



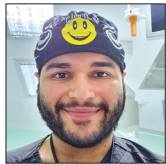
Review Article

Bibliometric analysis of the top 100 most-cited articles in neurofibromatosis

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ABSTRACT

Background: Neurofibromatosis (NF) is an umbrella term that refers to three distinct disease entities: NF Type 1, Type 2, and schwannomatosis. Here, we reviewed the scientific performance and the most influential publications on NF.

Methods: A keyword-based search was performed using the Scopus database. The top 100 articles were grouped based on NF types and the studied entities. The differences between the articles, authors, and journals were quantified based on certain parameters. Other parameters were collected for the complete citational analysis.

Results: The top 100 articles were published between 1961 and 2020. The most trending period of research was in the 1990s and articles studying the clinical aspect and the underlying genetic correlation made up 84% of all articles from the list. The United States of America (USA) had the highest number of contributions (69 articles, 69%). The top institute of contribution to the list was the Howard Hughes Medical Institute, USA (14 articles, 14%). Author-based analysis reveals that the neurologist D. H. Gutmann from St. Louis Children's Hospital, USA, was the most active and authored 11 articles (11%) on the list.

Conclusion: The publication trends show that articles studying medical and surgical management were of little interest. The top 100 articles did not include any randomized control trials, and the highest level of evidence was obtained from reviews of pooled knowledge as well as population-based and longitudinal studies.

Keywords: Bibliometric, Neurocutaneous disorders, Neurofibroma, Neurofibromatosis, Von Recklinghausen disease

INTRODUCTION

The term neurofibromatosis (NF) was first introduced to the medical literature by Frederick von Recklinghausen in 1882 to characterize the structural relation and mutual involvement of neuromas and fibromas.^[20,100] NF Type 1 (NF1) and Type 2 (NF2) are both dominantly inherited; nonetheless, they are distinct disease entities.^[53,85] NF1 is caused by a mutated tumor suppressor gene on the long arm of chromosome 17 (17q11.2).^[8,117] The disorder is most commonly defined by the cutaneous stigmata, café-au-lait spots, and neurofibromas.^[42] NF2 is caused by a different mutated gene on the long arm of chromosome 22 (22q1.2) and is characterized by the development of multiple neurologic lesions as well as cutaneous and ocular manifestations.^[99,113] The overall reported rates of NF1 and NF2 are 1/3000 and 1/25,000, which make them relatively

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rare diseases.^[34,39] The National Institutes of Health (NIH) in 1987 (updated in 1997) identified the diagnostic criteria of NF1 and NF2 after which the ambiguity between the two types has considerably resolved in the literature.^[53,85]

A major type of NF and challenging differential of NF2 are schwannomatosis, also known as NF Type 3 (NF3).^[77] The reported incidence of schwannomatosis is 1/68,956, which is less than half the incidence of NF2.^[36] Unlike NF2, schwannomatosis is caused by mutated *SMARCB1* and *LZTR1* on chromosome 22 and delineated by multiple non-intradermal schwannomas and the absence of bilateral vestibular schwannomas.^[56,89]

The management of NF involves many disciplines.^[85] Medically, to date, there is no specific curable pharmacological treatment for NF1, but trials to treat some of the clinical manifestations are ongoing.^[31,51,54] Recently, a mitogen-activated protein kinase inhibitor (Selumetinib) was approved, but its use is currently limited to children with plexiform neurofibroma.^[79] For NF2, targeted therapy for the progressive vestibular schwannoma is promising.^[13,63,70,90,91] Even so, there is no specific therapeutic agent yet approved.

Bibliometric analysis is an objective method to evaluate scientific publications' performance in various fields.^[10,119] Publication data are analyzed through multiple indicators to measure the impact, and more precisely, the effect of utility.^[119] Citations are votes that often reflect the importance and reputation of a scientific paper.^[10,119] Similar bibliometric studies have been published previously.^[1,2,33,125-129] The top 100 cited articles will be discussed in this study, and their significant results and impact on the NF field will be detailed.

MATERIALS AND METHODS

A bibliometric keyword-based search using the Scopus database was utilized to perform a citation analysis of the top 100 most-cited articles on NF. A title-specific search using "NF," "neurofibroma," and "von Recklinghausen's" was performed as search terms. The articles were rearranged based on their citation count (CC) in descending fashion. The top 100 articles were collected after excluding non-English, conference papers, erratum publications, and unpublished articles. The list of the top 100 articles on NF was categorized based on NF types to Type 1 and Type 2. Further subcategorization based on the studied entities of the top 100 articles yielded the following categories: (1) clinical, (2) genetics, (3) experimental, (4) histopathological, (5) radiological, (6) medical management, and (7) surgical management. The following parameters were considered when quantifying the difference between articles, authors, and journals: CC, citation per year (CY), Journal's SCImago Journal Rank (SJR), Journal's Source Normalized Impact Per Paper, Hirsch index (H-Index), and Journal Impact

Factor (IF). The H-Index measures the productivity and the impact of an author by calculating the number of publications, he has been cited for at least the same number of times.^[57] The Journal IF is defined as the average count of citations received in a given year per article published in the preceding 2 years.^[48,50] Other significant parameters of interest were collected for the complete citational analysis of publications, which involved the authors, first author's specialty, article title, country of origin, contributing institutions, journals, and year of publications. Furthermore, a two tailed correlation analysis at 5% level of significance was carried out between the number of citations and the duration of publication in an Excel spreadsheet and SPSS version 26. Selection of the studies included in the discussion section was based on the following criteria to establish narrative review: 1 – highly cited article in relation to other articles within the same category, 2 – the degree of scientific contribution, and 3 – historical or scientific relevance to the top cited articles.

RESULTS

The keyword-based search identified 12,718 articles in which 8564 articles were included after excluding mismatched articles. The publication dates ranged from 1906 to 2020 in which the top 100 articles were published between 1961 and 2020. The top 100 articles CC accounted for 28,957 CCs; the self-citations rate was 7.56%, and the citations from books were 8.21% [Table 1]. The top ten most-cited articles are listed [Table 2]. The most trending research period was the 1990s in which 54 articles from the list were published [Figure 1]. Articles studying the clinical (44%) aspect and the underlying genetic (40%) correlation constituted 84% of all articles from the list. The remaining 16% are histopathological (4%), experimental (8%), radiological (2%), surgical (1%), and medical (1%) management articles. The United States of America had the highest number of contributions to the list at 69 articles. The top institutes of contribution to the list showed that Howard Hughes Medical Institute was highest and produced 14 articles from the list [Figure 2]. Journal-based analysis showed that four journals had an IF range of 38.63 to 70.67. *Cell* was the most contributing journal and published nine articles from the list; it has the highest SJR score among the top journals [Figure 3]. The author-based analysis reveals that the neurologist D.H. Gutmann was the most active and published 11 articles on the list. The highest H-index was a paper from the geneticist F.S. Collins at 177 [Figure 4]. The most-cited article was authored by Wallace *et al.*, in 1990, by *Science* where they studied the large transcript disruption in NF1 subjects. The article was cited 1114 times and had a CY of 37.1.^[117] Results of the two tailed correlation test indicate a statistically significant ($P = 0.013$) relationship between the number of years since an article was published and its CC (correlation coefficient = 0.247). The

Table 1: The top 100 most-cited articles on neurofibromatosis.

Rank	Authors	Title	Year	Journal	CC	CY
1 st	Wallace <i>et al.</i> ^[117]	Type 1 neurofibromatosis gene: identification of a large transcript disrupted in three NF1 patients	1990	Science	1114	37.1
2 nd	Gutmann <i>et al.</i> ^[53]	The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2	1997	Journal of the American Medical Association	1028	44.7
3 rd	Trofatter <i>et al.</i> ^[113]	A novel moesin-, ezrin-, and radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor	1993	Cell	1014	37.6
4 th	Riccardi ^[96]	Von Recklinghausen Neurofibromatosis	1981	New England Journal of Medicine	913	23.4
5 th	Cawthon <i>et al.</i> ^[21]	A major segment of the neurofibromatosis Type 1 gene: cDNA sequence, genomic structure, and point mutations	1990	Cell	893	29.8
6 th	Xu <i>et al.</i> ^[123]	The neurofibromatosis Type 1 gene encodes a protein related to GAP	1990	Cell	838	27.9
7 th	Viskochil <i>et al.</i> ^[114]	Deletions and a translocation interrupt a cloned gene at the neurofibromatosis type 1 locus	1990	Cell	820	27.3
8 th	Evans <i>et al.</i> ^[35]	Malignant peripheral nerve sheath tumors in neurofibromatosis	2002	Journal of Medical Genetics	711	39.5
9 th	Martin <i>et al.</i> ^[80]	The GAP-related domain of the neurofibromatosis Type 1 gene product interacts with ras p21	1990	Cell	683	22.8
10 th	Basu <i>et al.</i> ^[9]	Aberrant regulation of ras proteins in malignant tumor cells from Type 1 neurofibromatosis patients	1992	Nature	529	18.9
11 th	Xu <i>et al.</i> ^[122]	The catalytic domain of the neurofibromatosis Type 1 gene product stimulates ras GTPase and complements ira mutants of <i>S. cerevisiae</i>	1990	Cell	516	17.2
12 th	Huson <i>et al.</i> ^[60]	Von recklinghausen neurofibromatosis: a clinical and population study in South-east Wales	1988	Brain	511	16.0
13 th	Ferner <i>et al.</i> ^[42]	Guidelines for the diagnosis and management of individuals with neurofibromatosis	2007	Journal of Medical Genetics	507	39.0
14 th	Barker <i>et al.</i> ^[8]	Gene for von Recklinghausen neurofibromatosis is in the pericentromeric region of chromosome 17	1987	Science	493	14.9
15 th	Brannan <i>et al.</i> ^[16]	Targeted disruption of the neurofibromatosis Type 1 gene leads to developmental abnormalities in heart and various neural crest-derived tissues	1994	Genes and Development	489	18.8
16 th	DeClue <i>et al.</i> ^[29]	Abnormal regulation of mammalian p21ras contributes to malignant tumor growth in von Recklinghausen (type 1) neurofibromatosis	1992	Cell	489	17.5
17 th	Evans <i>et al.</i> ^[37]	A clinical study of Type 2 neurofibromatosis	1992	QJM	486	17.4
18 th	Sørensen <i>et al.</i> ^[111]	Long-term Follow-up of von Recklinghausen Neurofibromatosis	1986	New England Journal of Medicine	445	13.1
19 th	Costa <i>et al.</i> ^[24]	Mechanism for the learning deficits in a mouse model of neurofibromatosis Type 1	2002	Nature	411	22.8
20 th	Listernick <i>et al.</i> ^[73]	Natural history of optic pathway tumors in children with neurofibromatosis Type 1: a longitudinal study	1994	Journal of Pediatrics	394	15.2
21 st	Ferner and Gutmann ^[41]	International consensus statement on malignant peripheral nerve sheath tumors in neurofibromatosis	2002	Cancer Research	383	21.3

(Contd...)

Table 1: (Continued).

Rank	Authors	Title	Year	Journal	CC	CY
22 nd	Martuza and Eldridge ^[81]	Neurofibromatosis 2	1988	New England Journal of Medicine	376	11.8
23 rd	Huson <i>et al.</i> ^[59]	A genetic study of von Recklinghausen neurofibromatosis in South-east Wales. I Prevalence, fitness, mutation rate, and effect of parental transmission on severity	1989	Journal of Medical Genetics	371	12.0
24 th	Williams <i>et al.</i> ^[121]	Neurofibromatosis Type 1 revisited	2009	Pediatrics	362	32.9
25 th	Listernick <i>et al.</i> ^[75]	Optic pathway gliomas in neurofibromatosis 1: controversies and recommendations	2007	Annals of Neurology	361	27.8
26 th	Friedman ^[46]	Epidemiology of neurofibromatosis Type 1	1999	American Journal of Medical Genetics - Seminars in Medical Genetics	360	17.1
27 th	Evans <i>et al.</i> ^[38]	A genetic study of Type 2 neurofibromatosis in the United Kingdom. I. Prevalence, mutation rate, fitness, and confirmation of maternal transmission effect on severity	1992	Journal of Medical Genetics	358	12.8
28 th	Rouleau <i>et al.</i> ^[99]	Genetic linkage of bilateral acoustic neurofibromatosis to a DNA marker on chromosome 22	1987	Nature	354	10.7
29 th	Listernick <i>et al.</i> ^[76]	Optic pathway gliomas in children with neurofibromatosis 1: Consensus statement from the NF1 optic pathway glioma task force	1997	Annals of Neurology	345	15.0
30 th	Shannon <i>et al.</i> ^[106]	Loss of the normal NF1 allele from the bone marrow of children with Type 1 neurofibromatosis and malignant myeloid disorders	1994	New England Journal of Medicine	344	13.2
31 st	Hyman <i>et al.</i> ^[61]	The nature and frequency of cognitive deficits in children with neurofibromatosis Type 1	2005	Neurology	343	22.9
32 nd	Wallace <i>et al.</i> ^[116]	A <i>de novo</i> Alu insertion results in neurofibromatosis Type 1	1991	Nature	343	11.8
33 rd	Cichowski <i>et al.</i> ^[22]	Mouse models of tumor development in neurofibromatosis Type 1	1999	Science	333	15.9
34 th	Legius <i>et al.</i> ^[68]	Somatic deletion of the neurofibromatosis Type 1 gene in a neurofibrosarcoma supports a tumor suppressor gene hypothesis	1993	Nature Genetics	327	12.1
35 th	Menon <i>et al.</i> ^[83]	Chromosome 17p deletions and p53 gene mutations associated with the formation of malignant neurofibrosarcomas in von Recklinghausen neurofibromatosis	1990	Proceedings of the National Academy of Sciences of the United States of America	326	10.9
36 th	Marchuk <i>et al.</i> ^[78]	cDNA cloning of the Type 1 neurofibromatosis gene: complete sequence of the NF1 gene product	1991	Genomics	325	11.2
37 th	Rasmussen <i>et al.</i> ^[94]	Mortality in neurofibromatosis 1: an analysis using U.S. death certificates	2001	American Journal of Human Genetics	320	16.8
38 th	Miettinen <i>et al.</i> ^[84]	Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases	2006	American Journal of Surgical Pathology	318	22.7
39 th	DeBella <i>et al.</i> ^[28]	Use of the National Institutes of Health criteria for diagnosis of neurofibromatosis 1 in children	2000	Pediatrics	316	15.8
40 th	Parry <i>et al.</i> ^[88]	Neurofibromatosis 2 (NF2): clinical characteristics of 63 affected individuals and clinical evidence for heterogeneity	1994	American Journal of Medical Genetics	305	11.7
41 st	Friedman and Birch ^[45]	Type 1 neurofibromatosis: a descriptive analysis of the disorder in 1728 patients	1997	American Journal of Medical Genetics	301	13.1

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Table 1: (Continued).

Rank	Authors	Title	Year	Journal	CC	CY
42 nd	Li et al. ^[71]	The HMG-CoA reductase inhibitor lovastatin reverses the learning and attention deficits in a mouse model of neurofibromatosis Type 1	2005	Current Biology	293	19.5
43 rd	Brems et al. ^[119]	Germline loss-of-function mutations in SPRED1 cause a neurofibromatosis 1-like phenotype	2007	Nature Genetics	292	22.5
45 th	Li et al. ^[72]	Somatic mutations in the neurofibromatosis 1 gene in human tumors	1992	Cell	291	10.4
44 th	Ferner ^[43]	Neurofibromatosis 1 and neurofibromatosis 2: a 21 st century perspective	2007	Lancet Neurology	291	22.4
46 th	Brasfield and Gupta ^[17]	Von Recklinghausen's disease: a clinicopathological study.	1972	Annals of surgery	287	6.0
47 th	Zöller et al. ^[124]	Malignant and benign tumors in patients with neurofibromatosis Type I in a defined Swedish population	1997	Cancer	284	12.3
48 th	Easton et al. ^[32]	An analysis of variation in expression of neurofibromatosis (NF) Type 1 (NF1): evidence for modifying genes	1993	American Journal of Human Genetics	283	10.5
49 th	D'Agostino et al. ^[25]	Sarcomas of the peripheral nerves and somatic soft tissues associated with multiple neurofibromatosis (von Recklinghausen's disease)	1963	Cancer	276	4.8
51 st	Giovannini et al. ^[49]	Conditional biallelic Nf2 mutation in the mouse promotes manifestations of human neurofibromatosis Type 2	2000	Genes and Development	270	13.5
50 th	Plotkin et al. ^[92]	Hearing improvement after bevacizumab in patients with neurofibromatosis Type 2	2009	New England Journal of Medicine	270	24.5
52 nd	AsthaGiri et al. ^[5]	Neurofibromatosis Type 2	2009	The Lancet	269	24.5
53 rd	Silva et al. ^[110]	A mouse model for the learning and memory deficits associated with neurofibromatosis Type 1	1997	Nature Genetics	265	11.5
54 th	Shen et al. ^[108]	Molecular genetics of neurofibromatosis Type 1 (NF1)	1996	Journal of Medical Genetics	264	11.0
55 th	Rasmussen and Friedman ^[93]	NF1 gene and neurofibromatosis 1	2000	American Journal of Epidemiology	263	13.2
56 th	Bianchi et al. ^[12]	High frequency of inactivating mutations in the neurofibromatosis Type 2 gene (NF2) in primary malignant mesotheliomas	1995	Proceedings of the National Academy of Sciences of the United States of America	260	10.4
57 th	Korf ^[65]	Plexiform neurofibromas	1999	American Journal of Medical Genetics - Seminars in Medical Genetics	259	12.3
58 th	Vogel et al. ^[115]	Mouse tumor model for neurofibromatosis Type 1	1999	Science	258	12.3
59 th	Walther et al. ^[118]	Von Recklinghausen's disease and pheochromocytomas	1999	Journal of Urology	254	12.1
60 th	Seizinger et al. ^[104]	Genetic linkage of von Recklinghausen neurofibromatosis to the nerve growth factor receptor gene	1987	Cell	252	7.6
61 st	Bollag and McCormick ^[14]	Differential regulation of rasGAP and neurofibromatosis gene product activities	1991	Nature	247	8.5
62 nd	Jett and Friedman ^[62]	Clinical and genetic aspects of neurofibromatosis 1	2010	Genetics in Medicine	246	24.6
63 rd	Ars et al. ^[4]	Mutations affecting mRNA splicing are the most common molecular defects in patients with neurofibromatosis Type 1	2000	Human Molecular Genetics	244	12.2

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Table 1: (Continued).

Rank	Authors	Title	Year	Journal	CC	CY
64 th	Boyd <i>et al.</i> ^[15]	Neurofibromatosis Type 1	2009	Journal of the American Academy of Dermatology	241	21.9
65 th	Evans ^[40]	Neurofibromatosis Type 2 (NF2): a clinical and molecular review	2009	Orphanet Journal of Rare Diseases	240	21.8
66 th	Sekido <i>et al.</i> ^[105]	Neurofibromatosis Type 2 (NF2) Gene Is Somatic Mutated in Mesothelioma but not in Lung Cancer	1995	Cancer Research	239	9.6
67 th	Friedman <i>et al.</i> ^[44]	Cardiovascular disease in neurofibromatosis 1: report of the NF1 Cardiovascular Task Force	2002	Genetics in Medicine	237	13.2
68 th	Daston <i>et al.</i> ^[27]	The protein product of the neurofibromatosis Type 1 gene is expressed at highest abundance in neurons, Schwann cells, and oligodendrocytes	1992	Neuron	237	8.5
69 th	Riccardi ^[95]	Neurofibromatosis: clinical heterogeneity	1982	Current Problems in Cancer	237	6.2
70 th	Lewis <i>et al.</i> ^[69]	Von Recklinghausen Neurofibromatosis: II. Incidence of Optic Gliomata	1984	Ophthalmology	236	6.6
71 st	Listernick <i>et al.</i> ^[74]	Optic gliomas in children with neurofibromatosis Type 1	1989	The Journal of Pediatrics	235	7.6
72 nd	Korf ^[64]	Malignancy in neurofibromatosis Type 1	2000	Oncologist	226	11.3
73 rd	Wellenreuther <i>et al.</i> ^[120]	Analysis of the neurofibromatosis 2 gene reveals molecular variants of meningioma	1995	American Journal of Pathology	226	9.0
74 th	Greene <i>et al.</i> ^[50]	Arterial lesions associated with neurofibromatosis	1974	American Journal of Clinical Pathology	226	4.9
75 th	Bader and Miller ^[6]	Neurofibromatosis and childhood leukemia	1978	The Journal of Pediatrics	222	5.3
76 th	Antinheimo <i>et al.</i> ^[3]	Population-based analysis of sporadic and Type 2 neurofibromatosis-associated meningiomas and schwannomas	2000	Neurology	220	11.0
77 th	Bajenaru <i>et al.</i> ^[7]	Astrocyte-specific inactivation of the neurofibromatosis 1 gene (NF1) is insufficient for astrocytoma formation	2002	Molecular and Cellular Biology	219	12.2
78 th	Lammert <i>et al.</i> ^[66]	Prevalence of neurofibromatosis 1 in German children at elementary school enrollment	2005	Archives of Dermatology	217	14.5
79 th	Side <i>et al.</i> ^[109]	Homozygous inactivation of the NF1 gene in bone marrow cells from children with neurofibromatosis Type 1 and malignant myeloid disorders	1997	New England Journal of Medicine	217	9.4
80 th	Hope and Mulvihill ^[58]	Malignancy in neurofibromatosis	1981	Advances in neurology	214	5.5
81 st	Sharif <i>et al.</i> ^[107]	Second primary tumors in neurofibromatosis 1 patients treated for optic glioma: Substantial risks after radiotherapy	2006	Journal of Clinical Oncology	212	15.1
82 nd	Ruttledge <i>et al.</i> ^[101]	Type of mutation in the neurofibromatosis Type 2 gene (NF2) frequently determines severity of disease	1996	American Journal of Human Genetics	210	8.8
83 rd	Gutmann <i>et al.</i> ^[55]	Identification of the neurofibromatosis Type 1 gene product	1991	Proceedings of the National Academy of Sciences of the United States of America	209	7.2
85 th	North <i>et al.</i> ^[86]	Cognitive function and academic performance in neurofibromatosis 1: Consensus statement from the NF1 cognitive disorders task force	1997	Neurology	208	9.0
86 th	Fuller and Williams ^[47]	Gastrointestinal manifestations of Type 1 neurofibromatosis (von Recklinghausen's disease)	1991	Histopathology	208	7.2

(Contd...)

Table 1: (Continued).

Rank	Authors	Title	Year	Journal	CC	CY
84 th	Evans <i>et al.</i> ^[39]	Incidence of vestibular schwannoma and neurofibromatosis 2 in the North West of England over a 10-year period: Higher incidence than previously thought	2005	Otology and Neurotology	208	13.9
87 th	Salyer and Salyer ^[102]	The vascular lesions of neurofibromatosis	1974	Angiology	208	4.5
88 th	Brems <i>et al.</i> ^[118]	Mechanisms in the pathogenesis of malignant tumors in neurofibromatosis Type 1	2009	The Lancet Oncology	206	18.7
89 th	DiPaolo <i>et al.</i> ^[30]	Neurofibromatosis Type 1: Pathologic substrate of high-signal-intensity foci in the brain	1995	Radiology	206	8.2
90 th	Bianchi <i>et al.</i> ^[111]	Mutations in transcript isoforms of the neurofibromatosis 2 gene in multiple human tumor types	1994	Nature Genetics	206	7.9
91 st	Mautner <i>et al.</i> ^[82]	The neuroimaging and clinical spectrum of neurofibromatosis 2	1996	Neurosurgery	205	8.5
92 nd	Dasgupta <i>et al.</i> ^[26]	Proteomic analysis reveals hyperactivation of the mammalian target of rapamycin pathway in neurofibromatosis 1-associated human and mouse brain tumors	2005	Cancer Research	204	13.6
93 rd	Seizinger <i>et al.</i> ^[103]	Common pathogenetic mechanism for three tumor types in bilateral acoustic neurofibromatosis	1987	Science	204	6.2
94 th	Lantieri <i>et al.</i> ^[67]	Repair of the lower and middle parts of the face by composite tissue allotransplantation in a patient with massive plexiform neurofibroma: A 1-year follow-up study	2008	The Lancet	203	16.9
95 th	Stiller <i>et al.</i> ^[112]	Neurofibromatosis and childhood leukemia/lymphoma: a population-based UKCCSG study	1994	British Journal of Cancer	198	7.6
96 th	Oderich <i>et al.</i> ^[87]	Vascular abnormalities in patients with neurofibromatosis syndrome Type 1: clinical spectrum, management, and results	2007	Journal of Vascular Surgery	194	14.9
97 th	Rosser <i>et al.</i> ^[98]	Cerebrovascular abnormalities in a population of children with neurofibromatosis Type 1	2005	Neurology	193	12.9
98 th	Ricciardone <i>et al.</i> ^[97]	Human MLH1 deficiency predisposes to hematological malignancy and neurofibromatosis type 1	1999	Cancer Research	191	9.1
99 th	Colman <i>et al.</i> ^[23]	Benign neurofibromas in Type 1 neurofibromatosis (NF1) show somatic deletions of the NF1 gene	1995	Nature Genetics	189	7.6
100 th	Guo <i>et al.</i> ^[52]	A neurofibromatosis-1-regulated pathway is required for learning in <i>Drosophila</i>	2000	Nature Genetics	187	9.4

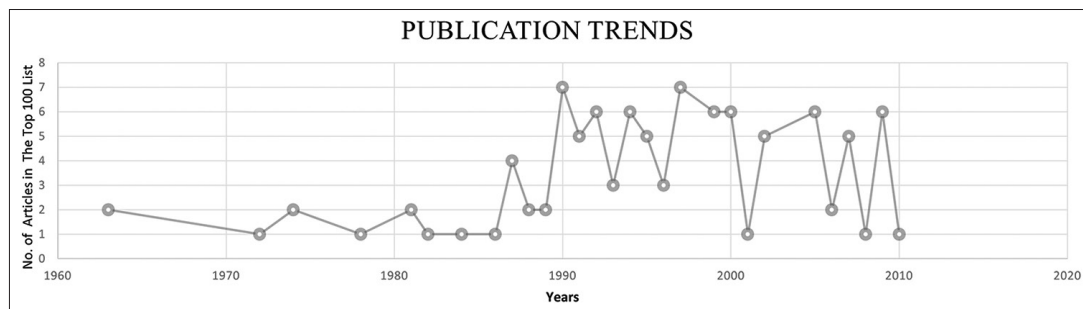
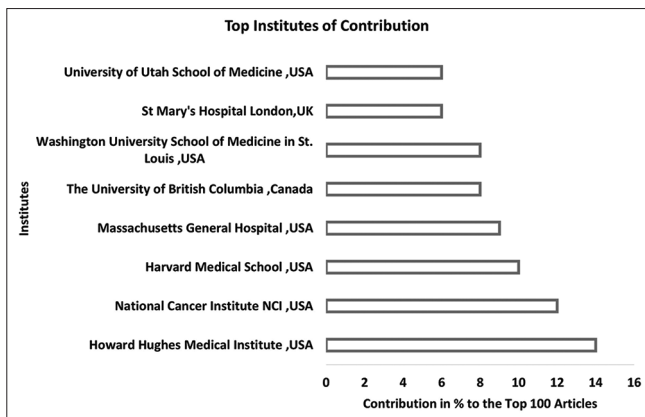


Figure 1: The publications trends in neurofibromatosis.

Table 2: The top 10 most-cited articles on neurofibromatosis.

Authors	Title	Category	Year	Journal	CC	CY
1 Wallace <i>et al.</i> ^[117]	Type 1 neurofibromatosis gene: Identification of a large transcript disrupted in three NF1 patients	Genetics	1990	Science	1114	37.1
2 Evans <i>et al.</i> ^[35]	Malignant peripheral nerve sheath tumors in neurofibromatosis	Clinical	2002	Journal of Medical Genetics	711	39.5
3 Trofatter <i>et al.</i> ^[113]	A novel moesin-, ezrin-, and radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor	Genetics	1993	Cell	1014	37.6
4 Huson <i>et al.</i> ^[60]	Von recklinghausen neurofibromatosis: a clinical and population study in South-east Wales	Clinical	1988	Brain	511	16.0
5 Xu <i>et al.</i> ^[123]	The neurofibromatosis Type 1 gene encodes a protein related to GAP	Genetics	1990	Cell	838	27.9
6 Costa <i>et al.</i> ^[24]	Mechanism for the learning deficits in a mouse model of neurofibromatosis Type 1	Experimental	2002	Nature	411	22.8
7 D'Agostino <i>et al.</i> ^[25]	Sarcomas of the peripheral nerves and somatic soft tissues associated with multiple neurofibromatosis (von Recklinghausen's disease)	Histopathological	1963	Cancer	276	4.8
8 Plotkin <i>et al.</i> ^[92]	Hearing improvement after bevacizumab in patients with neurofibromatosis Type 2	Medical	2009	New England Journal of Medicine	270	24.5
9 DiPaolo <i>et al.</i> ^[30]	Neurofibromatosis Type 1: pathologic substrate of high-signal-intensity foci in the brain	Radiological	1995	Radiology	206	8.2
10 Lantieri <i>et al.</i> ^[67]	Repair of the lower and middle parts of the face by composite tissue allotransplantation in a patient with massive plexiform neurofibroma: a 1-year follow-up study	Surgical	2008	The Lancet	203	16.9

*Top 10 articles in neurofibromatosis based on number of citations in each category genetics, clinical, experimental, radiological, medical and surgical and the significance of scientific contribution. Conferences summaries, criteria papers, and reviews were excluded from the study

**Figure 2:** The most contributing institutes.

same result was also obtained by inspecting the scatterplot which supported the test results [Figure 5].

DISCUSSION

In the 1960s to 1986, NF publications focused on the pathological and clinical aspects. The association of NF to soft-tissue sarcoma, vascular lesions, and other types of

malignancies was of great interest. Clinically, the literature offered updates on the current state of knowledge, established familiarity, and highlighted controversies and gaps for the future research.

In 1987–1997, the publications' focus remarkably shifted toward discussing molecular pathogenesis and its biological behaviors. In this decade, the literature was dominated by genetic discoveries including population-based and prospective longitudinal studies. After 1997, clinical and experimental publications took over the trend with particular attention to the associated risks, epidemiology, and multidisciplinary management approach.

The top three highly cited articles in the NF field

The most-cited article involved the discovery of the gene responsible for NF1 (17q11.2) with 1114 CC and 37.1 CY. The article was published in *Science* under the genetic studies category. In 1990, Wallace *et al.* isolated and cloned the responsible NF1.^[117]

The second most-cited article was published in the *Journal of the American Medical Association* and was a clinical study.

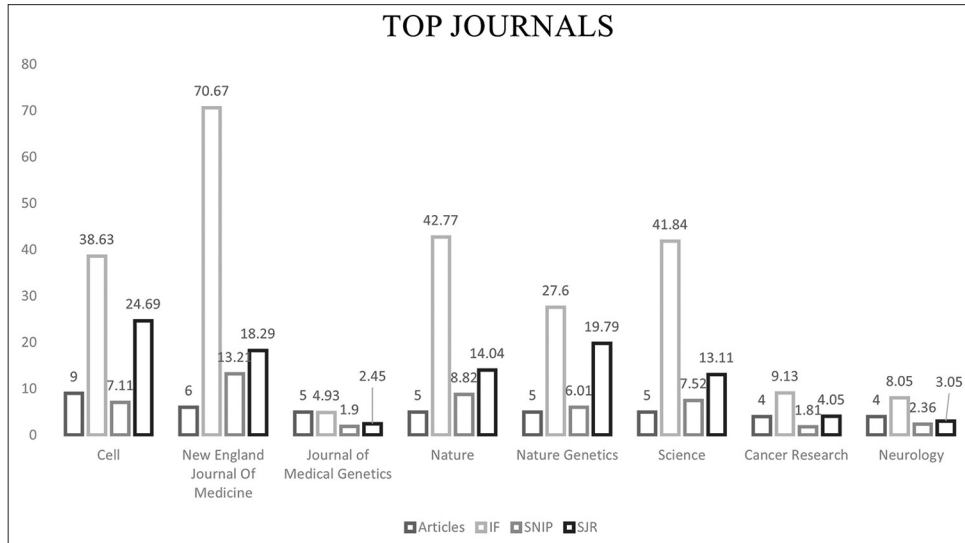


Figure 3: The most contributing journals.

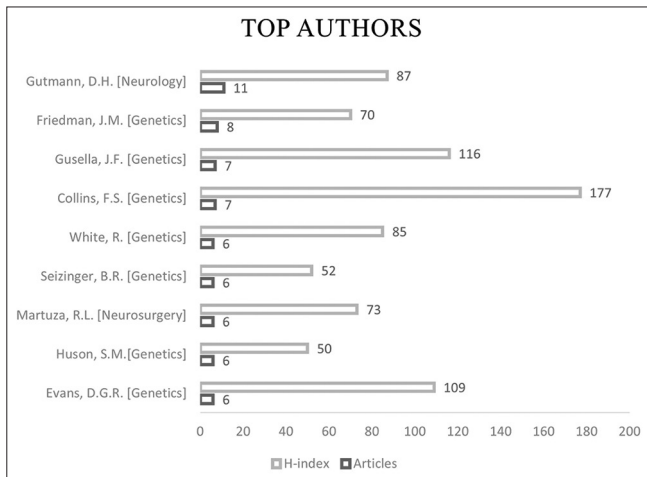


Figure 4: The most contributing authors.

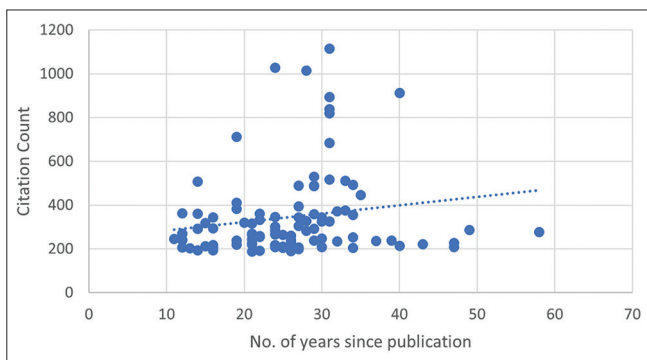


Figure 5: The scatterplot shows a positive relationship between the two variables, correlation coefficient of $r = 0.247$ ($P = 0.013$).

This had updated recommendations on NF diagnosis and management with 1028 CC and 44.7 CY. A thorough and

systematic review of the NF literature between 1966 and 1996 was performed by the NF Clinical Care Advisory Board members and published in 1997.^[53] These recommendations were different from the previous one founded in 1987 by NIH 4 in the following: (1) it was published 4–5 years after the discovery of NF1 and NF2 implicated genes. Therefore, the recommendations were set in the insight into the genetic advances of the disease. (2) They founded slightly different clinical diagnostic criteria of NF2 and introduced the categories of confirmed and presumptive NF2, through which they have widened the diagnosis window of the disease. (3) More comprehensive approach to management was proposed. However, the recommendations asserted on the clinical diagnostic criteria of NF1 were founded initially by NIH.^[85]

The third most-cited article was the identification, isolation, and cloning of the NF2 gene. The article was published in *Cell* under the genetic studies category with 1014 CC and 37.6 CY. In 1993, Trofatter *et al.* successfully identified the *NF2* gene in which they also found it to be altered in meningiomas.^[113]

NF publications by category

Clinical

In the late 20th century, publications were devoted to establishing a panoramic understanding of NF prevalence, natural history, specific clinical features, associated clinical disorders, and prognosis. In the early 21st century, the literature focused on the clinical category and slightly shifted to NF-associated risk of malignancy, management insights, and more in-depth knowledge about the disease epidemiology.^[6,15,17,28,35,40,41,44-47,52,58,60,61,62,64,66,69,73-76,84,86-88,94,95,97,98,102,103,107,111,112,114-116,118,121,124]

The second highly cited article in this category (ranked fourth overall with 913 CC and 23.4 CY) was a review article of NF authored by Riccardi and published in the *New England Journal of Medicine* (1981). In his review, Riccardi offered comprehensive NF information sources including its clinical features, hypothesized pathogenesis, laboratory features, gaps in knowledge, and a recommended approach of management.^[96] Although the review was not conducted systematically and bias cannot be ruled out, the careful selection of information sources from extensive surveys and prospective studies is useful. The paper was also written before the NIH statement on NF diagnostic criteria in 1987. Hence, the term “classical NF” (i.e., NF1) was used to differentiate it from “bilateral acoustic NF” (i.e., NF2).^[85,96]

Complementing Riccardi’s review and after NIH diagnostic criteria have been established (1987), Martuza and Eldridge published a review article of NF2 in the *New England Journal of Medicine* in 1988, (376 CC, 11.8 CY, ranked 22nd overall). The article added a valuable contribution to NF literature by distinguishing NF2 in light of the most updated diagnostic criteria.^[81,85]

The third highly cited article in the clinical studies category was ranked 8th overall with 711 CC and 39.5 CY. A population-based and longitudinal study published in the *Journal of Medical Genetics* (2002) and was authored by Evan *et al.* In light of conflicting reports discussing rates of malignant peripheral nerve sheath tumors (MPNST) among NF1, this study investigated the survival rates and lifetime risk of MPNST in NF1 patients for 13 years (1984–1994). The data of MPNST and NF1 patients were obtained from regional cancer and genetic registries. The annual risk of MPNST in NF1 patients was 1.6/1000 and the estimated risk of a lifetime was 8–13%.^[35] Concurrently, a comprehensive international statement based on expertise and available evidence from the literature was published in the *Cancer Research* journal in 2002 (383 CC, 21.3 CY, ranked 21st overall). The statement highlighted the features that should raise the suspicion of underlying malignancy in NF1 patients. They also recommended increased surveillance of MPNST in NF1 patients with plexiform neurofibroma and discussed the usefulness of variable imaging and molecular studies.^[35,41]

Given the genetic basis and hereditary nature of NF of all types, population-based studies played a significant role in understanding the disease epidemiology and identifying patients at risk. The fourth highly cited article in the clinical studies’ category (ranked 12th overall) was a population-based study of NF1 authored by Huston *et al.* and published in *Brain* in 1988 (511 CC, 16 CY). The NF1 prevalence was 0.02% (1 in 5000). In addition to café-au-lait spots, axillary (64%) and groin (44%) freckling were standard associated features. Plexiform neurofibroma was identified in 32% of the cohort. The survey was conducted before the NIH diagnostic

criteria of NF1; therefore, the criteria used did not include Lisch nodules, bony dysplasia, nor optic pathway glioma. However, Huston *et al.* selected the highly sensitive clinical features of NF1 and mentioned the recently established diagnostic criteria at the time, the paper was published.^[60,85]

A similar population-based study on NF2 was performed (ranked 17th overall). The paper was published in the *Quarterly Journal of Medicine*, in 1992, and authored by Evan *et al.* (486 CC, 17.4CY). A comprehensive and regional method of data collection was conducted between 1989 and 1992. The reported age of onset was 21.57 years. Deafness was present in almost half of the cases; 80% was unilateral. Café-au-lait spots and nodular cutaneous manifestations were common findings at 43% and 68%.^[37] A significant finding was the poor survival rate. Forty patients (39%) died because of NF2-related complications with a mean age of 36.^[37]

The eighth highly cited article in the clinical category (Ranked 20th overall) with 394 CC and 15.2 CY was authored by Listernick *et al.* and published in the *Journal of Pediatrics* (1994). A prospective and longitudinal study was conducted between 1985 and 1993. The primary goal was to determine the natural history of the optic pathway tumor (OPT) in children with NF. Repeated imaging and clinical exams in this subgroup of patients — with a median follow-up of 2.4 years and 3.4 years — confirmed a benign natural history with no evidence of either tumor growth or visual deterioration. Although a minority of cases progressively worsened, the study concluded that the risk of developing rapidly progressive OPT is at its greatest during the first 6 years of life, and regular ophthalmologic screening is recommended among this age group.^[73]

Genetics

In the late 1980s, genes implicated in NF1 and NF2 were located on 17q11.2 and 22q1.2. Shortly after, the defective genes were identified, isolated, and cloned in multiple synergetic studies in 1990. These discoveries provided a groundwork for further studies to be performed on the encoded protein. Subsequently, and for over a decade, publications in the genetic category were directed toward a deeper understanding of the intermolecular interactions, molecular pathogenesis, phenotypic, genotypic correlation, and variations.
[3,4,5,7,11,12,14,16,18,19,21,23,27,29,32,38,43,55,59,65,68,72,78,83,104-106,108,109,114,116,120,122,123]

Xu *et al.* authored the fourth highly cited article in the genetic studies category (Ranked sixth overall; *Cell* in 1990 with 838 CC and 27.9 CY). It described the discovery of the cloned NF1 gene peptide. The peptide had a 360 residue long sequence of amino acids similar to guanosine triphosphate hydrolase stimulatory proteins (GAPs).^[123]

The sixth highly cited article in the genetic studies (ranked ninth overall) discovered a critical intermolecular

interaction of the *NF1* gene-encoded peptide. The study was authored by Martin *et al.* and published in *Cell* in 1990 with 683 CC and 22.8 CY. The GAP domain of the NF1 peptide enhanced the intrinsic GTPase activity of the intercellular P21ras protein. This finding hypothesized the encoded protein's role in down-regulating and controlling cellular proliferation — a regular function that might have been impaired because of a mutated NF1 gene.^[80] This theory was supported further in the seventh highly cited article in the genetic studies category (Ranked 10th overall), which was authored by Basu *et al.* and published in *Nature* journal in 1992, (529 CC, 18.9 CY).^[9]

A population-based genetic study was performed in 1992 to complement the previous clinical study of NF2.^[37] This follow-up study was authored by Evans *et al.* and published in the *Journal of Medical Genetics* (ranked 27th overall, 358 CC, 12.8 CY). The results confirmed the dominance pattern of inheritance. Furthermore, the affected members of one family were found to have similar phenotypic expressions. Furthermore, maternally inherited NF2 was associated with an earlier onset and the development of more severe forms of the disease.^[38]

The mutations implicated in severe NF2 were investigated in another study. Frame shift-deletion/insertion mutations (i.e., protein-truncating mutations) were found to be associated with severe forms. Nevertheless, missense mutations were more likely to cause milder NF2 manifestations. These findings were reported by Rutledge *et al.* and published in the *American Journal of Human Genetics* in 1996 (ranked 82nd overall, 210 CC, 8.8 CY).^[101]

Experimental

Eight articles were identified in this category. All articles were published between the late 1990s and mid-2000s. Two major clinical problems were investigated in mice models. The first was learning difficulties and cognitive deficits in NF1. The second was tumor development in NF1 and NF2.^[13,22,26,71,72,93,110,115]

The reported rates of cognitive deficits and learning disabilities in children with NF1 are higher than their regular counterparts. This domain was investigated by the highly cited article in the experimental studies category (Ranked 19th overall) on mice models. The article was authored by Costa *et al.* and published in *Nature* (2002; 411 CC and 22.8 CY). The experiment was performed on mice with an induced *NF1* heterozygous null mutation. The mice carrying this mutated gene expressed learning deficits that were responsive to genetic and pharmacologic suppression of Ras activity and, subsequently, the implicated increased GABA mediated inhibition. This experiment postulated that learning disabilities in NF1 affected individuals and might be reversed through targeting this molecular pathway.^[24]

Tumor development in NF2 was investigated in the fourth highly cited article in this category (ranked 51st overall). The study was authored by Giovannini *et al.* and published in *Genes and Development* (2000; 270 CC and 13.5 CY). The experiment used on mice models to show that schwannoma development requires two mutated alleles to express this phenotype. The mutated *NF2* gene is also involved in the development of multiple neurocristopathies.^[49]

Histopathological

D'Agostino *et al.* authored the highest cited article in histopathological studies (ranked 49th overall). Furthermore, it published in *Cancer* (1963; 276 CC and 4.8 CY). A retrospective and descriptive report of clinical course and histopathological findings of 21 patients with NF1. The report was one of earliest articles that detailed the cases' general profile, clinical manifestations, pathological findings, treatment, and clinical course. The high number of citations could be contributed to two reasons. First is the noticeable trending period of research investigating the association of NF to soft-tissue sarcoma and other malignancies between 1960s and 1986. Second is the possible correlation between the publication date and the number of citations.^[25]

Radiological

In the radiological studies category, two studies were in the top 100 list and were ranked 89th and 91st overall. The first paper (ranked 89th overall) was authored by Dipaolo *et al.* and published in *Journal of Radiology* (1995) with 206 CC and 8.2 CY. Brain autopsy findings in three NF1 patients were correlated with the findings on T2-weighted images.^[30] The second paper in the category (ranked 91st overall) discussed the clinical and radiological aspects of NF2 with particular attention given to imaging lesions. The article was authored by Mautner *et al.* and published in *Neurosurgery* (1996; 205 CC and 8.5 CY). Thorough clinical and radiological (MRI with contrast) evaluation was performed on 48 NF2 individuals diagnosed based on the NIH criteria. Significant observations were the high frequency of vestibular schwannomas (>90%) and, most importantly, spinal lesions (90%) detected on imaging. Given the relatively subtle and heterogeneous presentation of NF2, the study recommended “properly NF2” patients to be followed.^[82]

Medical management

In the medical management category, only one study was in the top 100 highest cited articles in NF (ranked 50th overall). The article was authored by Plotkin *et al.* and published in *New England Journal of Medicine* in 2009 with 270 CC and

24.5 CY. In this study, immunohistochemical analysis of the proportion of receptors expressed in NF2 vestibular schwannoma samples and sporadic schwannomas as controls were performed. Vascular endothelial growth factor (VEGF) receptors were found to be expressed in all NF2 vestibular schwannomas (21/21) and VEGFR-2 in 32% (7/21). Patients who were poor candidates for the standard treatment were offered bevacizumab — an anti-VEGF antibody. Among the patients' treated, an imaging response was seen in 60% of subjects (6/10). Clinically, a hearing response was evident in 57% (4/7).^[92]

Surgical management

The surgical management of a 29-year-male with diffuse facial plexiform neurofibroma who underwent composite tissue allograft facial transplantation was detailed by Lantieri *et al.* and published in *The Lancet* in 2008 (94th overall) with 203 CC and 16.9 CY. The article addressed surgical management and the postoperative course including immunosuppressive therapy and graft rejection monitoring. The benefits outweigh the risks in this case, which made the allotransplantation a possible treatment option in similar selected cases.^[67]

Limitations and strengths

The top 100 articles were extracted from a single database, which could have added bias to the data presented. In addition, the correlation test performed showed that the older a published article is the more its cited. A positive correlation of 0.2 is, however, weak which indicates the presence of other factors that could have influenced the number of citations.

Implications

We provided a historical reference with a recognized pattern for the future research in the field of NF. If complemented with reviews from expertise, bibliometric studies can be utilized to predict future research directions and identify gaps in evidence.

CONCLUSION

We have presented the top 100 most influential publications on NF. Most articles addressed clinical and genetic aspects. In addition to extensive surveys and prospective and longitudinal studies, multidisciplinary statements produced from pooled evidence and expertise provided the highest level of evidence in these articles.

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Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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