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

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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

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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.