Contemporary Clinical Trials 34 (2013) 305–311

Contents lists available at SciVerse ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

# Development of an international internet-based neurofibromatosis Type 1 Patient registry ☆,☆☆

Kimberly J. Johnson [a,b,c,*], Ibrahim Hussain [d], Katherine Williams [a], Ryan Santens [a], Nancy L. Mueller [a], David H. Gutmann [d]

[a] Brown School, Washington University in St. Louis, St. Louis, MO 63130, USA
[b] Department of Pediatrics, Washington University School of Medicine, St. Louis, MO 63110, USA
[c] Siteman Cancer Center, Washington University in St. Louis, St. Louis, MO, USA
[d] Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA

ARTICLE INFO

*Article history:*
Received 30 August 2012
Received in revised form 8 November 2012
Accepted 5 December 2012
Available online 14 December 2012

*Keywords:*
Neurofibromatosis type 1
Rare disease
Genetic syndrome
Registry
Internet
Online

ABSTRACT

Internet technology provides unprecedented opportunities to assemble large numbers of individuals with rare diseases from across the world to conduct clinical research studies. One such rare disease is Neurofibromatosis Type 1 (NF1), a cancer predisposition syndrome affecting ~1/3000–4000 individuals worldwide. To enable large epidemiological research studies on NF1, we developed an online NF1 Patient Registry Initiative (NPRI) (https://nf1registry.wustl.edu/). Our objective is to describe the methods for registry development and implementation as well as the characteristics of participants during the first year of registry operation. Following electronic consent, participants completed a 30–45 minute questionnaire with 11 sections that asked about demographic, health, and social information. During the first year, 308 individuals from 44 U.S. states, the District of Columbia, and 19 countries participated. Of these, 98% provided demographic information and ~85% completed all questionnaire sections, of which 95% reported the presence of at least two NF1 diagnostic criteria. Most participants who completed the questionnaire indicated willingness for future contact (99%) and for providing biological samples (94%). Based on this first year of experience, we conclude that online registries provide a valuable tool for assembling individuals with a rare disease from across the world for research studies.



## 1. Introduction

Neurofibromatosis type 1 (NF1) is one of the most common hereditary cancer syndromes. The prevalence of NF1 is commonly reported to be between 1/3000 and 4000 with estimates ranging from 1/2500 to 1/7800 [1–6]. NF1 is a single gene disorder caused by a germline mutation in the *NF1* gene [7] that affects both sexes equally with no evidence to suggest that the prevalence varies by race and ethnic background [6,8].

NF1 is usually diagnosed based on the presence of individuals harboring at least two of the established diagnostic features, including café-au-lait macules, skinfold freckling, Lisch nodules, neurofibromas, optic gliomas, distinctive bone abnormalities, and a first-degree family relative with NF1. In addition, affected people have an increased predisposition for the development of benign and malignant tumors, particularly pediatric brain tumors and soft tissue sarcomas [8–14]. Cancer is the leading cause of death in this population, and has been associated with a reduction in overall life expectancy of 8–15 years [11,12].

There is notable variation in expressivity of NF1 clinical features, even between family members who carry the same germline *NF1* gene mutation. Previous research has suggested

*Abbreviations:* NF1, neurofibromatosis type 1; MPNST, malignant peripheral nerve sheath tumor; NPRI, NF1 Patient Registry Initiative

☆ Grant support: American Cancer Society Institutional Research Grant, Alex's Lemonade Stand Foundation for Childhood Cancer Research, St. Louis Children's Hospital Foundation.

☆☆ Financial disclosures: The authors have no financial disclosures to report.

* Corresponding author at: Master of Public Health Program, George Warren Brown School, 237 Goldfarb Hall, Campus Box 1196, Washington University in St. Louis, One Brookings Drive, St. Louis, MO 63130, USA. Tel.: +1 314 935 9154; fax: +1 314 935 8511.

*E-mail address:* kijohnson@wustl.edu (K.J. Johnson).

1551-7144/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.cct.2012.12.002

an important role for modifying genes in variation of clinical signs [15,16]; however, studies also suggest that environmental factors could play defining roles in influencing health outcomes in individuals with NF1 [17,18]. Characterizing the genetic and environmental factors that modify health outcomes in individuals with NF1 is a critical step toward the development of effective and more individualized therapeutic strategies as well as the identification of individuals at high risk for specific NF1-associated medical problems.

A challenge to NF1 and other rare disease research is the difficulty of assembling sufficient numbers of individuals with NF1 for research studies. To overcome this barrier, we recently developed a web-based international NF1 registry (NF1 patient registry initiative (NPRI)). The overarching goal of the registry is to assemble a large number of individuals and associated clinical data to facilitate research that advances an understanding of the range of conditions associated with NF1 and the factors that contribute to health outcomes. The specific objectives of this paper are to: (1) detail the scientific rationale used to develop and implement the internet-based NF1 registry, (2) describe the methodological details of the registry study design, data collection, and data management, (3) characterize participants enrolled during the first year of operation, and (4) describe the representativeness of registry participants according to demographic and clinical characteristics.

## 2. Methods

### 2.1. Scientific rationale for the registry

The NF1 Patient Registry Initiative (NPRI) was launched on May 17, 2011 (https://nf1registry.wustl.edu/) to fulfill an unmet research need. Prior to the launch of the registry, there was no international NF1 patient research registry. Importantly, the registry provides the opportunity for individuals to participate in research who may have been under-represented in previous predominantly clinic-based research studies. To achieve the overarching goal of the registry described above, the registry collects contact information from participants for future research studies as well as cross-sectional and prospective data on demographic, clinical, social, and educational variables (further detailed below). The registry design incorporated the input of numerous NF1 healthcare providers and researchers with a range of different expertise (e.g., NF1 clinicians, nurses, neuropsychologists, physical and occupational therapists, and epidemiologists).

### 2.2. Eligibility criteria and consent for participation

Both children and adults with NF1 are eligible to participate. Individuals self-identify as having NF1 through on-line registration. In addition, eligibility is assessed through a number of questions about clinical features commonly used to diagnose individuals with NF1 [19] as described below.

Upon accessing the NPRI website, registrants provide their email address as their username and then select a password. Participants are given an electronic version of a consent form that describes the purpose of the registry, instructions for completing the questionnaire, a statement of confidentiality, benefits and risks of participation, contact information for the principal investigator of the registry, and HIPPA information. Electronic consent for registry participation is provided by clicking on two boxes at the end of the consent form (also available on the registry website) indicating that (1) the participant understands the purpose, instructions, confidentiality, benefits, risks, and the HIPAA disclaimer for the NF1 registry and (2) the NF1 registry team can release de-identified data to researchers at Washington University and other research centers for future studies. No information is retained from participants who do not consent. The statement of confidentiality includes information regarding certification from the United States Department of Health and Human Services [20] to ensure additional privacy protection by allowing researchers "who have access to research records to refuse to disclose identifying information in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level" (except under certain circumstances such as court order or subpoena). Participants can elect to revoke their authorization for participation in the study at any time by completing a withdrawal letter, found in the participant section of the Human Research Protection Office website at http://hrpo.wustl.edu or by requesting that the Principal Investigator send them a copy of the letter. All protocols for data collection were approved by the Washington University Institutional Review Board.

Participants are screened for eligibility through several questions. The questionnaire asks participants to indicate (yes, no, don't know) whether they have ever been diagnosed with any of the following criteria selected to align with standard NIH NF1 diagnostic criteria [19]: $\geq 6$ café-au-lait spots (light brown birthmarks), $>2$ freckles in the armpit area and/or groin area, Lisch nodules (hamartomas on the colored portion of the eye), plexiform neurofibroma, forearm bowing (curving of the bone in the arm between the hand and elbow), lower leg bowing (curving of the "shin bone"), or a brain tumor. In addition, participants are asked whether they have a blood relative who has been diagnosed with NF1, and if they had *NF1* genetic testing (yes, no, don't know). A scoring system was then developed to determine eligibility based on participants' questionnaire responses. Participants were given one point for each positive response to the questions pertaining to the clinical features, relatives with NF1, and a positive *NF1* genetic test. In addition, there is an ongoing effort to obtain medical record release forms (MRRFs) from all participants to verify eligibility. Participants can download MRRFs from the registry website and return them to study personnel by mail. Participants who do not return forms are sent forms by mail with a business reply envelope that is addressed to study personnel.

### 2.3. Recruitment

During the first year, registry recruitment employed a variety of methods, including informational cards that were distributed to several clinics in the U.S. and Australia, announcements on the Washington University NF Center and Facebook websites (http://nfcenter.wustl.edu/research/washington-university-nf-center/; http://www.facebook.com/#!/pages/Washington-University-Neurofibromatosis-NF-Center/113582822073732), Google advertising, the clinicaltrials.gov website (www.clinicaltrials.gov), and emails to NF1 and rare disease advocacy groups requesting that their organization post registry information on their websites.

### 2.4. Data collection

The data collected through the registry is self-reported. Participants provide contact information and complete a 30–45 minute questionnaire that inquires about demographics, medical, and social history. The questionnaire is comprised of 11 distinct sections that each constitute a separate web page: (1) basic demographic information, (2) doctor(s) information, 3) birth history, (4) family history, (5) clinical history, (6) asthma/allergy/autoimmune history, (7) child and family tumor/cancer history, (8) educational/social/behavioral related history, (9) growth and puberty questions, (10) pregnancy related questions (for females and parents of minors only), and (11) willingness to participate in future research studies and to provide biospecimens. The data collected through the registry allow for evaluation of the representativeness of the population with respect to demographic features (e.g. sex, age, state, country) compared to other published NF1 case series and the general population, assessment of the validity of reported NF1 diagnoses according to reported clinical characteristics, and initial evaluation of hypotheses that could stimulate new research. An important feature of the registry is that it collects contact information from registrants, which allows efficient identification of potential subjects for future research studies. In addition, emails are sent to participants annually to remind them to update their registry information, which will allow for prospective data analyses.

### 2.5. Data security

All data and records from the NPRI web application are stored on a secure password protected server behind a firewall at Washington University following current HIPAA guidelines. The data are also encrypted in transmission for further security. Upon registration, each participant is assigned a unique study ID number that is used to de-identify the data. The data submitted by participants is only accessed from the server by registry personnel and is subsequently stripped of identifying information to create a de-identified analytic dataset. A master list containing information that links the subject ID to their contact information (but not health information) is stored on a password-protected server accessible only to authorized study personnel.

### 2.6. Data management

Study personnel regularly review participant information for missing or incomplete questionnaire entries, and follow up with these participants through email and phone calls to encourage them to complete their registration and to return MRRFs. Duplicate entries are removed by examining individual files for identical names, phone numbers, and addresses to ensure that the dataset corresponds to one unique entry per individual.

### 2.7. Data sharing plan

Investigators interested in accessing de-identified registry data or in recruiting registry participants for research studies can contact the registry's Principal Investigator (K.J.J.) for initial discussion of feasibility. One- to two-page concept proposals can then be submitted for peer review of scientific merit by a panel of experts not affiliated with the registry. Upon human subject approval by both Washington University and the collaborating investigator(s) institution(s), de-identified data can then be shared and/or participants can be contacted about research studies by registry personnel.

### 2.8. Statistical analysis

SAS version 9.2 (Cary, NC) was employed to calculate all statistics and to summarize demographic and clinical characteristics of participants enrolled in the registry. Analysis of variance (ANOVA) was used to determine the r-squared ($r^2$) statistic for the proportion of variation explained in registry participation by the state population as determined from 2010 census data [21]. ARC-GIS mapping software (ESRI, Redlands, CA) was used to generate a map of United States participant density by region. Of note, only U.S. regions (Northeast, Midwest, South, and West) are shown on the map to protect the anonymity of participants from states with small populations.

## 3. Results

### 3.1. Enrollment and questionnaire completion

From the period of 5/17/2011–5/16/2012, 308 individuals registered. Participation rates generally increased over the course of the year with 29 participants enrolling in the first three months of registry operation compared to 110 participants in the last three months (data not shown). Ninety-eight percent ($n=303$) of participants completed the section containing demographic information (sex, race, and age). In addition, all participants provided their email address, which also served as their username (100%). Approximately 85% of participants ($n=262$) answered questions in all questionnaire sections.

### 3.2. Geographic representation of participants

Participants represented 44 U.S. states, the District of Columbia (Fig. 1), and 19 countries (Table 1). Most participants reported living in the United States ($n=253$, 83%), followed by Canada ($n=13$, 4.3%) and India ($n=9$, 3.0%). U.S. states with the highest participant rate were Missouri and Illinois, followed by Michigan, California, Florida, New York, and Texas (Fig. 1). The proportion of variability ($r^2$) in participation explained by state population density was 0.21 (ANOVA $F$-test $p=0.0009$). After excluding participants who were seen in the NF Clinical Program at the registry's home institution, the $r^2$ increased to 0.43, indicating that a substantial proportion of the variance in state participation was explained by state population density (ANOVA $F$-test $p<0.0001$).

### 3.3. Demographic characteristics of participants

More adult females participated than males (69.2% vs. 30.9%), while, for minor participants, females and males each comprised 50% of registrants (Table 2). The racial distribution for U.S. participants was ~81% white ($n=204$), 9.9% multiple

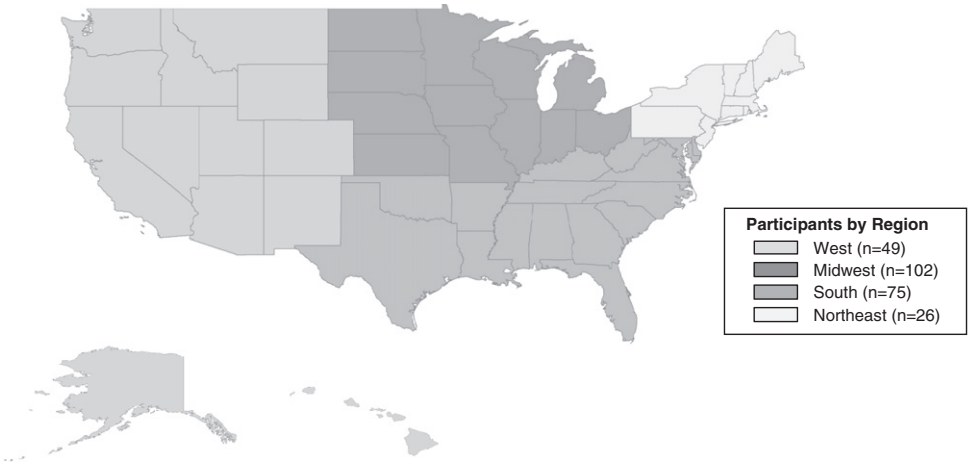


**Fig. 1.** Map of U.S. participants ($n=253$). Darker shading in states represents higher densities of participants.

races ($n=25$), 3.2% unknown ($n=8$), 3.2% Black or African American ($n=8$), 2% Asian ($n=5$), and 1.2% American Indian or Alaskan Native ($n=3$). A similar number of adult participants reported having an affected family member as those who reported having no affected family member. For minor registrants, a majority (62.1%) were reported as having no relatives with NF1. The age distribution of participants was bimodal with a mean of $28.2 \pm 17.8$ years and median of 28.4 (Fig. 2). Notably, participation among adolescents/young adults from 15–19 years was lower relative to the younger and older age groups.

### 3.4. Eligibility according to clinical criteria for NF1 diagnosis

Eighty-six percent ($n=265$) of participants responded to questions inquiring about NF1 clinical features ($\geq 6$ café-au-lait spots, $>2$ freckles in the armpit area and/or groin area, Lisch nodules, plexiform neurofibroma, forearm or lower leg bowing, a brain tumor diagnosis, a positive *NF1* genetic test, and a first-degree relative with NF1). The distribution of the number of clinical features reported by participants is shown in Fig. 3. Ninety-five percent of respondents would be considered to have NF1 based on reporting $\geq 2$ NF1 clinical features ($n=250$) or a positive *NF1* genetic test ($n=3$). The most frequently reported clinical features were $\geq 6$ café au lait spots (95%, $n=$

**Table 1**
Countries of residence reported by registry participants.

| Country[a] | No. | % |
|---|---|---|
| Argentina | 1 | 0.33 |
| Australia | 5 | 1.63 |
| Bosnia | 1 | 0.33 |
| Cameroon | 1 | 0.33 |
| Canada | 13 | 4.25 |
| France | 1 | 0.33 |
| Ghana | 1 | 0.33 |
| India | 9 | 2.94 |
| Israel | 1 | 0.33 |
| Jamaica | 1 | 0.33 |
| Malaysia | 1 | 0.33 |
| Philippines | 4 | 1.31 |
| Scotland | 1 | 0.33 |
| Serbia | 1 | 0.33 |
| Spain | 1 | 0.33 |
| Switzerland | 2 | 0.65 |
| Tunisia | 2 | 0.65 |
| United Kingdom | 7 | 2.29 |
| United States | 253 | 82.32 |

[a] Three participants had missing countries.

**Table 2**
Characteristics of participants ($n=308$).

| Characteristic | Total | | Adults | | Minors | |
|---|---|---|---|---|---|---|
| | No.[a] | % | No.[b] | % | No.[c] | % |
| Sex | | | | | | |
| Male | 115 | 37.5 | 62 | 30.9 | 53 | 50 |
| Female | 192 | 62.5 | 139 | 69.2 | 53 | 50 |
| Race[d] | | | | | | |
| White | 204 | 80.6 | 129 | 81.7 | 75 | 79.0 |
| Black/African American | 8 | 3.2 | 5 | 3.2 | 3 | 3.2 |
| Asian | 5 | 2.0 | 2 | 1.3 | 3 | 3.2 |
| American Indian/Alaskan Native | 3 | 1.2 | 2 | 1.3 | 1 | 1.1 |
| Unknown | 8 | 3.2 | 7 | 4.4 | 1 | 1.1 |
| Multiple races | 25 | 9.9 | 13 | 8.2 | 12 | 12.6 |
| Citizenship | | | | | | |
| USA | 253 | 82.7 | 158 | 79.4 | 95 | 88.8 |
| Non-USA | 53 | 17.3 | 41 | 29.6 | 12 | 11.2 |
| Affected family member | | | | | | |
| Yes | 106 | 40.0 | 77 | 44.7 | 30 | 31.6 |
| No | 134 | 50.6 | 75 | 44.1 | 59 | 62.1 |
| Don't Know | 25 | 9.4 | 19 | 11.2 | 6 | 6.3 |
| Agreeing to future contact about research studies | | | | | | |
| Yes | 246 | 98.8 | 159 | 98.2 | 87 | 100 |
| No | 3 | 1.2 | 3 | 1.9 | 0 | 0 |
| Willingness to provide biological samples | | | | | | |
| Yes | 230 | 94.3 | 150 | 93.7 | 81 | 95.3 |
| No | 14 | 5.7 | 10 | 6.3 | 4 | 4.7 |

[a] Missing data (total): Sex ($n=1$), race ($n=0$), citizenship ($n=2$), affected family member ($n=43$), agreeing to future contact about research studies ($n=59$), willingness to provide biological samples ($n=64$).
[b] Missing data (adult participants): Sex ($n=0$), race ($n=0$), citizenship ($n=2$), affected family member ($n=31$), agreeing to future contact about research studies ($n=39$), willingness to provide biological samples ($n=42$).
[c] Missing data (minor participants): Sex ($n=1$), race ($n=0$), citizenship ($n=0$), affected family member ($n=12$), agreeing to future contact about research studies ($n=20$), willingness to provide biological samples ($n=22$).
[d] Includes U.S. participants only.

248) and freckles in the armpit or groin area (84%, $n=221$). Fifty percent of participants reported Lisch nodules ($n=130$) and a minority reported plexiform neurofibromas (34.7%, $n=91$), a pediatric brain tumor diagnosis (16.2%, $n=42$), leg bowing (13.4%, $n=35$), or arm bowing (4.6%, $n=12$).

A characteristic feature of NF1 is an increased risk for a number of different tumor types. The most frequently reported tumor types are shown in Table 3. Plexiform neurofibromas were the most commonly reported tumor (34.7%), followed by pediatric brain tumor (16.2%). In addition, pediatric brain tumors were more commonly reported on minor than on adult questionnaires (38.9% vs. 3.9%). Among adults (≥18 years of age), 4.8% of participants reported having been diagnosed with a brain tumor after the age of 18 years. Other tumors characteristic of NF1 reported by participants included spine tumors (4.2% and 3.2% of adult and pediatric participants), and malignant peripheral nerve sheath tumors (MPNSTs) (4.2% and 1.1% of adult and pediatric participants). A total of two participants each reported melanoma, neuroblastoma, and pheochromocytoma.

## 4. Discussion

Rare disease registries are an important component of clinical research efforts aimed at understanding the underlying disease mechanisms in patients with uncommon conditions. NF1 is a rare cancer predisposition syndrome that presents a particular enigma for clinicians: While NF1 is 100% penetrant, there is extreme variability in the clinical features between individuals in the same family with the identical germline *NF1* mutation as well as between monozygotic twins [6,22]. This variability limits our ability to predict the natural course of NF1 in any given individual. The identification of predictive factors that influence health outcomes in individuals with NF1 requires the assembly of large numbers of individuals for clinical epidemiologic research.

The NPRI design permitted rapid enrollment of a large number of participants with NF1 from most U.S. states and 19 countries during a one year time period. NF1 has been reported to affect all races and both sexes equally. However, most adult registry participants were female, consistent with the higher participation in health research studies by females reported in other studies [23–25]. In contrast, for minors whose questionnaires were completed by a parent or guardian, the sex distribution was equal. By race, most U.S. participants were Caucasian (~81%), which is higher than the U.S. general population (72% Caucasian) [21]. An important future objective for the registry will be to increase the representativeness of the under-reported minorities with respect to the general population. We are currently evaluating a number of different recruiting mechanisms including internet advertising and clinic-based recruiting to determine the efficacy of different methods by demographic characteristics (sex, age, and race). This information may inform strategies for increasing enrollment by under-represented groups.

The distribution of U.S. participants across states displays concordance with the overall U.S. state population, especially when individuals who were patients at the Washington University School of Medicine/St. Louis Children's Hospital Clinical Program were removed from the analysis ($r^2=0.43$). The high participation by the Washington University School of Medicine/St. Louis Children's Hospital Clinical Program patient population likely reflects increased awareness about the registry through regular clinic communication. Although the registry is not population based, these data suggest that most states have representation by individuals with NF1, and that internet-based registries are an effective means of assembling individuals from a wide geographic distribution across the U.S. and internationally.

A potential concern for patient driven registries that are being employed for research is the potential for inaccuracy of the rare disease diagnosis. Most NPRI participants (95%) who completed their questionnaire indicated responses to questions about clinical features of NF1 consistent with having this condition. A large case series of 1893 individuals <21 years of age reported that 97% of patients have ≥2 NF1 clinical features by age 8 years [9]. The most commonly reported clinical features in this case series were café-au-lait macules (99% of subjects by age one year), axillary freckles (90% of subjects by age seven years), neurofibromas (2 dermal or 1 plexiform, 84% of subjects by 20 years), Lisch nodules (70% of subjects by age 10 years), osseous lesions (14% of subjects by age one year), and symptomatic optic gliomas (4% of subjects by age 3 years). The percentage of registrants with these clinical features was consistent with this large case series, with the most commonly reported clinical features being café-au-lait macules (95%),

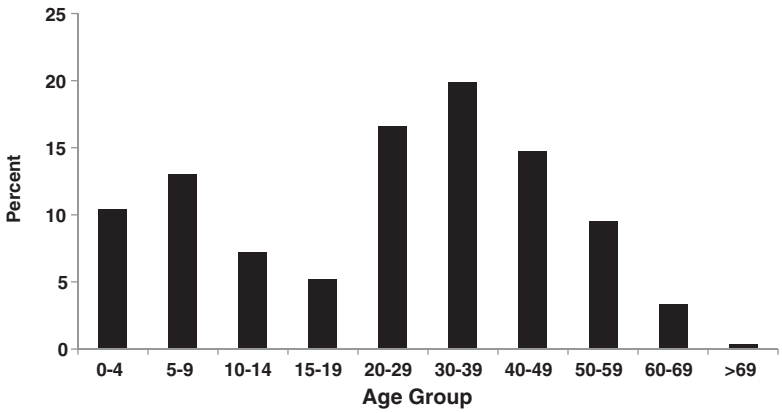


**Fig. 2.** Age distribution of participants in the NF1 registry. The number of participants included in this analysis is $n=307$; one individual had missing data on age.

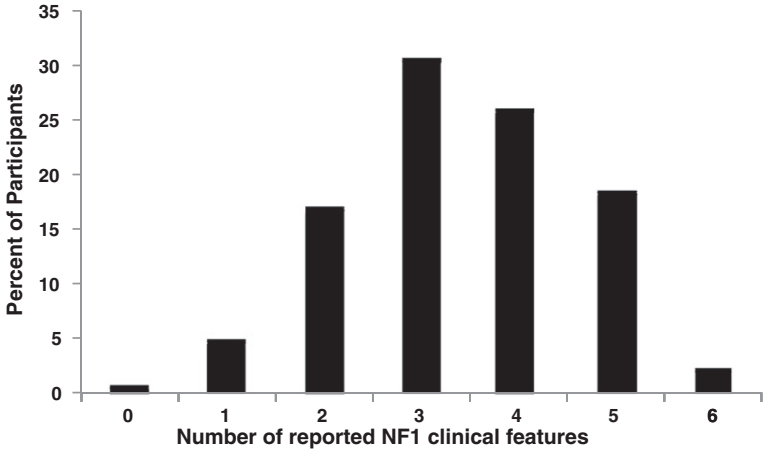


**Fig. 3.** Number of reported clinical features of NF1 ($n=265$). Clinical features included the following: ≥6 café-au-lait spots, >2 freckles in the armpit area and/or groin area, Lisch nodules, plexiform neurofibroma, forearm bowing, lower leg bowing, a brain tumor diagnosis, positive NF1 genetic test, and relative with NF1.

axillary freckles (84%), Lisch nodules (50%), and leg or arm bowing (14%). We did not ask about dermal neurofibromas; however, smaller case series have reported the prevalence of plexiform neurofibromas to vary with age. Plexiform neurofibromas have been reported in 27–28% of individuals with NF1 >20 years of age [26,27], an estimate slightly lower than the 36% of registry participants in this age group who reported this feature (data not shown). Leg bowing is considered a marker for osseous lesions [28]; the percentage of registry participants reporting this abnormality was similar to the large case series described above. While we did not specifically collect comparable data on symptomatic optic pathway gliomas, the high percentage of participants who reported pediatric brain tumors (see below) is consistent with previous reports demonstrating that this is the most frequent tumor type in children with NF1 [29–32]. In total, these data suggest that the clinical features of NF1 as reported by participants are similar to those described in previously published case series. To increase the quality of the registry data, we are currently in the process of obtaining MRRFs from all participants and conducting medical record validation of NF1 diagnoses to determine the extent of verification necessary to ensure high quality data.

**Table 3**
Tumor types reported by participants ($n=263$).[a]

| Tumor diagnosis | Total ($n=263$) | | Adults ($n=168$) | | Minors ($n=95$) | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| None | 127 | 48.3 | 87 | 51.8 | 40 | 42.1 |
| Any | 136 | 51.7 | 81 | 48.2 | 55 | 57.9 |
| *Most frequent tumor types* | | | | | | |
| Plexiform neurofibromas | 91 | 34.7 | 61 | 36.3 | 30 | 31.6 |
| Pediatric brain tumor[b] | 42 | 16.2 | 5 | 3.0 | 37 | 38.9 |
| Spine | 10 | 3.8 | 7 | 4.2 | 3 | 3.2 |
| Adult brain tumor[b] | 8 | 3.1 | 8 | 4.8 | NA | NA |
| MPNST | 8 | 3.1 | 7 | 4.2 | 1 | 1.1 |
| Breast | 5 | 1.9 | 5 | 3.0 | 0 | 0 |
| Melanoma | 2 | 0.8 | 2 | 1.2 | 0 | 0 |
| Neuroblastoma | 2 | 0.8 | 1 | 6.0 | 1 | 1.1 |
| Pheochromocytoma | 2 | 0.8 | 2 | 1.2 | 0 | 0 |

[a] A total of 45 participants of 308 participants had missing information on any tumor diagnoses.
[b] Adult and pediatric brain tumors were defined as brain tumors occurring ≥18 years and <18 years respectively.

The types of tumors reported by participants were those most commonly reported in individuals with NF1. After plexiform neurofibromas, the tumor type participants reported most frequently was pediatric brain tumor. The reported prevalence of optic pathway glioma (OPG), the most common brain tumor type in children with NF1, shows marked variation by study from 1.5% to 58% (reviewed by Patil and Chamberlin [33]), The wide variation in the prevalence of OPGs is primarily due to differences in MRI screening practices, with some clinical programs routinely screening patients in the absence of visual symptoms. The markedly higher prevalence of reported brain tumors among pediatric compared to adult registry participants is most likely due to introduction of MRI screening in the early 1990s [34,35]. An increased frequency of brain tumors in adults with NF1 has been previously reported [12,36]. MPNSTs, a tumor that is known to be increased in individuals with NF1 [37], were also reported in 8 participants. In the general population, the incidence of these tumors reported by registry participants is very low. For example, pediatric brain tumors (diagnosed at <18 years of age) and MPNSTs are estimated to occur in 29 and ~1 per million people respectively [38]. The reported frequency of these rare tumors in the NF1 registry participants is over 20,000 times more common than in the general population.

Rare disease registries have both strengths and limitations. A main strength of the NPRI, especially owing to the ever-growing access to internet technologies across the world, is the ability to rapidly assemble a large number of subjects with a rare condition at a relatively low cost for analysis of data and contact for research studies. However, because participation is based on self-selection, participants may not be representative of the general population with NF1. In addition, there are limitations to self-reported information, including reporting errors about their medical and social histories. Given these potential biases, it will be important to consider any results from the registry regarding associations between participant characteristics and outcomes as hypothesis generators requiring replication in other cohorts of individuals with NF1 as well as validation in experimental animal model systems. Finally,

our registry is currently limited to English-speaking individuals with access to the internet, which may reduce participation among individuals without these capabilities.

In conclusion, the experience with a web-based international online registry for NF1 during the first year of operation demonstrates that internet registries represent a viable mechanism for assembling individuals with rare diseases from across the world for etiologic studies of cancer and other outcomes.

## Acknowledgements

We thank Taylor Ferguson for her excellent technical and administrative assistance as well as Shea Roesel and Charles Rathmann of the Washington University Recruitment Enhancement Core.

## References

[1] Poyhonen M, Kytola S, Leisti J. Epidemiology of neurofibromatosis type 1 (NF1) in northern Finland. J Med Genet 2000;37(8):632–6.
[2] Evans DG, Howard E, Giblin C, Clancy T, Spencer H, Huson SM, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A 2010;152A:327–32.
[3] Sergeyev AS. On the mutation rate of neurofibromatosis. Humangenetik 1975;28(2):129–38.
[4] Samuelsson B, Axelsson R. Neurofibromatosis. A clinical and genetic study of 96 cases in Gothenburg, Sweden. Acta Derm Venereol Suppl (Stockh) 1981;95:67–71.
[5] Huson SM, Compston DA, Clark P, Harper PS. A genetic study of von Recklinghausen neurofibromatosis in south east Wales. I. Prevalence, fitness, mutation rate, and effect of parental transmission on severity. J Med Genet 1989;26:704–11.
[6] Lynch TM, Gutmann DH. Neurofibromatosis 1. Neurol Clin 2002;20(3): 841–65.
[7] Marchuk DA, Saulino AM, Tavakkol R, Swaroop M, Wallace MR, Andersen LB, et al. cDNA cloning of the type 1 neurofibromatosis gene: complete sequence of the NF1 gene product. Genomics 1991;11: 931–40.
[8] McGaughran JM, Harris DI, Donnai D, Teare D, MacLeod R, Westerbeek R, et al. A clinical study of type 1 neurofibromatosis in north west England. J Med Genet 1999;36:197–203.
[9] DeBella K, Szudek J, Friedman JM. Use of the national institutes of health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics 2000;105(3 Pt. 1):608–14.
[10] McKeever K, Shepherd CW, Crawford H, Morrison PJ. An epidemiological, clinical and genetic survey of neurofibromatosis type 1 in children under sixteen years of age. Ulster Med J 2008;77:160–3.
[11] Wilding A, Ingham SL, Lalloo F, Clancy T, Huson SM, Moran A, et al. Life expectancy in hereditary cancer predisposing diseases: an observational study. J Med Genet 2012;49:264–9.
[12] Rasmussen SA, Yang Q, Friedman JM. Mortality in neurofibromatosis 1: an analysis using U.S. death certificates. Am J Hum Genet 2001;68(5): 1110–8.
[13] Gutmann DH. Using neurofibromatosis-1 to better understand and treat pediatric low-grade glioma. J Child Neurol 2008;23(10):1186–94.
[14] Walker L, Thompson D, Easton D, Ponder B, Ponder M, Frayling I, et al. A prospective study of neurofibromatosis type 1 cancer incidence in the UK. Br J Cancer 2006;95:233–8.
[15] Carey JC, Baty BJ, Johnson JP, Morrison T, Skolnick M, Kivlin J. The genetic aspects of neurofibromatosis. Ann N Y Acad Sci 1986;486: 45–56.
[16] Sabbagh A, Pasmant E, Laurendeau I, Parfait B, Barbarot S, Guillot B, et al. Unravelling the genetic basis of variable clinical expression in neurofibromatosis 1. Hum Mol Genet 2009;18:2768–78.
[17] Lammert M, Friedman JM, Roth HJ, Friedrich RE, Kluwe L, Atkins D, et al. Vitamin D deficiency associated with number of neurofibromas in neurofibromatosis 1. J Med Genet 2006;43:810–3.
[18] Posma E, Aalbers R, Kurniawan YS, van Essen AJ, Peeters PM, van Loon AJ. Neurofibromatosis type I and pregnancy: a fatal attraction? Development of malignant schwannoma during pregnancy in a patient with neurofibromatosis type I. BJOG 2003;110:530–2.
[19] Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol May 1988;45(5):575–8.
[20] U.S. Department of Health & Human Services. Office of Extramural Research, N.I.o.H. Certificates of Confidentiality: Background Information. Available from: http://grants.nih.gov/grants/policy/coc/background.htm; 2011.
[21] U.S. Census Bureau. Profile of General Population and Housing Characteristics: 2010; 2010 Demographic Profile. Accessed 1/28/2011 from http://factfinder2.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=DEC_10_DP_DPDP1&prodType=table.
[22] Rieley MB, Stevenson DA, Viskochil DH, Tinkle BT, Martin LJ, Schorry EK. Variable expression of neurofibromatosis 1 in monozygotic twins. Am J Med Genet A 2011;155A:478–85.
[23] de Coul EL Op, Gotz HM, van Bergen JE, Fennema JS, Hoebe CJ, Koekenbier RH, et al. Who participates in the Dutch Chlamydia screening? A study on demographic and behavioral correlates of participation and positivity. Sex Transm Dis 2012;39:97–103.
[24] Le Retraite L, Eisinger F, Loundou A, Rinaldi Y, Seitz JF, Auquier P. Sociogeographical factors associated with participation in colorectal cancer screening. Gastroenterol Clin Biol 2010;34:534–40.
[25] Roberts JS, Barber M, Brown TM, Cupples LA, Farrer LA, LaRusse SA, et al. Who seeks genetic susceptibility testing for Alzheimer's disease? Findings from a multisite, randomized clinical trial. Genet Med 2004;6: 197–203.
[26] Noble F, Kornberg AJ, Elder JE, Delatycki MB. Retrospective analysis of patients attending a neurofibromatosis type 1 clinic. J Paediatr Child Health 2007;43:55–9.
[27] Huson SM, Harper PS, Compston DA. Von Recklinghausen neurofibromatosis. A clinical and population study in south-east Wales. Brain 1988;111(Pt. 6):1355–81.
[28] Stevenson DA, Viskochil DH, Schorry EK, Crawford AH, D'Astous J, Murray KA, et al. The use of anterolateral bowing of the lower leg in the diagnostic criteria for neurofibromatosis type 1. Genet Med 2007;9: 409–12.
[29] Blatt J, Jaffe R, Deutsch M, Adkins JC. Neurofibromatosis and childhood tumors. Cancer 1986;57:1225–9.
[30] Matsui I, Tanimura M, Kobayashi N, Sawada T, Nagahara N, Akatsuka J. Neurofibromatosis type 1 and childhood cancer. Cancer 1993;72: 2746–54.
[31] Shearer P, Parham D, Kovnar E, Kun L, Rao B, Lobe T, et al. Neurofibromatosis type I and malignancy: review of 32 pediatric cases treated at a single institution. Med Pediatr Oncol 1994;22:78–83.
[32] Cnossen MH, de Goede-Bolder A, van den Broek KM, Waasdorp CM, Oranje AP, Stroink H, et al. A prospective 10 year follow up study of patients with neurofibromatosis type 1. Arch Dis Child 1998;78: 408–12.
[33] Patil S, Chamberlain RS. Neoplasms associated with germline and somatic NF1 gene mutations. Oncologist 2012;17(1):101–16.
[34] Sevick RJ, Barkovich AJ, Edwards MS, Koch T, Berg B, Lempert T. Evolution of white matter lesions in neurofibromatosis type 1: MR findings. AJR Am J Roentgenol 1992;159:171–5.
[35] Ferner RE, Chaudhuri R, Bingham J, Cox T, Hughes RA. MRI in neurofibromatosis 1. The nature and evolution of increased intensity T2 weighted lesions and their relationship to intellectual impairment. J Neurol Neurosurg Psychiatry 1993;56:492–5.
[36] Gutmann DH, Rasmussen SA, Wolkenstein P, MacCollin MM, Guha A, Inskip PD, et al. Gliomas presenting after age 10 in individuals with neurofibromatosis type 1 (NF1). Neurology 2002;59:759–61.
[37] Evans DG, Baser ME, McGaughran J, Sharif S, Howard E, Moran A. Malignant peripheral nerve sheath tumours in neurofibromatosis 1. J Med Genet 2002;39:311–4.
[38] Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 13 Regs Research Data, Nov 2010 Sub (1973–2008) <Single Ages to 85+, Katrina/Rita Population Adjustment> — Linked To County Attributes - Total U.S., 1969–2009 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2011, based on the November 2010 submission.