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Validity of participant-reported diagnoses in an online patient registry: A report from the NF1 Patient Registry Initiative ☆

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ABSTRACT

Background: With increased internet accessibility worldwide, it is now possible to assemble individuals with rare diseases through web-based patient registries. However, the validity of participant-reported medical diagnoses is unknown. The objective of this study was to evaluate the accuracy of participant-reported Neurofibromatosis Type 1 (NF1) diagnoses among participants in the NF1 Patient Registry Initiative (NPRI).

Methods: Subjects enrolled in the NPRI from 5/17/2011 to 7/7/2014 were included. Medical records (MRs) were obtained for participants who returned medical record release forms (MRRFs) during the study period. Participants were classified as having definite, probable, suspected, or no NF1 diagnosis based on MR information. To assess whether a returned MRRF served as a reliable marker of MR-documented NF1, we calculated the positive predictive value (PPV) as the proportion of individuals with MR-documented NF1 among those from whom MRs were obtained. We further examined whether a returned MRRF predicted the number of reported NF1 clinical signs in multivariable linear regression analyses.

Results: A total of 1456 individuals were included in the analyses. Of 416 individuals who returned MRRFs, 205 MRs were reviewed within the study period. The PPV ranged from 72.0 to 98.5% when including definite or definite/probable/suspected cases, respectively. The mean number of reported NF1 clinical signs was similar between those who returned (mean = 3.3 ± 1.2) and did not return (mean = 3.2 ± 1.3) their MRRFs. MRRF return was not a significant predictor of the number of NF1 clinical signs after adjusting for covariates.

Conclusion: These data strongly suggest that individuals enrolling in the NPRI accurately report their NF1 diagnosis.

1. Introduction

A rare disease is a condition that affects <200,000 people in the U.S. [1] or 1/2000 in the European Union [2]. Although these disorders are of low prevalence by definition, the nearly 7000 rare diseases collectively affect ~10% of the total U.S. population [1]. In addition to being of direct benefit to the patient, rare disease research provides exceptional opportunities to clarify biological mechanisms and etiologies shared by many disorders, including common diseases such as cancer and heart disease [3]. However, it can be difficult to assemble adequate numbers of

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participants for research on a single rare disease [4]. As access to the internet is widespread, this obstacle can be partly surmounted using web-based recruitment and registry methods.

Neurofibromatosis Type 1 (NF1) is a rare autosomal dominant disorder with an estimated worldwide prevalence of ~1/3000 [5,6]. The condition results from inherited or de novo mutations in the *NF1* tumor suppressor gene [5–8]. While NF1 has complete penetrance, with all individuals showing some features of the disease, its expression is age-dependent and the clinical presentation can be variable and unpredictable, even between family members who carry identical germline *NF1* gene mutations [5–8]. While genetic testing for *NF1* mutations is now available, the diagnosis is most commonly established on the basis of clinical signs [9,10].

NF1 is associated with increased mortality and morbidity for several conditions [5–7], including certain cancer types [11–14], learning disabilities [15,16], and hypertension [17]. The web-based Neurofibromatosis Type 1 Patient Registry Initiative (NPRI) was launched in May 2011 to facilitate in-depth epidemiologic analyses of NF1 and associated complications through the assembly of demographic, medical, and psychosocial information from children and adults with NF1 worldwide [18].

An important part of advancing rare disease research through online patient registries is ensuring that enrolled participants actually have the condition of interest. As a part of NPRI participation, registrants complete an online questionnaire and are asked to return forms that authorize the release of their medical information from their providers to research personnel. However, some participants may not complete these forms for reasons including privacy concerns, lack of a current medical provider, and logistical barriers such as inability to print the form and scan and email or fax it back to researchers.

The current study had three objectives: (1) to confirm NF1 participant reported diagnoses in medical records that were obtained during the study period, (2) to determine whether a participant's authorization for release of medical information could serve as a proxy for a medical record-validated NF1 diagnosis, and (3) to evaluate differences in reported NF1 clinical features between participants for whom diagnosis validation was possible (since they returned an authorization for release of medical information form) and those where verification was not possible. This study will inform rare disease research that ascertains participants who enroll in online patient registries.

2. Methods

2.1. The NF1 Patient Registry Initiative (NPRI)

The web-based NPRI was launched on May 17, 2011. More comprehensive descriptions of registry design and recruitment methods have been published previously [18,19]. A variety of recruitment methods were employed to alert potential participants to the NPRI including social media and Google paid advertising, postings on government and academic websites, communication with NF1 advocacy groups, and informational material that was distributed through NF1 healthcare providers. Children and adults with self- or parent/legal guardian-identified NF1 are eligible to participate by completing a registry questionnaire on the NPRI website (http://nf1registry.wustl.edu). Individuals give informed consent for participation via an electronic consent form (parents/legal guardians give consent for participants <18 years of age), then provide contact information and complete a 30–45 minute questionnaire that includes demographic, medical (including NF1 clinical signs), and psychosocial information. Participant electronic data and records are stored at Washington University in St. Louis behind a secure firewall, in accordance with current HIPAA requirements. The Institutional Review Board at Washington University in St. Louis approved this study.

2.2. Validation of participants' self-reported NF1

Presence of NF1 is evaluated through multiple mechanisms. First, participants self-report whether they or their child has been diagnosed with NF1 by a healthcare professional in response to the question: "Have you ever been diagnosed by a physician or other health care professional with Neurofibromatosis Type 1?" Of note is that this question was added to the registry questionnaire approximately 10 months after the registry was launched, resulting in missing data on this question for respondents who registered prior to the addition of the question. In addition, participants provide information about their NF1 clinical signs that comprise the NF1 diagnostic criteria developed by the National Institutes of Health (NIH) [9,10]. NF1 clinical signs for this study were assessed through the questions shown in Table 1.

Finally, NPRI staff attempt to validate participant-reported NF1 diagnoses via medical record review as authorized by individual participants. Participants can obtain the authorization for release of medical information form, also referred to as the medical record release form (MRRF), online after they complete their registration or through follow-up with NPRI staff. This authorization form asks participants to list names and contact information for their healthcare provider(s). Completed and signed forms are returned to NPRI staff by email, mail, or fax. A signed release form authorizes NPRI staff to request medical records from the provider(s) listed, and then abstract medical information from relevant medical documentation.

For the purposes of the current study, NPRI staff reviewed 205 medical records received through 7/7/2014 for healthcare provider documentation of NF1. A participant was classified as

Table 1
Survey questions assessing NF1 clinical signs.

Question assessing NF1 clinical signs	Response choice
Have you noticed or has a doctor ever told you that you have any of the following?: • 6 or more café-au-lait spots, • greater than 2 freckles in the armpit area and/or greater than 2 freckles in the groin area, • Lisch nodules, • dermal neurofibromas, • forearm bowing, • lower leg bowing	Yes, no, don't know
Have you ever been diagnosed with a plexiform neurofibroma?	Yes, no, don't know
Do you have a blood relative that has also been diagnosed with NF1?	Yes, no, don't know
Have you ever had an *NF1* gene test?	Yes, no, don't know

having a definite NF1 diagnosis if his/her medical documentation included at least two of the following adapted NIH criteria for diagnosis of NF1 [9]: multiple café au lait macules, axillary or groin freckling, Lisch nodules, bony dysplasia, first degree relative with NF1, a neurofibroma, an optic glioma, or a positive genetic test. In a couple of cases, participants were classified as definite where we received direct physician confirmation of an NF1 diagnosis in response to a medical record request. Individuals were categorized as probable/suspected diagnoses when there were insufficient provider notes on the adapted NIH criteria. Specifically, participants were classified as having a probable NF1 diagnosis if his/her clinical documentation included "neurofibromatosis type 1," "neurofibromatosis 1," and/or "von Recklinghausen's disease" and one of the adapted NIH criteria, or as having a suspected NF1 diagnosis if clinical documentation included unspecified "neurofibromatosis" and one of the adapted NIH criteria, reference to the patient having NF1 and none of the adapted criteria, or one of the adapted criteria but no specific mention of NF1 or NF unspecified.

2.3. Data analysis

This study included participants who enrolled in the registry and completed the registry questionnaire between 5/17/11 and 7/7/2014. Questionnaire completeness was assessed using an algorithm based on whether a participant responded to questions in 8 of 11 sections that were applicable to all registrants.

To evaluate whether the MRRF could serve as a marker of a valid NF1 diagnosis, we calculated the positive predictive value (PPV) of this form using medical record confirmation for validation. The PPV was defined as the proportion of participants with a definite, probable, or suspected NF1 diagnosis, as determined by medical record review, out of everyone who returned a MRRF and for whom a medical record was obtained.

We used bivariate analyses to compare participant-reported demographic and clinical characteristics from the NPRI questionnaire by MRRF groups (participants who returned an authorization for release of medical information form vs. those that did not return the form). Pearson chi-square tests for categorical variables and t-tests for continuous variables were employed to test for statistical differences between groups. MRRF groups were compared on baseline age (<18, ≥18 years old), sex (male, female), education (high school or less; associate, occupational, or technical degree; and bachelor's or above), U.S. residence (yes, no), race (White, Black or African American, American Indian/Alaskan Native, Asian, or Other), ethnicity (Hispanic, non-Hispanic), reporting a physician (yes, no), reporting an NF1 specialist (yes, no), and number of self-reported NF1 clinical signs. Of note is that education was defined as the highest education level for the head of the household on the minor questionnaire and as the highest education level received by the participant on the adult questionnaire. The 'Other' race category includes those individuals who did not specify a race or indicated multiple race categories. The number of NF1 clinical signs was calculated by summing the following number of participant-reported signs: café au lait spots, freckles in the armpit area and/or groin area, Lisch nodules, plexiform neurofibroma, forearm or lower leg bowing, positive *NF1* genetic test, and relative with NF1. Thus, the possible range of self-reported NF1 signs was 0–7. Optic gliomas [9] were not included because the NPRI questionnaire does not include questions about specific brain tumor types. Of note, dermal neurofibromas were also not included because the question was not added to the NPRI questionnaire until 2/19/13.

To assess differences between individuals who returned and did not return MRRFs, a linear regression model was constructed to compare the adjusted mean number of participant-reported NF1 clinical signs between groups. We controlled for variables that could potentially confound this relationship, including baseline age, education, sex, race, U.S. residence, ethnicity, and reporting a current doctor or NF specialist (has current doctor/NF specialist and does not have current doctor/NF specialist). The final model included only those covariates that were statistically significant. Statistical analyses were performed using Statistical Analysis Software (SAS) version 9.3 (SAS Institute, Cary, NC). All statistical tests were two-sided and p-values < 0.05 were considered statistically significant.

3. Results

A total of 1456 NPRI participants were included in the analyses. Among these participants, the majority reported being ≥18 years old at registration (n = 930, 64.4%), being female (n = 894, 62.0%), U.S. residence (n = 1089, 76.6%), White race (n = 1133, 80.0%), non-Hispanic ethnicity (n = 1289, 90.2%), having a current physician (n = 894, 61.4%), and not currently seeing an NF specialist (n = 904, 62.1%). A minority of participants reported having a bachelor's degree or above (n = 498, 34.3%) (Table 2).

Approximately 29% (n = 416) of participants returned their MRRFs during the study period. NPRI staff requested and received records for 205 individuals who returned their forms during the study period. Twenty-one of these individuals (~10%) were non-U.S. residents (Australia: n = 3, Canada: n = 10, India: n = 1, Italy: n = 1, Mexico: n = 1, New Zealand: n = 1, Philippines: n = 1, Serbia: n = 1, Switzerland: n = 1, United Kingdom: n = 1).

To confirm NF1 participant reported diagnoses using medical records, we abstracted NF1 clinical signs from medical records as described above (Objective 1). NF1 was classified as definite for 147 participants with 35 and 20 meeting the probable and suspected diagnosis definitions, respectively. NF1 could not be confirmed for 3 participants whose medical records were reviewed. Based on these data, we evaluated whether the MRRF could serve as a proxy for medical record confirmation of NF1 by calculating the PPV (Objective 2). The PPV of a returned MRRF for medical record documentation was calculated as the percentage of NPRI subjects with an NF1 diagnosis confirmed by medical record, out of all whose medical records were reviewed. This value ranged from 72% (147/205) when including only definite cases to 98.5% (202/205) when including all three case definitions. These data indicate that evidence of an NF1 diagnosis was present at varying degrees in ~99% of records that were reviewed.

To evaluate differences in reported NF1 clinical features between participants for whom diagnosis validation was possible (since they returned an authorization for release of medical information form) and those where verification was not possible we conducted several analyses as described below and in Tables 2–3 and Fig. 1 (Objective 3). Bivariate analyses indicated that participants who returned and did not return a MRRF were significantly different at $p < 0.01$ for characteristics

shown in Table 2. However, the distribution of NF1 clinical signs and mean number of reported NF1 clinical signs was similar between the two groups (Fig. 1).

In multivariable linear regression analyses, returning a MRRF was not a significant predictor of the number of questionnaire-reported clinical signs, $\beta = 0.03$, $p = 0.68$. In contrast, baseline age ($p = 0.009$), female sex ($p = 0.002$), and reporting an NF specialist ($p = 0.003$) were all significant positive predictors of the number of reported NF1 clinical signs. Race category ($p < 0.0001$) was also significantly associated with the number of participant reported NF1 clinical signs with significant inverse associations for Black/African American ($\beta = -0.30$, $p = 0.05$) and Asian ($\beta = -0.70$, $p = <0.0001$) compared with White race categories (Table 3). We also ran models that additionally included Hispanic ethnicity, education, U.S. residence, and reporting a physician as covariates; none of these variables were significantly associated with the reported number of clinical signs so they were dropped from the model presented in Table 3. Excluding participants (n = 161) who had missing data (n = 112) or reported "no" or "don't know" (n = 49) to the question of whether they or the minor participant had ever been diagnosed by a physician or other healthcare professional with NF1 did not materially change the results (data not shown).

Table 3
Linear regression model predictors of number of participant-reported NF1 clinical signs among NPRI participants (n = 1405[a]).

Variable	β	95% CI	*p*-Value[b]
MRRF not received	0.03	−0.12–0.18	0.68
Baseline age	0.005	0.001–0.009	0.009
Female	0.21	0.08–0.35	0.002
Race[c]			
White	reference		
Black or African American	−0.30	−0.60–0.004	0.05
American Indian/Alaskan Native	−0.22	−0.75–0.32	0.43
Asian	−0.70	−1.00 to 0.40	<0.0001
Other	0.06	−0.17–0.28	0.62
Reported having an NF specialist	0.22	0.08–0.37	0.003

[a] Missing data: 51 individuals were excluded due to missing data on one or more variables included in the model.
[b] *p*-Value for t-test comparing whether the mean number of clinical signs is statistically different between the variable category and the reference category (e.g. MRRF not received vs. MRRF received, high school or less is the reference category for education).
[c] Type III sum of squares *p*-value indicating whether variable is significant after adjusting for all other variables in the model: race = <0.0001. Type III sum of squares *p*-value for binary variables is equivalent to the *p*-value shown in the table.

4. Discussion

Increased internet access throughout the world is facilitating the cost-effective and efficient assembly of geographically-dispersed individuals with rare diseases for research studies. A potential concern levied against online disease registries that rely on participants' self-reported information is the inclusion of subjects who do not actually have the diagnosis of interest

Table 2
Characteristics of participants overall and by MRRF status (n = 1456[a]).

Variable	Total (n = 1456)	MRRF received (n = 416) N (%)	MRRF not received (n = 1040) N (%)	*p*-Value[b]
Baseline age				
<18 years	514 (35.6)	219 (52.6)	295 (28.4)	<0.0001
≥18 years	930 (64.4)	197 (47.4)	733 (70.5)	
Sex				
Female	894 (62.0)	227 (54.6)	667 (64.1)	0.0003
Male	547 (38.0)	188 (45.2)	359 (34.5)	
Education				
High school or less	372 (25.7)	84 (20.2)	288 (27.9)	<0.0001
Some college, no degree	309 (21.3)	78 (18.8)	231 (22.3)	
Associate, occupational, or technical degree	271 (18.7)	76 (18.3)	195 (18.9)	
Bachelor's or above	498 (34.3)	178 (42.8)	320 (31.0)	
Residence				
U.S.	1089 (76.6)	362 (87.0)	727 (72.3)	<0.001
Non-U.S.	332 (23.4)	54 (13.0)	278 (27.7)	
Race				
White	1133 (80.0)	360 (90.0)	773 (77.1)	0.0003
Black or African American	68 (4.8)	9 (2.2)	59 (5.9)	
American Indian/Alaskan Native	20 (1.4)	5 (1.2)	15 (1.5)	
Asian	69 (4.9)	10 (2.4)	59 (5.9)	
Other	127 (9.0)	30 (7.3)	97 (9.7)	
Ethnicity				
Hispanic	140 (9.8)	25 (6.1)	115 (11.3)	0.003
Non-Hispanic	1289 (90.2)	385 (93.9)	904 (88.7)	
Reported having a physician				
Yes	894 (61.4)	347 (83.4)	547 (52.6)	<0.0001
No or unanswered	562 (38.6)	69 (16.6)	493 (47.4)	
Reported having an NF1 specialist				
Yes	552 (37.9)	252 (60.6)	300 (28.9)	<0.0001
No	904 (62.1)	164 (39.4)	740 (71.2)	

[a] Missing data on variables: baseline age (n = 12), sex (n = 15), country (n = 35), education (n = 6), race (n = 39), and ethnicity (n = 27).
[b] Pearson chi-square *p*-value for difference in frequencies between the two MRRF groups (i.e. received and not received).

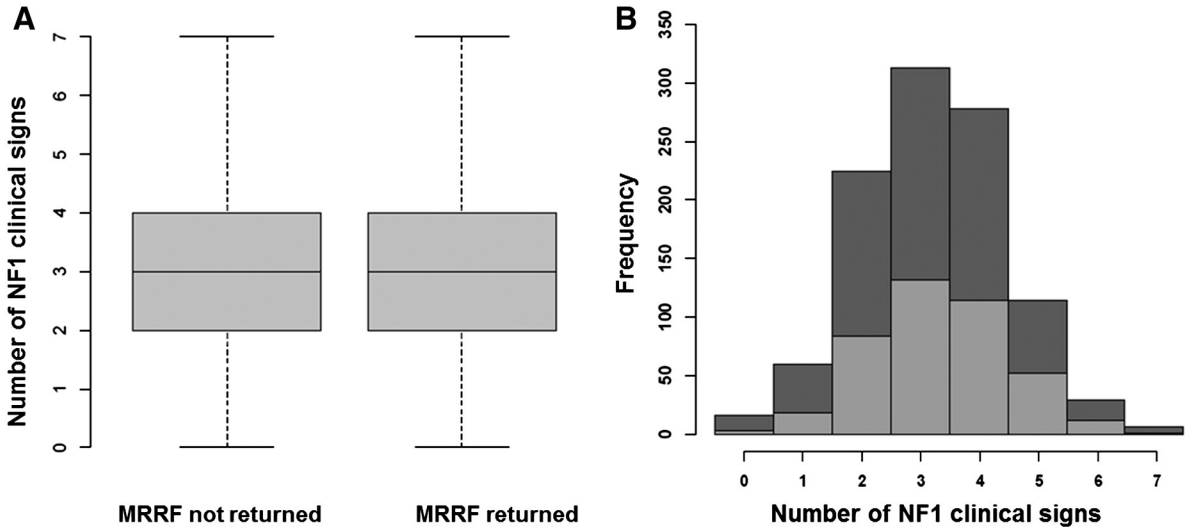

Fig. 1. Distribution of reported NF1 clinical signs among those who returned (n = 416) and did not return (n = 1040) a MRRF. Panel A shows box plots of the number of clinical signs in each group. The interquartile range is defined by the lower and upper hinges of the rectangle with the line in the middle of the rectangle representing the median. The lower and upper whiskers define the minimum and maximum number of reported NF1 clinical signs. Panel B shows overlaid histograms of the distribution of the number of NF1 clinical signs for each MRRF group (light gray = MRRF returned, dark gray = MRRF not returned). The mean number of reported NF1 clinical signs was 3.3 ± 1.2 for those who returned and 3.2 ± 1.3 for those who did not return their MRRF, $p = 0.19$.

[20]. To address this concern for the NPRI, we examined medical records to validate self-reported diagnoses. Analyses indicated that nearly all participants whose medical records we reviewed had documentation of NF1 to varying degrees in their medical record indicating that a returned authorization for release of medical information form is a highly predictive marker for medical record confirmation of an NF1 diagnosis. In addition, our analyses showed that individuals who returned a MRRF were not significantly different with respect to the mean number of reported NF1 clinical signs from those who did not return their forms.

We included several potential confounding variables in the model that might be related to both the number of reported clinical signs and the return of the MRRF. In addition, our results indicated expected associations between these covariates and NF1 clinical signs providing further evidence that the population of individuals assembled through the NPRI resembles the general population of individuals with NF1 as reported in previous publications. For example, manifestations of NF1 are known to be age-dependent and the number of NF1 clinical signs generally increases with age [5–8]. This is in accordance with our finding that a participant's age at registration was positively associated with the number of self-reported NF1 clinical signs. In addition, while it is generally accepted that NF1 occurs in all racial/ethnic groups [5], there is evidence that the condition [6] and some of its complications are more frequent in certain populations [5]. For example, a higher prevalence of optic gliomas has been reported in Whites compared to African Americans [21–23], but carcinoid tumors have been reported to be more common in African Americans [24]. Additionally, having an NF1 specialist may increase awareness of NF1 clinical signs, which is consistent with our finding that there was a significant positive association between this variable and the number of reported clinical signs. It is also possible that patients who see an NF1 specialist may have more NF1 clinical signs than those who do not see a specialist.

Previous research on other conditions has explored the accuracy of self-reported information collected through large epidemiological studies relative to diagnoses derived solely from medical information. For example, the North American Research Committee on Multiple Sclerosis (MS) (NARCOMS) registry compared self-reported diagnosis data to physician-reported diagnosis through medical chart review [25]. Two independent reviewers abstracted 41 medical records and classified 94.8% of patients as having definite/possible/suggestive MS, while 5.2% had insufficient data to confirm the MS diagnosis. Another study focusing on MS reported a strong correlation between patient-reported MS rating scale (MSRS) measures, an online instrument developed by PatientsLikeMe, and standard clinical assessment measures used in MS (Spearman rank-order correlation coefficient, $r_s = 0.838$, n = 117) [26]. Additionally, a study using data collected from the Shanghai Breast Cancer Survival Study (SBCSS), a population-based cohort study that had medical chart information for 98.1% (n = 4948) of participants, found high concordance between patient self-reported and medical chart information for the majority of disease-related variables [27]. Finally, a study of gout had a very high concordance (97%) between self-reported and medical record-reported gout diagnoses [28].

While patient registries such as the NPRI are considered less costly and time-intensive than multi-center clinic based studies that can achieve similar numbers of participants, the costs associated with creating and maintaining a registry can be a constraint. Therefore, it is important for researchers to find a balance between their data collection needs and resource availability. Medical record validation is the most common method employed to verify diagnoses in research studies, however, it can be costly, resource intensive, and time consuming [29,30]. In addition, it may not be possible to obtain the authorization for release of medical information needed for medical record validation from all study participants. Our results indicate that a returned MRRF can serve as a highly valid

alternative to medical record confirmation of NF1, and that participants who release their medical record information are similar to those who do not release their information with respect to participant-reported clinical signs of NF1. Although these results may only apply to people with NF1, we suspect that similar results will be obtained using registries of other conditions with clear diagnostic criteria.

This study, like other validation studies [29], is limited by the variable quality of information contained in medical records [31]. Some medical records lacked important documentation, including details about NF1 clinical signs and information from the appropriate physician seeing the patient for their diagnosis. Another challenge to validating participant-reported information through medical record review is that some participants may not have a current physician or NF specialist. This not only makes requesting and receiving medical records more challenging, but the data obtained through records from previous physicians may not accurately reflect the patient's current condition. Nevertheless, even with more challenging requests, the NPRI staff has been able to obtain the majority of medical records following the receipt of a participant's authorization for release of medical information.

In conclusion, although online patient registries pose some methodological challenges, the opportunity to assemble large populations of individuals with rare diseases is unprecedented. The results of our study suggest that registry participants reliably report their NF1 diagnosis and that medical record verification is concordant with participant-reported information. However, the strengths and limitations of this approach relative to other methods—together with considerations of available resources—should be considered.

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