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CONTRACTING ORGANIZATION: University Health Network

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14. ABSTRACT

We are using electronic medical records and administrative database to study health care use of people living with NF1 in Ontario, Canada. Using electronic medical record database (EMRPC, previously called EMRALD), we estimated a minimum prevalence of NF1 between 1:2532 to 1:3851.

A previously developed billing algorithm has poor performance and won't allow proper assessment of health utilization patterns. Therefore, we have moved forward with a mitigation strategy, whereby we have created a registry of people with confirmed NF1 followed at tertiary centers This registry has been linked to administrative database, and matched to healthy controls to compare mortally and use of health care.

We are also studying mortality and healthcare use in patients identified through electronic medical records, using EMRPC and UTOPIAN databases

15. SUBJECT TERMS
NF1, prevalence, billing codes, EMR

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TABLE OF CONTENTS

	Page
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	6
5. Change/Problems	7
6. Products	8
7. Participants & Other Collaborating Organizations	9
8. Special Reporting Requirements	11
9. Appendices	12

INTRODUCTION:

The objective of this study is to develop an algorithm to identify people with NF1 living in the province of Ontario, Canada (population ~ 14 million), through administrative health databases. This algorithm will be used to study incidence, prevalence, NF1-related mortality and health care utilization patterns of patients with NF1. The specific aims for this project are outlined below.

Specific Aim 1: To develop and validate an algorithm to identify patients with NF1 in the province of Ontario.

Specific Aim 2: To estimate the incidence, prevalence and mortality of patients with NF1 in Ontario, Canada. We hypothesize that we can obtain reliable estimates of incidence and prevalence of NF1 in the province which we expect to be within previously published ranges. We also plan to calculate mortality ratios stratified by age and hypothesize that individuals with NF1 have higher mortality ratios compared to the general population.

Specific Aim 3: To study the health-utilization patterns of NF1 patients which includes the number of primary care, specialist and emergency visits, outpatient surgeries, hospital admissions, mental health care and pain treatments Compared to a matched cohort of healthy controls, we hypothesize that patients with NF1 will have, on average, significantly more visits at all levels of health care.

1. KEYWORDS:

NF1, neurofibromatosis 1, electronic medical record, EMR, administrative health databases, algorithm, prevalence, health utilization.

2. ACCOMPLISHMENTS:

Mayor goals/tasks for reporting period (as stated in SOW)

1. **Specific Aim 1, Major task 4:** 100% completion Manuscript submitted, revisions requested and re-submitted
2. **Specific Aim 2, Major task 1 :** Create dataset and obtain data: 100% completion. Datasets cleaned up in late 2021 and transferred to ICES. Data validated and duplicated removed, final cohort meeting inclusion/exclusion criteria has 1,213 individuals with NF1.
3. **Specific Aim 2, Major task 2:** Analyze data for incidence, prevalence, mortality: 100% completed. Prevalence estimated from EMRALD data (manuscript published), re-assessed in UTOPIAN data. From registry data, 15 (1.2%) NF1 individuals died during study window, no difference to controls (manuscript in preparation)
4. **Specific aim 3, Major task 1:** 100% complete. NF1 registry complete and linked to ICES. Cohort fully matched to population controls, excellent balance between groups.
5. **Specific Aim 3, Major task 2:** 80% complete**.** Common diagnostic and assessment billing codes in primary care practices assessed though UTOPIAN database. Inpatient and outpatient utilizations assessed in large linked cohort. Pending analyses of mental health, pain and skin.

As stated in our annual report for the first year, the billing algorithm had poor performance, therefore we are using our mitigation strategies to accomplish Aims 2 and 3. In our proposal we had 2 mitigation strategies and we are using both: using electronic medical records data to assess health utilization, and also creating a registry of individuals with NF1 from tertiary care and linking it to the administrative databases at ICES.

We have used a different EMR database (UTOPIAN), which is also linked to ICES. We demonstrated that our original EMR search strategy was feasible in UTOPIAN, although required minimal validation of identified cases by a clinician. Overall, we found that using NF1-secific terms in the cumulative patient profile to identify cases of NF1, works reasonably well in the UTOPIAN database even though the specific neurofibromatosis terms are different. Within UTOPIAN eligible individuals (n=**421,971)** we identified 127 individuals with possible/probable NF1 (estimated prevalence 1 in 3,322). The 127 NF1 cases were matched to 635 controls. In this cohort from primary health care records, individuals with NF1 had a similar prevalence of a diagnosis of anxiety/depression than controls, but needed more primary mental health services. NF1 patients had fewer healthy child and immunization visits than controls, which could reflect concomitant follow up by pediatricians. There were more primary health visits in adults than controls; however, there were fewer billings for mammogram tracking in NF1, despite increased risk of breast cancer in this population, and fewer contraceptive-related visits.

We also developed a registry of individuals with NF1 seen until December 2020, at the main academic centres with specialised NF1 care in Ontario: the University Health Network and the Hospital for Sick Children. The cohort has 1,205 individuals with NF1 (after removing duplicated and those with exclusion criteria). We have linked this registry to ICES databases, and matched to 6,025 controls. At the end of the observation window, the mean age in the NF1 group was 26.7 ± 17.6 years (median 23, IQR: 13-37-11), and 612 (50.8%) were female. Mean follow up time was 19.6 ± 8.7 years in NF1, and 18.8 ± 8.5 years in controls. Individuals with NF1 had a higher proportion of hypertension (8.7% vs 6.1 %) and cancer (11.7% vs 2.3%). Using negative binomial modelling and after full adjustment for covariates, NF1 patients had more visits to the emergency department (RR:1.35, 95% CI: 1.25-1.45), hospital admissions (RR: 3.41, 95%CI: 3.16-3.8), primary care visits (RR: 1.26, 95%CI: 1.2-1.3), specialist visits (RR:2.98, 95%CI: 2.8-3.2) and same-day surgeries (RR:1.93, 95%CI: 1.74-2.14). During the study window, there were 21 (1.7%) deaths in the NF1 group, compared to 111 (1.8%, p=ns) in the controls; there was no difference in the mean age (47.9±24.3 vs. 45.8±21.5) between groups, however, there was a higher proportion of women who died in the NF1 group compared to controls (47.6% vs. 38.7%, SMD:0.18). We also found a higher proportion of individuals receiving disability benefits, in those eligible (17.6% in NF1 vs. 6.6% controls, SMD:0.34).

What opportunities for training and professional development has the project provided?

Nothing to report

How were the results disseminated to communities of interest?

Presented at Children/s Tumor Foundation meeting, June 2023

What do you plan to do during the next reporting period to accomplish the goals?

i. UTOPIAN manuscript to be submitted in October 2023.

ii. Manuscript on general healthcare utilization (primary, specialty and inpatient) is under final review by authors and will be submitted for publication in the fall 2023. Data on associated healthcare costs to be analyzed and published separately.

iii. Manuscript on use of pain services, pain medication and mental health use will be completed.

iv. Data on access to care for cutaneous neurofibromas under analysis, and manuscript to be completed Spring 2024.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

i. We have created a large, fully linked registry of individuals with confirmed NF1, fully matched to general population controls. We have been able to compare use of common primary and specialty care services, as well as admissions to hospital and mortality.

ii. We have assessed the feasibility of using our previously developed EMR algorithm in a new database. We have preliminary assessment of commonly billed codes by primary care providers looking after people with NF1.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

We have already validated a simple EMR search that may be used in any healthcare setting that uses electronic medical records, to identify individuals with NF1. We have also created a large registry of NF1 individuals, fully linked to administrative health care databases.

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

No new issues in the past year.

Actual or anticipated problems or delays and actions or plans to resolve them

As expected, we had many delays over the past years, as ICES has prioritized COVID-related projects. However, we have a fully matched cohort of individuals with NF1 and population controls. We have been able to obtain relevant data to complete our aims. The pending tasks are mostly in relation to manuscript writing. We have two manuscripts that will be ready for submission this fall, plus another 2-3 manuscripts that will be prepared and submitted in late 2023-early 2024.

Changes that had a significant impact on expenditures

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report

Significant changes in use or care of human subjects

No changes from last report. All approvals are updated and in place.

Significant changes in use or care of vertebrate animals

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

Barnett C, Candido E, Chen B, Pequeno P, Parkin P, Tu K. Development of algorithms to identify individuals with Neurofibromatosis type 1 within administrative data and electronic medical records in Ontario, Canada. Orphanet J Rare Dis. 2022 Aug 26;17(1):321. doi: 10.1186/s13023-022-02493-5. PubMed PMID: 36028856; PubMed Central PMCID: PMC9419337.

Books or other non-periodical, one-time publications.

Nothing to Report

Other publications, conference papers and presentations.

1. Meera Chopra, Tin-Suet Joan Lee, Ellen Stephenson, Jemisha Apajee, Karen Tu, Patricia Parkin, Elisa Candido, Carolina Barnett. Primary healthcare utilization in individuals with NF1 in Ontario, Canada. Presented Children's Tumor Foundation Meeting. June 2023, Scottsdale, Arizona. Manuscript in preparation
2. Ajith Sivadasan, Alejandro Hernandez, Elisa Candido, Patricia Parkin, Karen Tu, Allan Puran, Meg Mendoza, Carolina Barnett. Outpatient and Inpatient Health Care Utilization in Patients with Neurofibromatosis 1 in Ontario, Canada. Presented Children's Tumor Foundation Meeting. June 2023, Scottsdale, Arizona. Manuscript in preparation

- **Website(s) or other Internet site(s)**

Nothing to Report

- **Technologies or techniques**

EMR search strategy to identify NF1 cases, in manuscript.

- **Inventions, patent applications, and/or licenses**

Nothing to Report

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Carolina Barnett-Tapia*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	ORCID ID 0000-0001-5546-0221
Nearest person month worked:	3.6
Contribution to Project:	*Dr. Barnett-Tapia coordinated this project. She performed final chart review to classify records as definitive or possible NF1. She reviewed all billing codes from cases to develop the algorithms. She supervised registry development and matching to population controls, and supervises all analyses on matched cohort.*
Funding Support:	

Name:	*Elisa Candido*
Project Role:	Co-investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1.2
Contribution to Project:	*Ms. Candido coordinates the ICES personnel, directed the algorithm development, and coordinates all ICES analyses as well as regulatory approvals.*
Funding Support:	NA

Name:	Karen Tu
Project Role:	*Co-investigator*
Researcher Identifier (e.g. ORCID ID):	ORCID ID: 0000-0003-0883-4934
Nearest person month worked:	1.2
Contribution to Project:	*Dr. Tu provided expertise in developing search strategy within EMRALD and developing billing algorithms. She has provided access to UTOPIAN for external validation of EMR algorithm, and*

	assessment of ICES dta.
Funding Support:	

Name:	*Patricia Parkin*
Project Role:	*Co-investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1.0
Contribution to Project:	*Dr. Parkin has provided clinical expertise to determine billing codes to use in algorithms; she also has helped with registry of patients followed at the Hospital for Sick Children since the 1990s.*
Funding Support:	

Name:	*Branson Chen*
Project Role:	Health Information Analyst
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	*Mr. Chen conducted the search within EMRALD, analyzed abstractor reliability, and developed EMR algorithm*
Funding Support:	

Name:	*Priscila Pequeno*
Project Role:	Senior Research Analyst
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	*Ms. Pequeno developed and tested all the billing algorithms*
Funding Support:	

Name:	Meg Mendoza
Project Role:	Research Analyst
Researcher Identifier (e.g. ORCID ID):	

Nearest person month worked:	2
Contribution to Project:	*Mr.* Mendoza prepared UHN REB application for linkage to ICES data and coordinated with HSC
Funding Support:	
Name:	Samantha Lee
Project Role:	ICES epidemiologist
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	MS. Lee has helped coordinate linkage project, and plan data collection for health care utilization
Funding Support:	

Name:	Alejandro Hernandez
Project Role:	ICES research analyst
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	Mr. Hernandez is working on the linked data, creating matched cohort and will work on health care utilization analysis
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

1. **Organization Name:** Institute for Clinical Evaluative Science (ICES)
2. **Location of Organization:** *Toronto, Canada*
3. **Partner's contribution to the projec**t: Collaboration

The ICES hosts all health administrative data for the province of Ontario, and we contracted their services for this study.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *NA*

QUAD CHARTS: *NA*

9. APPENDICES:

2 Posters presented at 2023 Children's Tumor Foundation

Primary healthcare utilization in individuals with NF1 in Ontario, Canada

Meera Chopra[1], Tin-Suet Joan Lee[1], Ellen Stephenson[2], Jemisha Apajee[2], Karen Tu[2], Patricia Parkin[3], Elisa Candido[4], Carolina Barnett[5]

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[4] Institute for Clinical Evaluative Sciences, Toronto, Ontario [5] Elisabeth Raab Neurofibromatosis Clinic, Toronto General Hospital, Toronto, Ontario

Introduction

- Previous studies have examined healthcare utilization patterns in patients with NF1, however, this has not been conducted in Canada.[1,2]
- Given the range of comorbid conditions and complications that are associated with NF1, being aware of areas of increased healthcare expenditures will aid in improving planning and healthcare promotion amongst this cohort.[3]

Objective

- To assess the use of primary healthcare in individuals with NF1 compared to those without NF1.

Methods

- UTOPIAN is a database of electronic medical records (EMRs). of primary care in Ontario, Canada
- A validated free text search strategy was used to identify individuals with NF1 and a clinician with NF1 experience validated the records.
- NF1 patients were matched 1:5 by age, sex, and EMR start date to control patients.
- The prevalence of the most common diagnostic codes and their billing rates were compared between both patient populations between 2015 and 2019.

Results

In December 2020, there were 421,971 eligible patients in UTOPIAN, and 127 were classified as having NF1 (prevalence of 1 in 1,323).

During the study window, NF1 patients had a higher rate of visits for anxiety or depression compared to control patients (rate difference: +32.6 per 100 patients, 95%CI: 27.9-37.3); however, there was no significant difference in the prevalence of diagnostic codes for anxiety or depression (22.1% vs 18.0%, p=ns). More NF1 patients had diagnostic codes for skin/subcutaneous tissue disorders (10.2% vs 5.4%, p<0.0001) and essential hypertension (11.0% vs. 9.7%, p<0.001).

NF1 patients had more periodic health visits for adults (18-64 years) than controls (rate difference: +13.1/100, 95%CI:9.2-16.9), but had fewer healthy child visits (rate difference: -15.3 /100, 95%CI: -20.5, -10.0). NF1 patients had fewer billings for contraception management than controls (5.5% vs. 8.4% p<0.001), with a rate difference of -11.3 billings/100 (95%CI:-14.5, -8.2). NF1 patients also had fewer billings for immunizations (rate difference: -9.9/100, 95%CI: -12.9, -6.9) and mammogram tracking (rate difference: -4.9/100, 95%CI: -8.0, -1.8).

Table 1. Demographic characteristics of NF1 and control cohorts.

	Cohort			
	Control patients		Definitely/Possibly NF1	
	N	%	N	%
Total	**635**		**127**	
Sex				
Female	340	53.5%	68	53.5%
Male	295	46.5%	59	46.5%
Neighborhood income quintile				
1 (lowest)	137	21.6%	30	23.6%
2	114	18.0%	21	16.5%
3	107	16.9%	25	19.7%
4	102	16.1%	16	12.6%
5 (highest)	160	25.2%	34	26.8%
Missing	15	2.4%	1	0.8%
Rurality				
Rural	60	9.4%	11	8.7%
Urban	568	89.4%	115	90.6%
Missing	7	1.1%	1	0.8%
Age at December 2020				
Mean age in years (SD)	36.39	22.61	36.39	22.61
Median age in years (IQR)	33	(19-55)	33	(19-55)
Age at last visit				
Mean age in years (SD)	34.93	23.03	35.17	22.90
Median age in years (IQR)	31	18-54	32	18-54
Length of time on the EMR				
Mean number of years (SD)	8.27	4.68	8.10	4.50
Median number of years (IQR)	8	(5-10)	8	(5-10)

Table 2. OHIP diagnostic codes with significantly increased usage in patients with NF1 compared to control patients.

Diagnostic Code	Diagnosis	Rate difference confidence interval	Control rate of records per 100 patients	NF rate of records per 100 patients
300	Anxiety, dissociative and somatoform disorders	32.60 (27.92, 37.28)	54.02	86.61
401	Essential hypertension	17.32 (13.13, 21.51)	37.01	54.33
250	Diabetes mellitus	15.12 (10.48, 19.76)	62.83	77.95
724	Other and unspecified disorders of back	11.65 (8.22, 15.09)	14.33	25.98
785	Symptoms involving cardiovascular system	10.24 (6.91, 13.56)	12.60	22.83
311	Depressive disorder, not elsewhere classified	8.03 (4.89, 11.17)	10.08	18.11
216	Benign neoplasm of skin	7.40 (4.71, 10.10)	3.62	11.02
917	General medical examination	6.93 (3.03, 10.83)	31.65	38.58
709	Other disorders of skin and subcutaneous tissue	6.30 (3.34, 9.25)	7.87	14.17
682	Other cellulitis and abscess	6.14 (3.29, 9.00)	6.46	12.60
379	Other disorders of eye	5.98 (3.65, 8.32)	1.10	7.09

Table 3. OHIP diagnostic codes with significantly decreased usage in patients with NF1 compared to control patients.

Diagnostic Code	Diagnosis	Rate difference confidence interval	Control rate of records per 100 patients	NF rate of records per 100 patients
896	Need for prophylactic vaccination and inoculation against combinations of disease	-16.85 (-20.61, -13.09)	43.62	26.77
916	Other healthy infant or child receiving	-15.28 (-20.54, -10.01)	131.81	116.54
895	Encounters for contraceptive management	-11.34 (-14.50, -8.18)	23.94	12.60
626	Disorders of menstruation and other abnormal bleeding from female genital tract	-7.72 (-10.54, -4.90)	15.59	7.87
493	Asthma	-7.56 (-10.43, -4.69)	16.22	8.66
272	Disorders of lipoid metabolism	-5.67 (-7.74, -3.60)	7.24	1.57
786	Symptoms involving respiratory system and other chest symptoms	-5.51 (-8.45, -2.57)	15.75	10.24
244	Acquired hypothyroidism	-4.57 (-6.96, -2.18)	8.50	3.94

Conclusion

- In this cohort, individuals with NF1 had a similar prevalence of diagnoses of anxiety and depression than controls, but received more primary mental health services.
- NF1 patients had fewer healthy child and immunization visits than controls, which may reflect concomitant follow-up by pediatricians.
- There were more primary health visits in adults than controls; however, there were fewer billings for mammogram tracking in NF1, despite the increased risk of breast cancer in this population, and fewer contraceptive-related visits.

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2. Stewart DR, Korf BR, Nathanson KL, Stevenson DA, Yohay K. Care of adults with neurofibromatosis type 1: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018 Jul;20(7):671-82.
3. Tonsgard JH. Clinical manifestations and management of neurofibromatosis type 1. In: Seminars in pediatric neurology 2006 Mar 1 (Vol. 13, No. 1, pp. 2-7). WB Saunders.

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Outpatient and Inpatient Health Care Utilization in Patients with NF1 in Ontario, Canada

A. Sivadasan , A. Hernandez, E. Candido, P. Parkin, K. Tu, A. Puran, M.Mendoza, C. Barnett

Background and Aims

- There are limited data regarding the health care utilization use of people with Neurofibromatosis type 1 (NF1).
- We aimed to assess the use of different health services in people with NF1 compared to the general population

Methods

1. We created a registry of individuals with NF1 attending pediatric and adult NF clinics in Ontario, Canada, between 1990 and December 31, 2020.
2. We linked the registry to administrative databases held at ICES, using de-identified unique identifiers.
3. Index date was birth year or eligibility for the Ontario Health Plan. NF1 individuals were matched 1:5 to general population controls

Clinic and Demographic Characteristics at End of Study Window

	NF1 (n=1,240)	Controls (n=6,025)	P value
Age	26.7 ± 18	26.1 ± 17	n.s
Mean follow-up time (years)	19.7 ± 9	18.8 ± 9	n.s
Sex (Female)	612 (50.8%)	3,060 (50.8%)	n.s
Rurality	64 (5.3%)	467 (7.8%)	<0.0001
Hypertension	105 (8.7%)	368 (6.1%)	0.0008
Cancer	141 (11.7%)	140 (2.3%)	<0.0001

Health Care Utilization Outcomes

	NF1 (n=1,240)	Controls (n=6,025)	Incidence Rate Ratio (visits per person-years)
Emergency Department (ED)	1,093 (91%)	4,994 (83%)	1.35 (1.25-1.44)
Hospitalizations	996 (82.7%)	2,067 (34.3%)	3.47 (3.16-3.80)
Primary Care Visits	1,174 (97.4%)	5,815 (96.5%)	1.26 (1.20-1.33)
Specialty Visits	1,203 (99.8%)	5,392 (89.5%)	2.98 (2.77-3.20)
Same-day Surgery	660 (54.8%)	2,139 (35.5%)	1.93 (1.74-2.14)

A higher proportion of people with NF1 used each health service studied compared to controls during study window. Individuals with NF1 also had a higher number of visits in all categories, as seen in the increased risk ratio column.

Specialty Visits

Specialty	NF1 (n=1,240)	Controls (n=6,025)	P value
Dermatology	632 (52.4%)	1,815 (30.1%)	<0.0001
Genetics	566 (47%)	54 (0.9%)	<0.0001
General Surgery	438 (36.3%)	1,215 (20.2%)	< 0.0001
Neurology	727 (60.3%)	643 (10.7%)	<0.0001
Neurosurgery	487 (40.4%)	115 (1.9%)	<0.0001
Medical Oncology	33 (2.7%)	45 (0.7%)	<0.0001
Radiation Oncology	93 (7.7%)	77 (1.3%)	<0.0001
Ophthalmology	1,075 (89.2%)	1,271 (21.1%)	<0.0001
Pediatrics	1,006 (83.5%)	3,424 (56.8%)	<0.0001
Plastic Surgery	487 (40.4%)	928 (15.4%)	<0.0001
Psychiatry	301 (25%)	938 (15.6%)	<0.0001

Disability Benefits
(eligible 25-64 years)

NF1: 17.6% (95/541)
Controls: 6.6% (178/2,693)

Mortality:
There were 21 deaths in the NF1 group (1.7%) and 111 (1.8%) in the controls.

No difference in mean age of death.

- People with **NF1** had **more**: visits to the ED, hospital admissions, visits to specialists, primary care and same day surgery.
- **Individuals** with **NF1** had **5-times higher** prevalence of cancer than controls.
- **1 in 5** Individuals with **NF1** received **disability benefits,** compared to 1 in 15 controls.

Limitations:
Registry developed from individuals attending specialized NF clinics, may indicate individuals with higher disease burden, and may not be generalizable to the general NF1 population.

Funding: This study received funding from the US Department of Defense, award number: W81XWH-19-1-0177, NF180027

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