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Evaluation of Participant Recruitment Methods to a Rare Disease Online Registry

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Internet communication advances provide new opportunities to assemble individuals with rare diseases to online patient registries from wide geographic areas for research. However, there is little published information on the efficacy of different recruitment methods. Here we describe recruitment patterns and the characteristics of individuals with the self-identified autosomal dominant genetic disorder neurofibromatosis type 1 (NF1) who participated in an online patient registry during the 1-year period from 1/1/2012 to 12/31/2012. We employed four main mechanisms to alert potential participants to the registry: (1) Facebook and Google advertising, (2) government and academic websites, (3) patient advocacy groups, and (4) healthcare providers. Participants reported how they first heard about the registry through an online questionnaire. During the 1-year period, 880 individuals participated in the registry from all 50 U.S. States, the District of Columbia, Puerto Rico, and 39 countries. Facebook and Google were reported as referral sources by the highest number of participants (n = 550, 72% Facebook), followed by healthcare providers (n = 74), and government and academic websites (n = 71). The mean participant age was 29 ± 18 years and most participants reported White race (73%) and female sex (62%) irrespective of reported referral source. Internet advertising, especially through Facebook, resulted in efficient enrollment of large numbers of individuals with NF1. Our study demonstrates the potential utility of this approach to assemble individuals with a rare disease from across the world for research studies. © 2014 Wiley Periodicals, Inc.

Key words: neurofibromatosis type 1; rare disease; genetic syndrome; registry; Internet; online; NF1

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INTRODUCTION

A rare disease is defined as a medical condition that affects fewer than 200,000 individuals in the United States or 1/2,000 individuals in the European Union [Health-Eu, 2013; Rarediseases.org, 2013]. An estimated 30 million Americans are affected with one of 7,000 rare diseases [Rubinstein et al., 2010]. Their rarity makes it difficult for any single institution to assemble sufficient patient numbers for large-scale observational or experimental research studies.

Patient registries are one method to assemble individuals with rare diseases for research studies. They are often physician/healthcare provider-driven, where recruitment and clinical data input are performed by clinic/hospital personnel. There are also an increasing number of patient-driven registries, where patients self-enroll and contribute their clinical data, including some that have been initiated by academic centers [WSPCRR, 2013], research committees [North American Research Committee on Multiple Sclerosis, 2013], advocacy groups [Myotonic Dystrophy Family Registry, 2013], and family members [Patients Like Me, 2013].

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Abbreviations: NF1, neurofibromatosis type 1; NPRI, NF1 patient registry initiative.

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Although patient-driven registries have disadvantages over physician/healthcare provider-driven registries including limitations associated with self-reported clinical data relative to that captured in medical records, a major strength of this registry type is the ability to amass large geographically and socio-economically diverse populations with rare diseases. In addition, patient-driven registries can also facilitate data collection from multiple family members with a rare disease and may provide a larger number of affected individuals with the opportunity for research participation.

Neurofibromatosis type 1 (NF1) is an autosomal dominant rare disease caused by a germ-line mutation in the *NF1* tumor suppressor gene that affects an estimated 1/3,000 individuals [Crowe, 1956; Marchuk et al., 1991]. It is estimated that half of the individuals with NF1 have an affected parent, while the other half arise through a de novo mutation [Jett and Friedman, 2010]. NF1 incurs a high-risk for the development of both benign and malignant tumor types, including connective tissue sarcomas, breast cancer, and adult and pediatric brain tumors [Rasmussen et al., 2001; Gutmann et al., 2002; Masocco et al., 2011; Wilding et al., 2012; Seminog and Goldacre, 2013]. Cancer is the leading cause of death in NF1 resulting in a reduced life expectancy of ~8–20 years compared to the general population [Rasmussen et al., 2001; Masocco et al., 2011; Wilding et al., 2012]. NF1 has also been associated with a variety of other health conditions, including learning disabilities [Gilboa et al., 2010], epilepsy [Creange et al., 1999; Mastrangelo et al., 2009; Hsieh et al., 2011], and multiple sclerosis [Johnson et al., 2000; Perini and Gallo, 2001; Spinicci et al., 2010; Pipatpajong and Phanthumchinda, 2011].

Epidemiological research of rare diseases, including NF1, is challenged by the inherent difficulty of assembling data from sufficient subject numbers. To facilitate NF1 clinical and epidemiologic research, we launched the NF1 patient registry initiative (NPRI) in May 2011 [Johnson et al., 2012]. To accelerate enrollment of patients in this registry, we implemented several different web- and clinic-based recruiting strategies over a 1-year period. Limited methodological data exists on the efficacy of different recruiting methods for assembling a large population with a rare disease. The primary objective of this study is to describe the impact of various recruitment techniques on enrollment of an international population of subjects with NF1 and on the characteristics of the participants registered as a function of recruitment source. This information may be instructive for other investigators interested in employing Internet-based methodology for assembling individuals with other rare genetic diseases for clinical and/or epidemiologic research studies.

MATERIALS AND METHODS

The NF1 Patient Registry Initiative (NPRI)

The NPRI was launched on May 17, 2011 and detailed methods have been previously reported [Johnson et al., 2012]. Briefly, all individuals with NF1 (self-identified) are eligible to participate by accessing the NPRI website (http://nf1registry.wustl.edu). All data and records are stored behind a firewall at Washington University following current HIPAA guidelines. This study has been approved by the Washington University in St. Louis Institutional Review Board. Participants provide informed consent electronically (parents provide consent for participants <18 years), supply contact information, and complete a 30–45 min questionnaire containing 11 sections that inquire about demographics, medical, and social history. Participant reported recruitment sources are assessed through the question, "How did you *first* hear about the registry?" Participants indicate their recruitment source by checking a box for one of the following: "Google search results," "Facebook page," "Advocacy group," "Children's Tumor Foundation (CTF)," "NF Inc.," "Clinicaltrials.gov," "National Organization of Rare Diseases," "healthcare provider," "NF conference," "Washington University Neurofibromatosis Center website," "Other," or "Referred by a participant through an email." The latter option is facilitated through a link on a thank you page at the end of the registration that allows participants to send an email directly from the registry website. If participants select either the Google or Facebook recruitment option, they are asked to indicate if they linked to the website through a Facebook/Google advertisement. Participants who select "Other" are asked to specify the other recruitment source.

Recruitment Methods

During the 1-year period from 1/01/2012 to 12/31/2012, we employed several different methods to recruit potential participants to the NPRI including: paid online advertisements, postings through advocacy groups, academic and government website listings, mailed letters, and informational cards that were sent to major NF Centers in the United States and Australia for distribution to their NF1 patients.

Paid online advertising was conducted through two separate Facebook Ad and Google Adwords (www.google.com/ads/adwords2/) campaigns. Of note is that we decided not to create a no cost NPRI Facebook page that would allow us to post recruitment ads in the news of "friends" liking our page for two main reasons: (1) the need to create connections for dissemination of registry recruitment ads and, (2) concerns about potential human subjects issues associated with "friends" posting health information on a NPRI Facebook page. The first Google and Facebook campaigns were conducted during 4/17/2012–8/16/2013 and 5/31/2012–8/16/2013, respectively. Both Google Adwords and Facebook Ads allow the user to set a daily budget maximum with the user paying on a cost-per-click basis until the maximum daily budget is reached. The first Google advertisement included a brief descriptive heading and a link to the registry (Supplementary Fig. 1A). The ad targeted individuals searching or viewing webpages in English in countries with access to the Google search engine. Fifty NF1-related keywords, phrases that trigger the ad to display, were selected including "NF1," "Neurofibromas," and "café au lait spots." The first Facebook advertisement included a descriptive heading, a link to the registry web page, and a study logo image (Supplementary Fig. 1B in supporting information online). The ad targeted adults (≥18 years) in English speaking countries (United States, Canada, United Kingdom, and Australia). NF1-related groups and pages were targeted based on users' "interests"-information the users added to their timelines including pages they like, apps they use, and other information [Facebook, 2013]. The amount spent on advertising during the first campaign averaged ~$12/day for Google and ~$10/day for Facebook Ads.

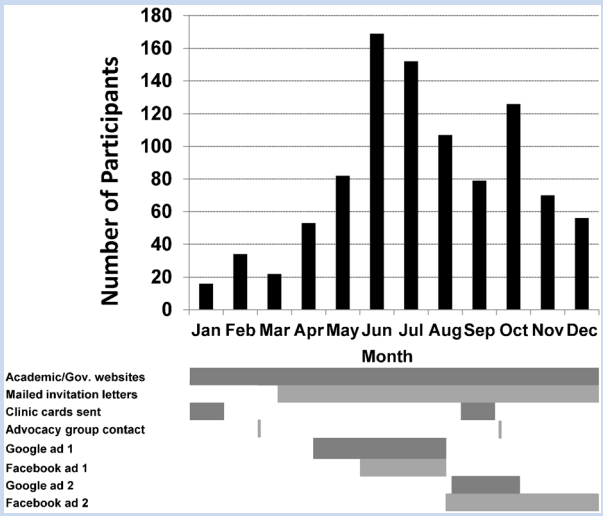

FIG. 1. NPRI enrollment rate by month during the study period (1/1/2012–12/31/2012). The table below the graph indicates time periods that each advertising mechanism was active. The time periods are as follows: Clinicaltrials.gov and advertisement (ongoing throughout); Google Ad 1 (4/17/12–8/16/12); Facebook Ad 1 (5/31/12–8/16/12); Google Ad 2 (8/22/12–10/21/12); Facebook Ad 2 (8/16/12–ongoing through end of year); Advocacy group contact (3/1/12 and 10/2/2012); mailed invitation letters (3/16/12–12/5/12 with follow-up phone calls continuing through 2012); clinic cards sent during Jan 2012 and Sep 2012. Abbreviation: government, Gov.

In August 2012, we conducted a second 2-month advertisement campaign (8/22/2012–10/21/2012), that was designed to directly compare registry enrollment in response to Facebook and Google advertising using substantially similar ads and targeted populations (Supplementary Figs. 1C and D in supporting information online). We selected 25 target countries for both Google and Facebook based on (1) having Facebook access, (2) country representation in the registry population, and (3) having a majority English-speaking population. NF-related keywords from the initial Google Adwords campaign that received the most clicks were selected for the secondary campaign. The second Google Ad used the keywords "Neurofibromatosis," "NF," "NF1," and "Neurofibromas." The Facebook campaign used similar keywords and also included the NF1 advocacy and support group keywords from the original campaign: "#Neurofibromatosis type 1," "#Neurofibromatosis or neurofibromatosis," "#Texas Neurofibromatosis Foundation," "Neurofibromatosis Inc. Midwest," "neurofibromatosis support," and "neurofibromatosis inc." The maximum budget for both campaigns during the direct comparison trial was set at $10/day.

We identified 43 advocacy groups (23 U.S., 20 international) through web searches and the NF Inc. and Children's Tumor Foundation support group pages (http://www.nfnetwork.org/nf-community-near-you/local-groups and http://www.ctf.org/). We contacted all advocacy groups with a working email or contact form (n = 33) in March 2012, introduced the registry, and requested that they post an announcement about the NPRI on their web platforms or include the information in emails to their respective group members. We sent follow-up emails to all advocacy groups that interact with NF1 patients and have a working email or contact form (n = 28; 15 U.S., 13 international) in October 2012.

Throughout the study the registry was listed on www.Clinicaltrials.gov (study number: NCT01410006) and the Washington University NF Center website (http://nfcenter.wustl.edu) that provides viewers with a wealth of resources about NF. In addition, information about the registry was placed on other University-based (Research Participant Registry Facebook Fanpage at "Washington University School of Medicine, Research Participant Registry Washington University School of Medicine, Research Participant Registry" Washington University Volunteers for Health website: https://vfh.wustl.edu) and a non-University research website (http://www.centerwatch.com/clinical-trials/listings/studydetails.aspx?StudyID=181282) in late April 2012.

We also recruited participants through healthcare providers at major NF centers who predominantly see individuals with NF1. Recruitment mechanisms included: (1) study invitation letters sent to patients with NF1 ICD-9 codes (237.70 and 237.71) who were patients at Washington University and (2) informational cards that were sent to several NF centers for distribution to their patients in the U.S. and Australia. For the mailed study invitation letters, the standard procedure was to follow-up with the participants by phone at least three times before marking them as "unable to contact." Mailing of letters and follow-up was conducted by Washington University's Institute of Clinical and Translational Sciences Recruitment Enhancement Core.

Data Analysis

SAS version 9.3 (Cary, NC) was used to calculate all statistics. Frequencies were calculated to determine the number of enrollees per month and the number of participants from each recruitment source. Google Analytics (http://www.google.com/analytics/) was installed on February 29, 2012 and was employed to analyze traffic patterns to the registry website during the study period. The percent response to our mailed letter recruitment effort was calculated as the number of participants who enrolled in the registry following mailing of the letter and associated follow-up divided by the number of letters mailed, excluding letters returned due to change of address or unknown address. Arc GIS generated maps (ESRI, Redlands, CA), and contingency tables were used to summarize participant demographic characteristics, overall, and by recruitment source. Fisher's exact test was used to test the statistical significance of differences in characteristics between participants recruited through Facebook and Google for the direct comparison trial described above. Pearson's correlation coefficient was used to determine the linear correlation between 2010 U.S. Census state population and participant number in each U.S. State [U.S. Census, 2010]. Both variables were log-transformed to meet the normality assumption for calculating Pearson's correlation coefficient.

RESULTS

Enrollment Overall and According to Recruitment Strategy

A total of 880 individuals participated in the NPRI during the 1-year study period. Of these, approximately 76% completed the entire questionnaire. Enrollment/month rapidly increased with the start of Google advertising on 4/17/2012. During the month following the start of Google advertising, participants/month increased from an average of 23 (January–March) to 63. Participant enrollment showed a second surge with the inception of Facebook advertising on 5/31/2012 with 152 individuals enrolling in June, but declined in the following months with 54 participants enrolling in December (Fig. 1). The graph shows a spike in enrollment in October. During this month, 10 participants reported hearing about the registry through the social media site "Inspire" (https://www.inspire.com/) that provides a forum for discussion for people with medical conditions, including NF1. No participants reported having heard about the registry through Inspire during any other month of the 1-year study period (data not shown).

Approximately 89% of participants reported first hearing about the registry through one of the direct recruiting methods. Nearly 70% of participants reported hearing about the registry through Facebook or Google, followed by healthcare providers (9.1%), government and academic websites (8.8%), and advocacy groups (3.1%). Thirteen of the 33 (39%) advocacy groups either indicated that they would post or distribute registry information or were confirmed by one of our staff members to have posted information on their website. Finally, indirect recruiting sources generated ~11% of participants during the study period, each with ≤19 recruits (Table I). Of note, for Facebook and Google advertising the estimated number of participants enrolled per week who reported these recruitment sources while the ads were running was over twice as high for Facebook at 12.3 versus 6.0 for Google (data not shown).

TABLE I. First Recruitment Sources Reported by NPRI Participants (n = 811)

Recruitment source	Number	%
Direct methods		
Facebook page	395	48.7
Google search	155	19.1
Health care provider	74	9.1
Academic/government websites	71	8.8
Advocacy group	25	3.1
Indirect methods		
Other	19	2.3
Word of mouth	16	2.0
NF conference	11	1.4
Inspire	10	1.2
Referred by participant through an email	10	1.2
Wikipedia	8	1.0
Twitter	7	0.9
Internet not otherwise unspecified	5	0.6
NF website not otherwise specified	5	0.6
Total[a]	811	100

[a]Excludes 69 participants who did not provide data on the referral source.

We used Google Analytics to further understand registry traffic patterns. The registry website received 13,622 visits from February 29, 2012 to December 31, 2012, 87% of which were new visits. The traffic pattern generally corresponded with enrollment patterns shown in Figure 1 with increased website visits following the start of Google advertising. The top three traffic sources were Google Ads (n = 3,541; 26%), Facebook.com (n = 2,672; 20%), and direct visits (n = 2,587; 19%) (Supplementary Fig. 2 in supporting information online), which was consistent with the top participant reported referral sources. While Google Ads generated the most traffic to the NPRI website, individuals coming from this source had the lowest average number of pages visited during a single visit and average visit duration of the top 10 traffic sources. Visitors who linked to the registry website through a Google Ad also had the highest bounce rate (defined as visiting only one page before leaving the site). In contrast, individuals linking to the registry website through the Washington University NF Center website, directly entering in the registry website (or linking from an email or bookmark), and Facebook visited more registry pages/visit, spent more time on the registry website before leaving, and had the lowest bounce rates of the top ten traffic sources (Supplementary Table I in supporting information online).

To compare the efficacy of Facebook and Google paid advertising on participant recruitment, we first limited our analysis to participants who reported hearing about the registry specifically through Facebook or Google Ads; however, some participants reported linking to the registry through a Google advertisement after the ad was discontinued in October, suggesting they were unable to distinguish between being referred by a Google search listing or ad. Therefore, we analyzed results according to whether the participant reported hearing about the registry through Google or Facebook (independent of whether they reported linking through one of our ads). During the first Google advertising campaign (4/17/2012–8/16/2012), a total of 110 registrants reported hearing about the registry through a Google search at a total advertising cost of $1,477.47. During the first Facebook advertising campaign that was of shorter duration (5/31/2012–8/16/2012), nearly twice as many participants (n = 203) reported hearing about the registry through Facebook versus Google with a total advertising cost of $771.35. In the 2-month direct comparison trial that used similar ads and targeted the same countries, 79 and 28 participants reported hearing about the registry through Facebook and Google, respectively, at a total advertising cost of $609.38 for Facebook Ads and $531.20 for Google Ads.

We also evaluated the recruitment efficacy of mailing registry invitation letters to individuals with ICD-9 codes for NF1 identified through a hospital administrative database search. A total of 307 individuals with NF1 ICD-9 codes identified through this mechanism were mailed recruitment letters during the study period. Ninety-seven individuals enrolled in the registry, with 70 enrolling after receiving the recruitment letter and 27 enrolling prior to the letter. Of the 70 who registered after the mailed letter18, 20, and 8 registered after one, two, and three phone calls, respectively. Fourteen participants registered with assistance from a staff mem-

ber over the phone. Fourteen were identified as having incorrect mailing addresses. The estimated total response rate as a result of the mailed letter was 26% (70/(307 − 27 − 14)). The cost of the mailed campaign (staff time and postage) during the 1-year study period was $10,846.32.

Demographic Characteristics of Participants

We next examined the demographic characteristics of participants who registered during the study period, overall, and by recruitment source. Participants represented all 50 U.S. States, the District of Columbia, Puerto Rico, and 39 countries (Fig. 2). We compared the number of participants from each U.S. State to 2010 U.S. Census data on state populations to examine geographic representation of participants relative to U.S. State populations and observed a strong positive correlation between U.S. State population and participant number ($r = 0.82$) (Fig. 3).

Participant characteristics varied by recruitment source (Table II). Overall more females registered than males (62.2% vs. 37.8%) independent of the recruitment mechanism. The participant reported race distribution of the sample was 73.1% White, 6.8% Asian, 4.7% Black or African American, 1% American Indian/Alaskan Native, and 14.4% multiple races, with more Asians reporting having heard about the registry through Google search results than other mechanisms. Approximately, 10% of the cohort reported Hispanic ethnicity overall with Internet sources yielding slightly more Hispanics than health care providers. The mean age of participants at baseline enrollment was 29.0 ± 17.9 years with ~1/3 each of the sample at enrollment was between the ages of 0–19 (34.4%), 20–39 (33.2%), and ≥40 (32.4%) years of age with more adults reporting being referred through Internet sources rather than through a healthcare provider. Overall, more respondents were from the U.S. than from other countries (73.1% vs. 27.0%). An approximately equivalent percentage of participants reported having no family history of NF1 (44.2%) relative to those with a known family history (46.2%) with no marked variation between recruitment sources.

Although based on small numbers, participants recruited through Google ($n = 28$) and Facebook ($n = 79$) during the 2-month direct comparison campaign were similar, with no significant differences in demographic characteristics (sex, race, age category, geographic origin, and family history of NF1) (Supplementary Table II in supporting information online).

A higher percentage of participants with incomplete versus complete NPRI questionnaires reported first hearing about the registry through a Google search (27.6% vs. 20.5%) and Facebook (59.8% vs. 55.9%). In contrast, a lower percentage of participants with incomplete surveys reported hearing about the registry through health care providers (6.9% vs. 11.9%) and government and academic websites (5.8% vs. 11.7%). Those with incomplete NPRI questionnaires were more likely to be male (43.1% vs. 36.9%), less likely to be White (63% vs. 76.3%), and less likely to reside in the USA (68% vs. 76%). The median age was similar between the two groups (29.1 vs. 29.0 years for participants with incomplete vs. complete questionnaires, respectively) (data not shown).

DISCUSSION

Patient registries are a critical resource to advancing clinical and public health research of rare diseases where no population-based registries exist. With increasing access to the Internet world wide, an unprecedented opportunity exists to rapidly assemble large numbers of individuals with rare diseases into patient registries for research focused on health outcomes. However, there are limited published data on methods for effective recruitment. In the current study, we employed our recently developed patient-driven NF1

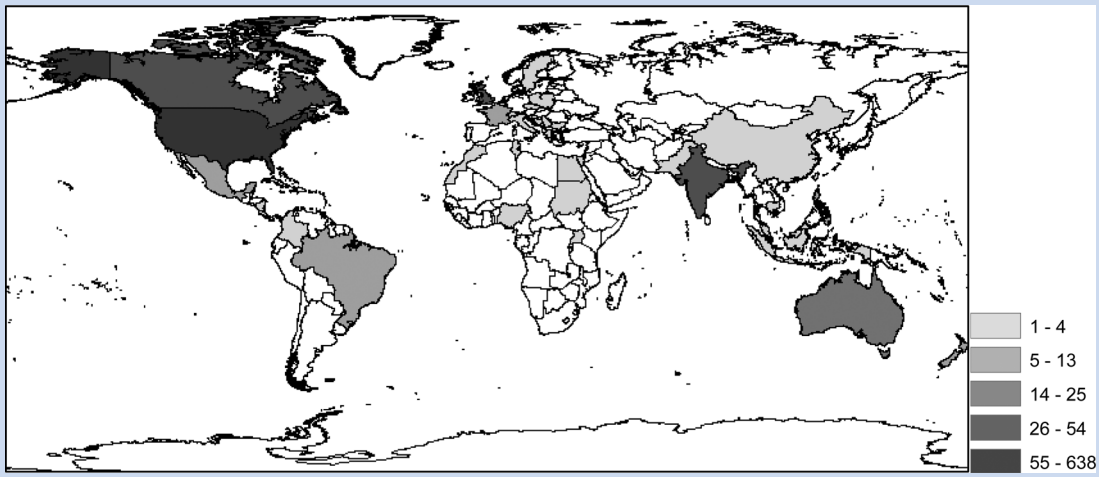

FIG. 2. World map location of NPRI participants ($n = 851$), excluding representation of Sudan, Puerto Rico, and Uganda (not available in the ARC-GIS world map version). Shading corresponds to the number of participants with darker shading indicating higher numbers of participants.

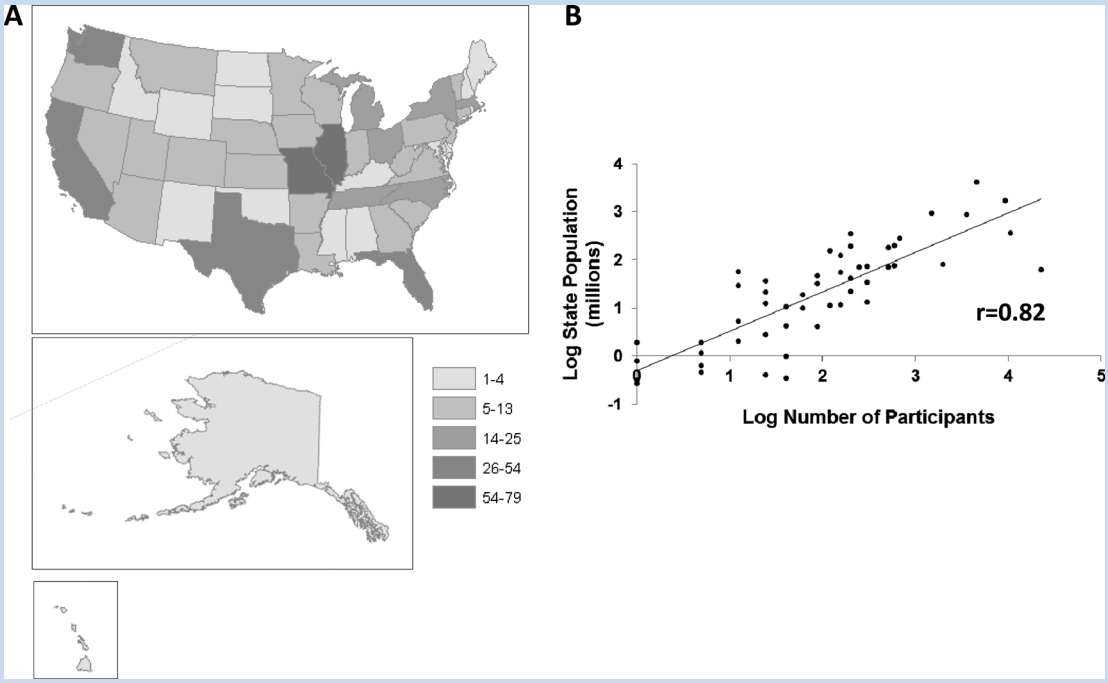

FIG. 3. Representation of NPRI participants by U.S. State/District of Columbia. A: Map of participants by U.S. State. Shading corresponds to the number of participants with darker shading indicating higher numbers of participants. B: Plot of log number of participants in each state by log U.S. Census [2010] state population (r = 0.82).

registry as a virtual laboratory to understand the effectiveness of different recruitment mechanisms for assembling an international population of patients with NF1.

Analysis of the different recruiting mechanisms employed over a 1-year time period provided evidence that online advertising (especially Facebook) is an effective recruitment tool for assembling individuals with NF1. In contrast, a direct mailed letter recruitment campaign was less effective resulting in 70/880 (~8%) recruits over the study period at a substantially higher cost. Additional sources of advertising, including government and academic websites, also yielded some participants but generally less than the other methods employed. Advocacy groups that we contacted were surprisingly the least effective method of the direct methods employed with respect to participant yield. However, we note that some of the NPRI participants who reported being recruited through Facebook may have heard about the registry through a posting on the Facebook page of an advocacy group that we had contacted. We are aware that some of the advocacy groups we contacted posted announcements regarding the registry on their social media pages, including Facebook. However, the temporal patterns in recruitment associated with the inception of paid advertising and the limited amount of time that a posting about the registry as a Facebook status is available to viewers suggest that this mechanism did not result in most of the recruits from Facebook.

The use of social media as a potential recruitment tool for reaching hard-to-access populations for medical genetics research has recently been highlighted in this journal [Reaves and Bianchi, 2013] and has also gained recognition in a few studies, in part for the low cost and user targeting potentials [Battistella et al., 2010; Jones and Magee, 2011; Tweet et al., 2011; Fenner et al., 2012; Close et al., 2013]. Facebook reported that in 2012 it had over one billion monthly active users [Facebook, 2012], suggesting enormous potential to reach individuals with rare diseases from wide geographic areas for research study enrollment. Two previously published studies support the use of social media as a method for accessing hard-to-reach populations with rare medical conditions [Tweet et al., 2011; Close et al., 2013]. Researchers from the Mayo Clinic reported that they were able to meet their recruitment goal of 12 individuals with an extremely rare condition, spontaneous coronary artery dissection (SCAD), within 1 week through advertising on the social networking site "Inspire" [Tweet et al., 2011]. Furthermore, the authors reported that six additional individuals had to be subsequently wait-listed for participation. Our results from October where 10 participants reported having heard about the registry through "Inspire" also suggest that this source may facilitate recruiting of individuals with other rare conditions such as NF1. A study of individuals with Klinefelter syndrome reported limited efficacy of clinic-based recruitment with only four recruits obtained in 3 months (1.3/month), despite distribution of 150 brochures in clinical offices and mailing 850 letters to physicians. However, following web-based and social media advertising, the authors reported a rapid increase in participant enrollment, and were able to recruit 39 individuals (~5/month) through web-based mechanisms over approximately 8 months [Close et al., 2013].

TABLE II. Demographic Characteristics of NPRI Participants by Reported Recruitment Source from 1/1/2012 to 12/31/2012

	Overall[a] (n = 880)		Google search results (n = 155)		Facebook page (n = 395)		Health care provider (n = 74)		Government and academic websites (n = 71)	
	n	%	n	%	n	%	n	%	n	%
Sex										
Female	547	62.2	101	65.2	247	62.5	44	59.5	43	60.6
Male	333	37.8	54	34.8	148	37.5	30	40.5	28	39.4
Race										
White	643	73.1	86	55.1	303	76.7	58	78.4	57	80.3
Black/African American	41	4.7	9	5.8	18	4.6	3	4.1	3	4.2
Asian	60	6.8	25	16.0	17	4.3	2	2.7	6	8.5
American Indian/ Alaskan Native	9	1.0	2	1.3	5	1.3	0	0	1	1.4
>1 race selected	127	14.4	33	21.3	52	13.2	11	14.9	4	5.6
Ethnicity										
Hispanic	89	10.3	17	11.3	40	10.3	6	8.2	8	11.4
Non-Hispanic	772	90.0	133	88.7	347	89.7	67	91.8	62	88.6
Age category										
0–19	302	34.4	39	25.2	122	30.9	42	56.8	31	44.3
20–39	292	33.2	62	40.0	131	33.2	20	27.0	19	27.1
≥40	285	32.4	54	34.8	142	36.0	12	16.2	20	28.6
<18	293	33.3	35	22.6	121	30.6	41	54.1	31	44.3
≥18	586	66.7	120	77.4	274	69.4	35	46.0	39	55.7
Geographic origin										
USA	626	73.1	85	56.3	262	67.9	72	97.3	62	88.6
Other	231	27.0	66	43.7	124	32.1	2	2.7	8	11.4
Family history of NF1										
Yes	323	44.2	52	43.7	155	48.1	27	41.5	28	43.1
No	338	46.2	49	40.8	143	44.4	31	47.7	29	44.6
Don't know	70	9.6	19	16.0	24	7.4	7	10.8	8	12.3

[a]Missing data for variables: age (n = 1), Hispanic ethnicity (n = 19), geographic origin (n = 23), and family history (n = 149).

Our results and those of others suggest that Internet advertising, especially through social media provides an efficient mechanism to assemble populations with rare conditions for research studies. Our results suggest that Google advertising may also be effective but at a higher cost and less specific targeting as indicated by the higher bounce rates of individuals referred to the NPRI website by this mechanism. Specifically, a search of Facebook groups focused on NF1 revealed that as of 8/1/2013 there were over 100 NF-dedicated Facebook groups. This large number of Facebook social media sites for this one rare disorder highlights the enormous potential to reach affected individuals for large-scale epidemiologic, clinical, and genomic studies.

However, researchers should be aware of some potential challenges of online patient-driven registries. Participants enrolling in online registries represent convenience samples; therefore the characteristics of registry participants may not necessarily be representative of the entire underlying population with the rare condition of interest. For example, our study population was over-represented by females, despite the fact that NF1 affects males and females equally. This finding is not unique to NF1, as it has previously been reported that females participate at higher rates in health studies than males [Roberts et al., 2004; Le Retraite et al., 2010; Op de Coul et al., 2012]. However, data from Facebook suggests that our registry participants who reported Facebook as their referral source have similar demographics to Facebook users (62.5% female registry participants vs. 58% female for Facebook users; 76.7% White for registry participants vs. 78% White for Facebook users [PewInternet.org, 2011]), suggesting that participants may be representative of the population of the referral source. In addition, participants are similar to the general population of NF1 with respect to inheritance, with an approximately equal percentage of participants reporting having a family history versus no family history of NF1 [Jett and Friedman, 2010].

Online patient-driven registries may also be limited by the validity of participant reported information, duplicate registrations, and completeness of questionnaire information. Participants self-report their NF1 diagnosis, which could lead to false subjects (i.e., participation by individuals who do not actually have the disease). We are currently addressing this issue by collecting authorization for release of medical record forms to validate NF1 and other reported outcome diagnoses. We plan to report findings from this effort in a future report. In addition, data on how

participants first heard about the registry was self-reported and was associated with some degree of error. However, our analyses of website traffic sources using Google Analytics was generally consistent with participant reported data. For example, the top three traffic sources were Google Ads, Facebook, and direct website entry with 26%, 20%, and 19% of website visitors coming from these sources, respectively (see Supplementary Fig. 2 in supporting information online). With respect to completeness of information, approximately 25% of registrants did not complete the entire questionnaire. Participants can save progress for each questionnaire section and choose to complete the entire questionnaire at a later time, which may act to reduce completion rates if participants do not remember to return to the registry website to finish their questionnaire. Duplicate registrations can also be an issue with online registries as noted previously [Reaves and Bianchi, 2013]. We identified and eliminated duplicate registrations, which required extensive personnel effort (data not shown).

Researchers should also be aware of two other limitations of our study design when considering how to apply these results to their own studies. First, our online patient-driven registry was designed to enable potential participants to freely register following implied consent as indicated by marking associated checkboxes and completing the questionnaire. Therefore, it is assumed that each person who registers is a competent adult able to provide consent for themselves or the minor participant. Second, we did not establish the Google Analytics Goals tool [Google, 2014] and thus were limited in the analyses we were able to perform using Google Analytics. We recommend employing the Google Analytics Goals tool to provide researchers with an additional mechanism to evaluate traffic flow through registry pages and self-reported traffic data.

In conclusion, we found that online advertising, especially through Facebook, provides a highly effective recruitment tool for rapidly assembling large numbers of patients with a rare disease to an online registry for research studies. However, strengths and limitations of this approach relative to other approaches that assemble patients with diseases for medical genetics research should be considered.

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REFERENCES

Battistella E, Kalyan S, Prior JC. 2010. Evaluation of methods and costs associated with recruiting healthy women volunteers to a study of ovulation. J Womens Health (Larchmt) 19:1519–1524.

Close S, Smaldone A, Fennoy I, Reame N, Grey M. 2013. Using information technology and social networking for recruitment of research participants: Experience from an exploratory study of pediatric klinefelter syndrome. J Med Internet Res 15:e48.

Creange A, Zeller J, Rostaing-Rigattieri S, Brugieres P, Degos JD, Revuz J, Wolkenstein P. 1999. Neurological complications of neurofibromatosis type 1 in adulthood. Brain 122:473–481.

Crowe FW. 1956. A clinical, pathological, and genetic study of multiple neurofibromatosis. Springfield, IL: Thomas. p 181.

Facebook. Facebook reports fourth quarter and full year 2012 results. Facebook. http://investor.fb.com/releasedetail.cfm?ReleaseID=736911 (Accessed April 18, 2013).

Facebook. 2013. Like. Facebook. https://www.facebook.com/help/www/452446998120360 (Accessed October 8 2013).

Fenner Y, Garland SM, Moore EE, Jayasinghe Y, Fletcher A, Tabrizi SN, Gunasekaran B, Wark JD. 2012. Web-based recruiting for health research using a social networking site: An exploratory study. J Med Internet Res 14:e20.

Gilboa Y, Rosenblum S, Fattal-Valevski A, Josman N. 2010. Application of the international classification of functioning, disability and health in children with neurofibromatosis type 1: A review. Dev Med Child Neurol 52:612–619.

Google. 2014. About goals. https://support.google.com/analytics/answer/1012040?hl=en (Accessed 1/6 2014).

Gutmann DH, Rasmussen SA, Wolkenstein P, MacCollin MM, Guha A, Inskip PD, North KN, Poyhonen M, Birch PH, Friedman JM. 2002. Gliomas presenting after age 10 in individuals with neurofibromatosis type 1 (NF1). Neurology 59:759–761.

Health-Eu. Rare diseases. European Commission Health-Eu. http://ec.europa.eu/health-eu/health_problems/rare_diseases/index_en.htm (Accessed May 3, 2013).

Hsieh HY, Fung HC, Wang CJ, Chin SC, Wu T. 2011. Epileptic seizures in neurofibromatosis type 1 are related to intracranial tumors but not to neurofibromatosis bright objects. Seizure 20:606–611.

Jett K, Friedman JM. 2010. Clinical and genetic aspects of neurofibromatosis 1. Genet Med 12:1–11.

Johnson MR, Ferner RE, Bobrow M, Hughes RA. 2000. Detailed analysis of the oligodendrocyte myelin glycoprotein gene in four patients with neurofibromatosis 1 and primary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry 68:643–646.

Johnson KJ, Hussain I, Williams K, Santens R, Mueller NL, Gutmann DH. 2012. Development of an international Internet-based neurofibromatosis type 1 patient registry. Contemp Clin Trials 34:305–311.

Jones SC, Magee CA. 2011. Exposure to alcohol advertising and alcohol consumption among Australian adolescents. Alcohol Alcohol 46:630–637.

Le Retraite L, Eisinger F, Loundou A, Rinaldi Y, Seitz JF, Auquier P. 2010. Sociogeographical factors associated with participation in colorectal cancer screening. Gastroenterol Clin Biol 34:534–540.

Marchuk DA, Saulino AM, Tavakkol R, Swaroop M, Wallace MR, Andersen LB, Mitchell AL, Gutmann DH, Boguski M, Collins FS. 1991. cDNA cloning of the type 1 neurofibromatosis gene: Complete sequence of the NF1 gene product. Genomics 11:931–940.

Masocco M, Kodra Y, Vichi M, Conti S, Kanieff M, Pace M, Frova L, Taruscio D. 2011. Mortality associated with neurofibromatosis type 1: A study based on Italian death certificates (1995–2006). Orphanet J Rare Dis 6:11.

Mastrangelo M, Mariani R, Spalice A, Ruggieri M, Iannetti P. 2009. Complex epileptic (Foix–Chavany–Marie like) syndrome in a child with neurofibromatosis type 1 (NF1) and bilateral (opercular and paracentral) polymicrogyria. Acta Paediatr 98:760–762.

Myotonic Dystrophy Family Registry. http://www.myotonic.org/patient-registry (Accessed November 11 2013).

North American Research Committee on Multiple Sclerosis. http://narcoms.org/about (Accessed November 11 2013).

Op de Coul EL, Gotz HM, van Bergen JE, Fennema JS, Hoebe CJ, Koekenbier RH, Pars LL, van Ravesteijn SM, van der Sande MA, van den Broek IV. 2012. Who participates in the Dutch Chlamydia screening? A study on demographic and behavioral correlates of participation and positivity. Sex Transm Dis 39:97–103.

Patients Like Me. http://www.patientslikeme.com/about (Accessed November 11 2013).

Perini P, Gallo P. 2001. The range of multiple sclerosis associated with neurofibromatosis type 1. J Neurol Neurosurg Psychiatry 71:679–681.

PewInternet.org. 2011. Social networking sites and our lives. Pew Research Center's Internet & American Life Project. http://pewinternet.org/Reports/2011/Technology-and-social-networks.aspx (Accessed April 16, 2013).

Pipatpajong H, Phanthumchinda K. 2011. Neurofibromatosis type I associated multiple sclerosis. J Med Assoc Thai 94:505–510.

Rarediseases.org. Rare Disease Information. National Organization for Rare Disorders. http://www.rarediseases.org/rare-disease-information (Accessed May 3, 2013).

Rasmussen SA, Yang Q, Friedman JM. 2001. Mortality in neurofibromatosis 1: An analysis using U.S. death certificates. Am J Hum Genet 68:1110–1118.

Reaves AC, Bianchi DW. 2013. The role of social networking sites in medical genetics research. Am J Med Genet Part A. 161:951–957.

Roberts JS, Barber M, Brown TM, Cupples LA, Farrer LA, LaRusse SA, Post SG, Quaid KA, Ravdin LD, Relkin NR, Sadovnick AD, Whitehouse PJ, Woodard JL, Green RC. 2004. Who seeks genetic susceptibility testing for Alzheimer's disease? Findings from a multisite, randomized clinical trial. Genet Med 6:197–203.

Rubinstein YR, Groft SC, Bartek R, Brown K, Christensen RA, Collier E, Farber A, Farmer J, Ferguson JH, Forrest CB, Lockhart NC, McCurdy KR, Moore H, Pollen GB, Richesson R, Miller VR, Hull S, Vaught J. 2010. Creating a global rare disease patient registry linked to a rare diseases biorepository database: Rare disease-HUB (RD-HUB). Contemp Clin Trials 31:394–404.

Seminog OO, Goldacre MJ. 2013. Risk of benign tumours of nervous system, and of malignant neoplasms, in people with neurofibromatosis: Population-based record-linkage study. Br J Cancer 108:193–198.

Spinicci G, Cherchi MV, Murru R, Conti M, Marrosu MG. 2010. A case of neurofibromatosis and multiple sclerosis. Neurol Sci 31:631–634.

Tweet MS, Gulati R, Aase LA, Hayes SN. 2011. Spontaneous coronary artery dissection: A disease-specific, social networking community-initiated study. Mayo Clin Proc 86:845–850.

U.S. Census. Table 1. Annual estimates of the population for the United States, Regions, States, and Puerto Rico: April 1, 2010 to July 1, 2012 (NST-EST2012-01). Release Date: December 2012. U.S. Census. http://www.census.gov/popest/data/national/totals/2012/ (Accessed May 10, 2013).

Wilding A, Ingham SL, Lalloo F, Clancy T, Huson SM, Moran A, Evans DG. 2012. Life expectancy in hereditary cancer predisposing diseases: An observational study. J Med Genet 49:264–269.

WIlliams Syndrome Patient and Clinical Research Registry. https://registry.williams-syndrome.org/index.htm (Accessed November 11 2013).

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