: 12821741 [PubMed - indexed for MEDLINE]

Kluwe L, Mautner V, Heinrich B, Dezube R, Jacoby LB, Friedrich RE, MacCollin M. Molecular study of frequency of mosaicism in neurofibromatosis 2 patients with bilateral vestibular schwannomas. *J Med Genet*. 2003 Feb;40(2):109-14.

b. Please provide information on NF-related research ongoing in your clinic or performed by personnel affiliated with your clinic.

- "Whole body MRI evaluation of subjects with NF1, NF2, and schwannomatosis." This research study will perform whole body MRI scans on subjects with NF. The goals are (1) to risk stratify patients with NF1

with respect to MPNST, (2) clarify phenotypic differences between NF2 and schwannomatosis, and (3) study efficacy of the technique in evaluating offspring of subjects with sporadic schwannomatosis. The study is funded by the Department of Defense. Subjects with tumors > 5 cm will be eligible for whole body PET/CT to measure tumor metabolism.

- Molecular characterization of SMARCB1 in familial and sporadic schwannomatosis. We are analyzing our collection of tumors from patients with familial and sporadic schwannomatosis to extend the findings of Hulsebos et al.
- Clinical trials have been listed above in multiple locations.

10. PATIENT SUPPORT

Do you have an NF patient support group that meets in association with your NF Clinic?

NO

If 'yes' provide details.

If 'no', are you interested in starting such a group?

The MGH clinic has addressed this question in the past and has solicited input from the local patient foundations. In general, patients within the Boston community are not interested in a regular support group. For example, we have found some patients with NF to be fearful of meeting other patients with NF that are more severely affected. We have found that email between a select few patients can be helpful to patients. The nurse practitioner in the clinic helps coordinate patients who wish to email each other.

If our patients expressed an interest in developing such a support group, we would support it entirely.

What resources would help you to do this?

We have the necessary resources but would need a clear commitment from patients to expend resources in this manner.

11. OTHER INFORMATION

Please provide any additional information that is pertinent to your request to join the CTF NF Clinic Network.

The MGH is a comprehensive NF clinic with a particular focus on NF2 and schwannomatosis. We believe that it is essential to have members of the CTF NF Clinic Network have expertise in these forms of NF in order to share expertise. In addition, the clinic has an unusual number of adult patients and can share expertise in this regard, as well.