Evaluating the Evidence: Scientometric Analysis of Highly Cited Neurofibromatosis 1 Publications

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Abstract

The study of Neurofibromatosis 1 (NF1) is progressing rapidly. This study aimed to identify historical trends in publications focusing on NF1, to find the top 100 most cited publications on this topic, and to evaluate their level of evidence. This study identifies historical trends in publication regarding NF1 with the aim of providing readers useful information about the areas of research being performed, an educational guide to facilitate novice researchers in conducting effective evidence-based medical research, and unique insight into developments and trends of NF1 research. This study also evaluates the evidence of highly cited papers on NF1.

A search of all databases and journals accessible within Elsevier’s Scopus was performed on June 27th, 2020, using combinations of the Boolean queries “Neurofibromatosis 1,” “Von Recklinghausen,” and “NF1,” which yielded 13,599 documents. The top 100 most-cited papers were identified, analyzed, and evaluated for level of evidence. Evidence was assessed using the GRADE guidelines.

The top 100 most-cited articles span years 1963-2010 and are published in 50 different journals. The average number of citations per publication was 366.5 (range 189-1527). The most cited article is “Neurofibromatosis: Conference Statement” (Stumpf et al., 1988). In this study, the top 100 most-cited works in NF1 are identified, characterized, and analyzed. This study will serve as a historical point of reference for future research, a jumping point for those unfamiliar with the topic, and an educational foundation for future NF1 specialists and researchers.

Introduction And Background

Many medical specialties use bibliometrics to compile, publish, and review the most-cited works within their respective fields [1]. This is especially useful as the exponential rise in publications and resources makes it difficult for learners to process information efficiently. It likewise identifies and assesses the impact of publications, journals, and authors. Furthermore, bibliometrics takes a snapshot in time of objective metrics, which can highlight scientific progression, historical trends, and prolific individuals.

This study aimed to identify historical trends in publications focusing on Neurofibromatosis 1 (NF1), to find the top 100 most cited publications on this topic, and to evaluate their level of evidence. Our literature search revealed this had not previously been done. Reflecting not only on the trends of this research, but also their level of evidence, provides readers useful information about the areas of research being performed, provides an educational guide to facilitate novice researchers in performing effective evidence-based medical research, and provides unique insight into developments and trends of NF1 research.

Review

Methods

A search of all databases and journals accessible within Elsevier’s Scopus was performed on June 27th, 2020. Document search was performed using the Boolean query “[TITLE-ABS-KEY ("Neurofibromatosis type 1") OR TITLE-ABS-KEY ("Neurofibromatosis 1") OR TITLE-ABS-KEY ("Neurofibromatosis’s disease") OR TITLE-ABS-KEY ("Von Recklinghausen’s disease")],” without limitations on year or article type; and, which yielded 13,599 documents. Documents were ordered by the highest citations and screened for those papers whose primary focus was on NF1 or the NF1 gene, as well as the disease’s complications, incidence, management, pathogenesis, treatment, and diagnostic evaluation. The top 100 most-cited papers from Elsevier’s database were identified, and data were extracted. Data about these articles were collected and sorted. All references contained within the top 100 articles were obtained, sorted, and counted. Statistical analysis was performed using a combination of R-Studio and Bibliometrix [2]. The spectrographic analysis was performed using CRExplorer [3]. Two separate reviewers evaluated papers for the level of evidence using
the GRADE system described by Guyatt et al. [4-6]. Any discrepancies in scoring were resolved by a third reviewer and discussion to reach a consensus. Papers that did not provide new evidence such as review papers and conference statements were excluded from this evaluation. Graphs and tables were drawn to illustrate the relationships between factors.

Results

The top 100 most-cited articles for NF1 span between 1963-2010 and are published in 50 journals. The average years from publication was 29.8, and the average number of citations per publication was 366.5, with an average of 12.3 citations per year. The total number of references contained within the top 100 articles was 3,852. Of the top 100 most-cited articles, the total number of citations ranges from 189-1527 (Table 1). The most cited article is “Neurofibromatosis: Conference Statement” by Stumpf et al. in 1988 from the Archives of Neurology with 1527 citations (Table 1)[7].

| #  | Title                                                                 | Authors                                                                 | Year | Source title              | Cited by | Avg Citations per Year |
|----|-----------------------------------------------------------------------|------------------------------------------------------------------------|------|--------------------------|----------|------------------------|
| 1  | Neurofibromatosis: Conference Statement                              | Stumpf DA, Alksne JF, Annegers JF, Brown SS, Conneally PM, Leppert MF, Miller JP, Moss ML, Pileggi AJ, Rapin I, Strohman RC, Swanson LW, Zimmerman A. | 1988 | Archives of Neurology     | 1527     | 47.7188                |
| 2  | Type 1 neurofibromatosis gene: Identification of a large transcript disrupted in three NF1 patients | Wallace M.R., Marchuk D.A., Andersen L.B., Letcher R., Odeh H.M., Saulino A.M., Foutain J.W., Brereton A., Nicholson J., Mitchell A.L., Brownstein B.H., Collins F.S. | 1990 | Science                  | 1102     | 36.7333                |
| 3  | Malignant peripheral nerve sheath tumors A clinicopathologic study of 120 cases | Ducatman B.S., Scheithauer B.W., Piepgras D.G., Reiman H.M., Istrup D.M. | 1986 | Cancer                   | 1034     | 30.4118                |
| 4  | The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2 | Gutmann D.H., Aylsworth A., Carey J.C., Korf B., Marks J., Pyeritz R.E., Rubenstein A., Viskochil D. | 1997 | Journal of the American Medical Association | 1017     | 44.2174                |
| 5  | Von Recklinghausen Neurofibromatosis                                  | Riccardi V.M.                                                          | 1981 | New England Journal of Medicine | 912      | 23.3846                |
| 6  | A major segment of the neurofibromatosis type 1 gene: cDNA sequence, genomic structure, and point mutations | Cawthon R.M., Weiss R., Xu G., Viskochil D., Culver M., Stevens J., Robertson M., Dunn D., Gesteland R., O'Connell P., White R. | 1990 | Cell                     | 887      | 29.5667                |
| 7  | The neurofibromatosis type 1 gene encodes a protein related to GAP    | Xu G., O'Connell P., Viskochil D., Cawthon R., Robertson M., Culver M., Dunn D., Stevens J., Gesteland R., White R., Weiss R. | 1990 | Cell                     | 833      | 27.7667                |
| 8  | Deletions and a translocation interrupt a cloned gene at the neurofibromatosis type 1 locus | Viskochil D., Buchberg A.M., Xu G., Cawthon R.M., Stevens J., Wolf R.K., Culver M., Carey J.C., Copeland N.G., Jenkins N.A., White R., O'Connell P. | 1990 | Cell                     | 813      | 27.1                   |
| 9  | Malignant peripheral nerve sheath tumours in neurofibromatosis        | Evans D.G.R., Baser M.E., McGaughran J., Sharif S., Howard E., Moran A. | 2002 | Journal of Medical Genetics | 699      | 38.8333                |
| 10 | The GAP-related domain of the neurofibromatosis type 1 gene product interacts with ras p21 | Martin G.A., Viskoohil D., Bollag G., McCabe P.C., Crosier W.J., Haubruck H., Conroy L., Clark R., O'Connell P., Cawthon R.M., Innis M.A., McCormick F. | 1990 | Cell                     | 677      | 22.5667                |
| 11 | Tumour predisposition in mice heterozygous for a                      | Jacks T., Shih T.S., Schmitt E.M., Bronson R.T.                        | 1994 | Nature                   | 600      | 23.0769                |
| Reference | Title | Authors | Journal | Year | Page |
|-----------|-------|---------|---------|------|------|
| 12 | The NF1 locus encodes a protein functionally related to mammalian GAP and yeast IRA proteins | Ballester R., Marchuk D., Boguski M., Saulino A., Letcher R., Wigler M., Collins F. | Cell | 1990 | 598 19.3333 |
| 13 | Aberrant regulation of ras proteins in malignant tumour cells from type 1 neurofibromatosis patients | Basu T.N., Gutmann D.H., Fletcher J.A., Glover T.W., Collins F.S., Downward J. | Nature | 1992 | 525 18.75 |
| 14 | The catalytic domain of the neurofibromatosis type 1 gene product stimulates ras GTPase and complements ira mutants of S. cerevisiae | Xu G., Lin B., Tanaka K., Dunn D., Wood D., Gesteland R., White R., Weiss R., Tamaori F. | Cell | 1990 | 513 17.1 |
| 15 | Von recklinghausen neurofibromatosis: A clinical and population study in south-east Wales | Huson S.M., Harper P.S., Compston D.A.S. | Brain | 1988 | 509 15.9063 |
| 16 | Guidelines for the diagnosis and management of individuals with neurofibromatosis | Ferner R.E., Huson S.M., Thomas N., Moss C., Willshaw H., Evans D.G., Upadhya M., Towers R., Gleeson M., Steiger C., Kirby A. | Journal of Medical Genetics | 2007 | 500 38.4615 |
| 17 | Gene for von Recklinghausen neurofibromatosis is in the pericentromeric region of chromosome 17 | Barker D., Wright E., Nguyen K., Cannon L., Fain P., Goldgar D., Bishop D.T., Carey J., Baby B., Krilin J., Willard H., Waye J.S., Greig G., Leinwand L., Nakamura Y., O’Connell P., Leppert M., Lalouel J.-M., White R., Skolnick M. | Science | 1987 | 493 14.9394 |
| 18 | Abnormal regulation of mammalian p21ras contributes to malignant tumor growth in von Recklinghausen (type 1) neurofibromatosis | DeClue J.E., Papageorge A.G., Fletcher J.A., Diehl S.R., Ratner N., Vass W.C., Lowy D.R. | Cell | 1992 | 485 17.3214 |
| 19 | Targeted disruption of the neurofibromatosis type-1 gene leads to developmental abnormalities in heart and various neural crest-derived tissues | Brannan C.I., Perkins A.S., Vogel K.S., Ratner N., Nordlund M.L., Reid S.W., Buchberg A.M., Jenkins N.A., Parada L.F., Copeland N.G. | Genes and Development | 1994 | 484 18.6154 |
| 20 | Long-Term Follow-up of von Recklinghausen Neurofibromatosis | Sorensen S.A., Mulvihill J.J., Nielsen A. | New England Journal of Medicine | 1986 | 443 13.0294 |
| 21 | Loss of NF1 results in activation of the Ras signaling pathway and leads to aberrant growth in haematopoietic cells | Bollag G., Clapp D.W., Shih S., Adler F., Zhang Y.Y., Thompson P., Lange B.J., Freedman M.H., McCormick F., Jacks T., Shannon K. | Nature Genetics | 1996 | 429 17.875 |
| 22 | The NF1 tumor suppressor critically regulates TSC2 and mTOR | Johannaensen C.M., Reczek E.E., James M.F., Brems H., Legius E., Cichowski K. | Proceedings of the National Academy of Sciences of the United States of America | 2005 | 423 28.2 |
| 23 | Neurofibromas in NF1: Schwann cell origin and role of tumor environment | Zhu Y., Ghosh P., Charnay P., Burns D.K., Parada L.F. | Science | 2002 | 422 23.4444 |
|   | Title                                                                 | Authors                                                                 | Year | Journal                                      | Volume | Page  |
|---|-----------------------------------------------------------------------|-------------------------------------------------------------------------|------|----------------------------------------------|--------|-------|
|24 | Mechanism for the learning deficits in a mouse model of neurofibromatosis type 1 | Costa R.M., Federov N.B., Kogan J.H., Murphy G.G., Stern J., Ohno M., Kucherlapati R., Jacks T., Silva A.J. | 2002 | Nature                                       | 408    | 22.6667 |
|25 | Natural history of optic pathway tumors in children with neurofibromatosis type 1: A longitudinal study | Listerick R., Charrow J., Greenwald M., Mets M.                           | 1994 | Journal of Pediatrics                        | 391    | 15.0385 |
|26 | International consensus statement on malignant peripheral nerve sheath tumors in neurofibromatosis | Ferer R.E., Gutmann D.H.                                               | 2002 | Cancer Research                             | 379    | 21.0556 |
|27 | Ablation of NF1 function in neurons induces abnormal development of cerebral cortex and reactive gliosis in the brain | Zhu Y., Romero M.I., Ghosh P., Ye Z., Charnay P., Rushing E.J., Marth J.D., Parada L.F. | 2001 | Genes and Development                       | 376    | 19.7895 |
|28 | A genetic study of von Recklinghausen neurofibromatosis in southeast Wales I Prevalence, fitness, mutation rate, and effect of parental transmission on severity | Huson S.M., Compston D.A.S., Clark P., Harper P.S.                      | 1989 | Journal of Medical Genetics                 | 368    | 11.871  |
|29 | Epidemiology of neurofibromatosis type 1                              | Friedman J.M.                                                           | 1999 | American Journal of Medical Genetics - Seminars in Medical Genetics | 360    | 17.1429 |
|30 | Optic pathway gliomas in neurofibromatosis-1: Controversies and recommendations | Listerick R., Ferer R.E., Liu G.T., Gutmann D.H.                        | 2007 | Annals of Neurology                        | 354    | 27.2308 |
|31 | Neurofibromatosis type 1 revisited                                      | Williams V.C., Lucas J., Babcock M.A., Gutmann D.H., Bruce B., Maria B.L. | 2009 | Pediatrics                                 | 353    | 32.0909 |
|32 | Early inactivation of p53 tumor suppressor gene cooperating with NF1 loss induces malignant astrocytoma | Zhu Y., Guignard F., Zhao D., Liu L., Burns D.K., Mason R.P., Messing A., Parada L.F. | 2005 | Cancer Cell                               | 351    | 23.4 |
|33 | Exhaustive mutation analysis of the NF1 gene allows identification of 95% of mutations and reveals a high frequency of unusual splicing defects | Messiaen L.M., Callens T., Mortier G., Beysen D., Vandenburgroucke I., Van Roy N., Speleman F., De Paepe A. | 2000 | Human Mutation                             | 347    | 17.35  |
|34 | Optic pathway gliomas in children with neurofibromatosis 1: Consensus statement from the NF1 optic pathway glioma task force | Listerick R., Louis D.N., Packer R.J., Gutmann D.H.                    | 1997 | Annals of Neurology                        | 343    | 14.913 |
|35 | A de novo Alu insertion results in neurofibromatosis type 1             | Wallace M.R., Andersen L.B., Saulino A.M., Gregory P.E., Glover T.W., Collins F.S. | 1991 | Nature                                     | 342    | 11.7931 |
|36 | The nature and frequency of cognitive deficits in children             | Hyman S.L., Shores A., North K.N.                                       | 2005 | Neurology                                 | 339    | 22.6  |
| Page | Citation |
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| 37   | Loss of the normal NF1 allele from the bone marrow of children with type 1 neurofibromatosis and malignant myeloid disorders. Shannon K.M., O'Connell P., Martin G.A., Paderanga D., Olson K., Dinndorf P., McCormick F. 1994 New England Journal of Medicine 339 13.0385 |
| 38   | Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis): An update. Mulvihill J.J., Parry D.M., Sherman J.L., Pikus A., Kaiser-Kupfer M.I., Eldridge R. 1990 Annals of Internal Medicine 334 11.1333 |
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| 41   | Somatic deletion of the neurofibromatosis type 1 gene in a neurofibrosarcoma supports a tumour suppressor gene hypothesis. Legius E., Marchuk D.A., Collins F.S., Glover T.W. 1993 Nature Genetics 324 12 |
| 42   | cDNA cloning of the type 1 neurofibromatosis gene: Complete sequence of the NF1 gene product. Marchuk D.A., Saulino A.M., Tavakkol R., Swaroop M., Wallace M.R., Andersen L.B., Mitchell A.L., Gutmann D.H., Boguski M., Collins F.S. 1991 Genomics 323 11.1379 |
| 43   | Gastrointestinal stromal tumors in patients with neurofibromatosis 1: A clinicopathologic and molecular genetic study of 45 cases. Miettinen M., Fetsch J.F., Sobin L.H., Lasota J. 2006 American Journal of Surgical Pathology 315 22.5 |
| 44   | Mortality in neurofibromatosis 1: An analysis using U.S. death certificates. Rasmussen S.A., Yang Q., Friedman J.M. 2001 American Journal of Human Genetics 314 16.5263 |
| 45   | Use of the National Institutes of Health criteria for diagnosis of neurofibromatosis 1 in children. DeBella K., Szudek J., Friedman J.M. 2000 Pediatrics 310 15.5 |
| 46   | Type 1 neurofibromatosis: A descriptive analysis of the disorder in 1,728 patients. Friedman J.M., Birch P.H. 1997 American Journal of Medical Genetics 299 13 |
| 47   | The HMG-CoA reductase inhibitor lovastatin reverses the learning and attention deficits in a mouse model of Neurofibromatosis Type 1. Li W., Cui Y., Kushner S.A., Brown R.A.M., Jentsch J.D., Frankland P.W., Cannon T.D., Silva A.J. 2005 Current Biology 291 19.4 |
| 48   | Neurofibromatosis 1 and neurofibromatosis 2: a twenty first century perspective. Ferner R.E. 2007 Lancet Neurology 288 22.1538 |
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| 49   | Somatic mutations in the neurofibromatosis 1 gene in human tumors | Li Y., Bollag G., Clark R., Stevens J., Conroy L., Fults D., Ward K., Friedman E., Samowitz W., Robertson M., Bradley P., McCormick F., White R., Cawthon R. | 1992 | Cell                         | 288    | 10.2857   |
| 50   | Malignant peripheral nerve sheath tumor: Analysis of treatment outcome | Wong W.W., Hirose T., Scheithauer B.W., Schild S.E., Gunderson L.L.     | 1998 | International Journal of Radiation Oncology Biology Physics | 286    | 13        |
| 51   | Von Recklinghausen's disease: a clinicopathological study.          | Brasfield R.D., Das Gupta T.K.                                         | 1972 | Annals of surgery            | 286    | 5.95833   |
| 52   | An analysis of variation in expression of neurofibromatosis (NF) type 1 (NF1): Evidence for modifying genes | Easton D.F., Ponder M.A., Huson S.M., Ponder B.A.J.                    | 1993 | American Journal of Human Genetics | 283    | 10.4815   |
| 53   | Peripheral nerve tumors with rhabdomyosarcomatous differentiation (malignant "triton" tumors) | Woodruff J.M., Chernik N.L., Smith M.C., Millett W.B., Foote F.W., JR. | 1973 | Cancer                       | 276    | 5.87234   |
| 54   | Sarcomas of the peripheral nerves and somatic soft tissues associated with multiple neurofibromatosis (von Recklinghausen's disease) | D'Agostino A.N., Soule E.H., Miller R.H.                               | 1963 | Cancer                       | 276    | 4.84211   |
| 55   | Neurofibromin Regulation of ERK Signaling Modulates GABA Release and Learning | Cui Y., Costa R.M., Murphy G.G., Elgersma Y., Zhu Y., Gutmann D.H., Parada L.F., Mody I., Silva A.J. | 2008 | Cell                         | 269    | 22.4167   |
| 56   | NF1;Trp53 mutant mice develop glioblastoma with evidence of strain-specific effects | Reilly K.M., Loisel D.A., Bronson R.T., McLaughlin M.E., Jacks T.       | 2000 | Nature Genetics               | 265    | 13.25     |
| 57   | A mouse model for the learning and memory deficits associated with neurofibromatosis type 1 | Silva A.J., Frankland P.W., Marowitz Z., Friedman E., Lazlo G., Cloff D., Jacks T., Bourchuladze R. | 1997 | Nature Genetics               | 265    | 11.5217   |
| 58   | NF1 gene and neurofibromatosis 1                                     | Rasmussen S.A., Friedman J.M.                                          | 2000 | American Journal of Epidemiology | 261    | 13.05     |
| 59   | Molecular genetics of neurofibromatosis type 1 (NF1)                | Shen M.H., Harper P.S., Upadhyaya M.                                   | 1996 | Journal of Medical Genetics    | 261    | 10.875    |
| 60   | Malignant peripheral nerve sheath tumors of the buttock and lower extremity. A study of 43 cases | Hruban R.H., Shiu M.H., Senie R.T., Woodruff J.M.                      | 1990 | Cancer                       | 261    | 8.7       |
| 61   | Mouse tumor model for neurofibromatosis type 1                       | Vogel K.S., Klesse L.J., Velasco-Miguel S., Meyers K., Rushing E.J., Parada L.F. | 1999 | Science                      | 257    | 12.2381   |
| 62   | Plexiform neurofibromas                                             | Korf B.R.                                                              | 1999 | American Journal of Medical Genetics - Seminars in Medical Genetics | 257    | 12.2381   |
|   | Malignant peripheral nerve sheath tumors. A clinicopathologic study of 28 cases | Wanebo J.E., Malik J.M., Vandenberg S.R., Wanebo H.J., Driesen N., Persing J.A. | 1993 | Cancer | 254 | 9.40741 |
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| 69 | Mutations affecting mRNA splicing are the most common molecular defects in patients with neurofibromatosis type 1 | Ars E., Serra E., Garcia J., Kruyer H., Gaona A., Lázaro C., Estivill X. | 2000 | Human Molecular Genetics | 243 | 12.15 |
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| 91   | Substantial risks after radiotherapy                                | Gattamaneni H.R., Baser M.E., Evans D.G.R.                                                                       | Oncology                     |        |      | 1997 | 206          | 8.95652  |
| 92   | Cognitive function and academic performance in neurofibromatosis 1: Consensus statement from the NF1 cognitive disorders task force | North K.N., Riccardi V., Samango-Sprouse C., Ferner R., Moore B., Legius E., Ratner N., Denckla M.B.              | Neurology                    | 206    |      | 1995 | 206          | 8.24     |
| 93   | Neurofibromatosis type 1: Pathologic substrate of high-signal-intensity foci in the brain | DiPaolo D.P., Zimmerman R.A., Rorke L.B., Zackai E.H., Bilaniuk L.T., Yachnis A.T.                            | Radiology                    |        |      | 2009 | 204          | 18.5455  |
| 94   | Mechanisms in the pathogenesis of malignant tumours in neurofibromatosis type 1 | Brems H., Beert E., de Ravel T., Legius E.                                                                      | The Lancet Oncology           | 204    |      | 2005 | 204          | 13.6     |
| 95   | Proteomic analysis reveals hyperactivation of the mammalian target of rapamycin pathway in neurofibromatosis 1-associated human and mouse brain tumors | Dasgupta B., Yi Y., Chen D.Y., Weber J.D., Gutmann D.H.                                                       | Cancer Research              | 205    |      | 2007 | 203          | 15.6154  |
| 96   | An absence of cutaneous neurofibromas associated with a 3-bp inframe deletion in exon 17 of the NF1 gene (c.2970-2972 delAAT): Evidence of a clinically significant NF1 genotype-phenotype correlation | Upadhhyaya M., Huson S.M., Davies M., Thomas N., Chuzhanova N., Giovannini S., Evans D.G., Howard E., Kerr B., Griffiths S., Consoli C., Side L., Adams D., Pierport M., Hachen R., Bamiccoa A., Li H., Wallace P., Van Bienvilet J.P., Stevenson D., Viskochil D., Baralle D., Haan E., Riccardi V., Tumpeny P., Lazaro C., Messiaen L. | American Journal of Human Genetics | 207    |      | 2008 | 202          | 16.8333  |
| 97   | 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 | Lantier L., Meningaud J.-P., Grimbert P., Bellivier F., Lefaucheur J.-P., Ortonne N., Benjoar M.-D., Lang P., Wolkenstein P. | The Lancet | 2008 |      |      | 2008          | 16.8333  |
| 98   | Pediatric malignant peripheral nerve sheath tumor: The Italian and German Soft Tissue Sarcoma Cooperative Group | Carli M., Ferrari A., Mattke A., Zanetti I., Casanova M., Bisogno G., Cecchetti G., Alaggio R., De Sio L., Koccieliak E., Sotti G., Treuner J. | Journal of Clinical Oncology | 2005  |      |      | 199          | 13.2667  |
| 99   | Optic Nerve Glioma in Mice Requires Astrocyte NF1 Gene Inactivation and NF1 Brain Heterozygosity | Bajenaru M.L., Hernandez M.R., Perry A., Zhu Y., Parada L.F., Garbow J.R., Gutmann D.H. | Cancer Research              | 2003  |      |      | 199          | 11.7059  |
| 100  | NF1-associated gastrointestinal stromal tumors have unique clinical, phenotypic, and genotypic characteristics | Andersson J., Sihto H., Meis-Kindblom J.M., Joensuu H., Nupponen N., Kindblom L.-G. | British Journal of Cancer     | 1994  | 1995 | 195 | 7.5          |   |
|      | Neurofibromatosis and childhood leukaemia/lymphoma: A population-based UKCCSG study | Stiller C.A., Chessells J.M., Fitchett M. | American Journal of Surgical Pathology | 2005  |      |      | 189          | 12.6     |
TABLE 1: The Top 100 Most Cited Articles for Neurofibromatosis 1

The mode of publication year was 1990, with ten publications. The latest year of publication included in the Top 100 is 2010 with a single publication (Figure 1). The top 100 most-cited publications consisted of 82 original articles, 17 review articles, and one conference paper.

FIGURE 1: Publications, by year, within the top 100 most-cited articles.

*Journals with only one publication were excluded from the figure but are as follows: Advances in Neurology, American Journal of Epidemiology, American Journal of Medical Genetics, Angiology, Annals of Internal Medicine, Annals of Surgery, Archives of Dermatology, Archives of Neurology, Brain, British Journal of Cancer, Cancer Cell, Current Biology, Current Problems In Cancer, Embo Journal, Genomics, Histopathology, Human Molecular Genetics, Human Mutation, International Journal of Radiation Oncology Biology Physics, Journal of Pediatrics, Journal of the American Academy of Dermatology, Journal of the American Medical Association, Journal of Urology, Lancet Neurology, Molecular, and Cellular Biology, Neuron, Oncologist, Ophthalmalogy, Radiology, The Lancet, The Lancet Oncology

Only 44 articles had funding sponsors. The most common funding sponsor was the National Institutes of Health (9), followed by the National Cancer Institute (5), the American Cancer Society (3), Merck (3), the National Institute of Neurological Disorders and Stroke (2), and the United States Department of Defense (2).

The top five journals these publications most frequently appeared in are (a) Cell with 11 publications, (b) Cancer with six, (c) Nature Genetics with six, (d) Science with five, and (e) The American Journal of Human Genetics, The Journal of Medical Genetics, Nature, and The New England Journal of Medicine with four publications each (Figure 2).
FIGURE 2: Journals in which the 100 most-cited articles were most frequently published

*Journals with only one publication were excluded from the figure but are as follows: Advances in Neurology, American Journal of Epidemiology, American Journal of Medical Genetics, Angiology, Annals of Internal Medicine, Annals of Surgery, Archives of Dermatology, Archives of Neurology, Annals of Surgery, Archives of Dermatology, Archives of Neurology, Brain, British Journal of Cancer, Cancer Cell, Current Biology, Current Problems In Cancer, Embo Journal, Genomics, Histopathology, Human Molecular Genetics, Human Mutation, International Journal of Radiation Oncology Biology Physics, Journal of Pediatrics, Journal of the American Academy of Dermatology, Journal of the American Medical Association, Journal of Urology, Lancet Neurology, Molecular, and Cellular Biology, Neuron, Oncologist, Ophthalmology, Radiology, The Lancet, The Lancet Oncology

The author with the most publications (Table 2) and most local citations (Table 3) within the top 100 most cited was D.H. Gutmann, with 13 articles in the Top 100. An author’s H-index did not correlate with the highest citation count or the number of publications within the top 100 (Table 2).
| Author       | # Papers within Top 100 | h_index | TC within Top 100 | Starting Year Within Top 100 |
|--------------|-------------------------|---------|-------------------|-----------------------------|
| GUTMANN DH   | 13                      | 87      | 4625              | 1991                        |
| PARADA LF    | 9                       | 91      | 2814              | 1994                        |
| FRIEDMAN JM  | 8                       | 69      | 2227              | 1997                        |
| COLLINS FS   | 7                       | 176     | 3075              | 1987                        |
| ZHU Y        | 7                       | 23      | 2073              | 2001                        |
| O'CONNELL P  | 6                       | 61      | 4042              | 1987                        |
| WHITE R      | 6                       | 84      | 3827              | 1987                        |
| JACKS T      | 6                       | 132     | 2297              | 1994                        |
| HUSON SM     | 6                       | 48      | 2112              | 1988                        |
| KORF BR      | 5                       | 55      | 1209              | 1987                        |
| MCCORMICK F  | 5                       | 113     | 1979              | 1990                        |
| VISKOCHIL D  | 5                       | 49      | 3753              | 1990                        |
| BOLLAG GE    | 4                       | 58      | 1640              | 1990                        |
| FERNER RE    | 4                       | 36      | 1521              | 2002                        |
| LEGIUS E     | 4                       | 60      | 1157              | 1993                        |
| LISTERNICK R | 4                       | 26      | 1322              | 1989                        |
| MULVIHILL JJ | 4                       | 59      | 1242              | 1981                        |
| RATNER N     | 4                       | 51      | 1409              | 1992                        |
| RICCARDI VM  | 4                       | 46      | 1709              | 1981                        |
| SILVA AJ     | 4                       | 80      | 1233              | 1997                        |

**TABLE 2: Top 20 authors in top 100 most cited**
TABLE 3: Top 20 authors that were cited most by the top 100 publications

| Authors         | Citations |
|-----------------|-----------|
| GUTMANN D H     | 118       |
| RICCARDI V M    | 117       |
| HUSON S M       | 79        |
| FRIEDMAN J M    | 73        |
| VISKOCHIL D     | 73        |
| UPADHYAYA M     | 61        |
| COLLINS F S     | 50        |
| JACKS T         | 50        |
| WALLACE M R     | 47        |
| XU G            | 47        |
| MARCHUK D A     | 46        |
| LISTERNICK R    | 45        |
| RATNER N        | 43        |
| HARPER P S      | 37        |
| O CONNELL P     | 37        |
| LEGIUS E        | 36        |
| MULVIHILL J J   | 34        |
| CAWTHON R M     | 33        |
| MAUTNER V F     | 33        |
| CAREY J C       | 32        |

Overall, there were 470 authors, with 655 total author appearances. Seven of the publications were from single authors, but most publications averaged 4.7 authors per document.

The historical roots of NF1 research were identified using spectrographic analysis according to the method of Marx et al. 2014 [8]. The largest peak occurs in the year 1990, which is indicative of the year when NF1 research took its firmest foothold (Figure 3).
Spectrographic analysis reveals quantitatively which historical papers are of particular interest in this specific research topic. This mode of analysis combats "obliteration by incorporation," where novel ideas are "rapidly absorbed into the body of scientific knowledge and their origins thus quickly forgotten due to familiarity," and "palimpsestic syndrome," where an "idea is covered by ascribing it to a more recent author who cites the original work" [8].

The institution affiliated with the most publications in the top 100 was the University of Michigan with 25 publications (Figure 4). The University of California was associated with 24 publications, Howard Hughes Medical Institute University had 25, Harvard Medical School had 22, Indiana University School of Medicine and University of Utah Medical Center had 16, Washington University School of Medicine had 15, Massachusetts General Hospital had 14, Istituto Nazionale Per Lo Studio E La Cura Del Tumori, Olghospital, and the Pediatric Oncology Unit–Istituto Nazionale Tumori had 12, the University of British Columbia had 11, University of Texas Southwestern Medical Center and the University of Wales College of Medicine had 10, the National Cancer Institute had nine, Ghent University Hospital and Charité Universitätsmedizin Berlin had eight, and Baylor College of Medicine, Cardiff University, and Children’s Hospital of Philadelphia each had six (Figure 4).

Table 3 lists the authors that the top 100 most-cited articles cited most in their references. These authors all appear as authors of the top 100 most-cited articles. Table 4 lists the most cited documents by the top 100 most-cited articles. The most locally cited document was "Deletions and a Translocation Interrupt a Cloned Gene at the Neurofibromatosis Type 1 Locus" by Viskochil et al. in 1990 with 26 local citations and 813 global citations (Table 1 and Figure 5).
| Document                          | Year | Local.Citations | Global.Citations |
|----------------------------------|------|-----------------|------------------|
| VISKOCHIL D, 1990, CELL          | 1990 | 26              | 813              |
| WALLACE MR, 1990,                | 1990 | 23              | 1102             |
| CAWTHON RM, 1990, CELL          | 1990 | 23              | 887              |
| XU G, 1990, CELL                 | 1990 | 21              | 833              |
| RICCARDI VM, 1981, NEW ENGL J MED| 1981 | 17              | 912              |
| MARTIN GA, 1990, CELL           | 1990 | 15              | 677              |
| GUTMANN DH, 1997, J AM MED ASSOC| 1997 | 12              | 1017             |
| XU G, 1990, CELL-a               | 1990 | 11              | 513              |
| BALLESTER R, 1990, CELL         | 1990 | 10              | 598              |
| BRANNAN CI, 1994, GENES DEV      | 1994 | 10              | 484              |
| BADER JL, 1978, J PEDIATR        | 1978 | 10              | 220              |
| DECLUE JE, 1992, CELL           | 1992 | 9               | 485              |
| FRIEDMAN JM, 1997, AM J MED GENET| 1997 | 9               | 299              |
| HOPE DG, 1981, ADV NEUROL        | 1981 | 9               | 213              |
| D'AGOSTINO AN, 1963, CANCER      | 1963 | 8               | 276              |
| STUMPF DA, 1988, ARCH NEUROL    | 1988 | 7               | 1527             |
| HUSON SM, 1988, BRAIN           | 1988 | 7               | 509              |
| LEGIUS E, 1993, NAT GENET       | 1993 | 7               | 324              |
| MARCHUK DA, 1991, GENOMICS      | 1991 | 7               | 323              |
| EASTON DF, 1993, AM J HUM GENET  | 1993 | 7               | 283              |

**TABLE 4: Top 20 most cited documents by top 100 most cited articles**

The geographic distribution of corresponding authors with NF1 publications was made up of 59%
publications from the US, 13% from the UK, 5% from Canada, 3% from Italy, 2% from Australia, Belgium, and Germany each, and 1% from Denmark, France, and Sweden (Figure 5). The top eight institutions contributing to the top 100 NF1 publications were all from the US, with the University of Michigan, University of California, Howard Hughes Medical Institute University, and Harvard Medical School, each being involved with more than 20 articles (Figure 4).

The distribution of publications by author (Figure 6) (Lotka’s Law) [9] shows that 381 authors published one paper, and 51 authors published two papers within the top 100 most-cited. Another 38 authors published more than three papers, with the most with 13 articles. The historical origins of NF1 research were also traced using a direct citation network (Figure 7) to compare to the spectrographic analysis seen in Figure 3. Four distinct groupings were branching from Declue Je et al.’s paper in 1992.

![Figure 6: The country of origin for the top 100 most-cited articles, based on the country of the corresponding author]
Figure 7 displays an evaluation of the top 100 most-cited articles by GRADE guidelines. The top 100 most cited articles consisted of 34 review articles, conference statements, or consensus statements, 36 basic science articles, and 30 retrospective/prospective studies. After excluding review articles and conference statements, GRADE guidelines [4-6] (Table 5) showed that the level of evidence for the remaining articles was very low for 19.7%, low for 68.4%, moderate for 11.8%, and high for 0% of the articles (Figure 8).
**TABLE 5: GRADE Guidelines**

| Study Design | Initial Quality of Evidence | Factors that Decrease the Quality Level | Factors that Increase the Quality Level |
|--------------|-----------------------------|----------------------------------------|----------------------------------------|
| Randomized trials or double-upgraded observational studies | High | High likelihood of bias | Large effect |
| Downgraded randomized trials or observational studies | Moderate | Indirectness of evidence | All plausible confounding would reduce a demonstrated effect or suggest a spurious effect if no effect was observed |
| Double-downgraded randomized trials or observational studies | Low | Imprecision | Dose response gradient |
| Triple-downgraded randomized trials, downgraded observational studies, or case series/reports | Very Low | High probability of publication bias | |

**Discussion**

Academic inquiries in the modern era are being pursued by a greater number of individual investigators than ever before, at around 7.8 million worldwide in 2013 [10]. A greater number of scientists correlates with a more considerable amount of scientific data. While an increased quantity of academic works leads to an overall increase in significant advancement in scientific understanding for the general public, it is worthwhile to analyze which articles seem to have risen above the rest. Such "foundational studies" are studies that have significantly impacted the course of academic progress in a particular field, resulting in frequent citation [11].

However, the argument can be made that an elevated number of overall citations may not be the best metric for determining an article’s influence. Instead, the best method may be to measure an article’s citations per year. If the paper continues to be cited over time, this demonstrates a continued impact on the scientific community. Bohl and Ponce 2017 found that when ranking articles based on citations per year as opposed to total citations, the citations that were in the top 100 were more recent publications that focused less on the understanding of the root cause or progression of a disease and more on surgical management and disease outcomes [12].

From our data of articles covering NF1 from 1963-2010, if all citations organize the articles, the premier publication is Neurofibromatosis: Conference Statement at 1527 citations since 1988 [7]. By this ranking, the second-most cited article is Wallace et al. 1990 at 1102 citations [13]. If the articles are organized by citations per year, Neurofibromatosis: Conference Statement is still the highest-ranked article at 47.7 citations per year, and Wallace et al.’s article from 1990 falls to rank five at 36.7 citations per year. The most recent publication within the top 10 within this ranking system is Williams et al. from 2009, with an average of 32.1 citations per year [14].

The Neurofibromatosis Conference Statement by Stumpf et al. in 1988 is referenced extensively throughout Neurofibromatosis literature as it is an early statement that set out to present information for the diagnosis of and management options for NF1, NF2, and NF variants [7]. Von Recklinghausen identified the disease in 1882, and over 100 years later, this panel consensus set forth the guidelines for clinical diagnosis of NF disorders based on physical characteristics [14-17]. Additionally, it discussed weak points in the current knowledge base, calling for academic research into topics that would serve as a springboard for future publications [7]. Some of the specific topics cited for future research include looking for possible genetic heterogeneity of NF patient families, isolating the NF genes to understand the pathophysiological progression of the disease, and acquiring prognostic data for survival and disease progression. One notable proposition that may have increased the amount this article was referenced is that the consensus panel calls for continued NF tumor DNA analysis. They state that NF2 tumor analysis had already shown potential for increasing understanding of all neoplasia, not simply neoplasia limited to NF [7].

Williams et al. 2009 is a review article that covers the history of NF1 disease presentation and makes recommendations for treatment based upon more recent findings [14]. The reason for its heightened citation count per year likely has to do with how recently the paper was published. A well-written review article summarizing the most relevant recent data about disease progression as well as the progress that has been made since foundational articles first laid forth the groundwork for treatment, is bound to be cited frequently within a certain duration of time. This is especially true immediately after publication, prior to new publications taking its place. Ultimately, guidelines will be updated as academic understanding
progresses, and more review articles summarizing modern findings will be produced. As for specific findings of this review article, one notable statement was that there is interest in using small animals to study NF1 therapeutic methodologies. This is something that was briefly suspected as a future avenue for research in the NIH Conference Statement [7]. The article states that in combination with small animal imaging modalities, these models could allow researchers to more easily observe disease progression [14].

Our Lotka’s law analysis (Figure 6) found that the most prolific author within the top 100 most cited articles on NF1 was D.H. Gutmann, producing 13 articles within the top 100. Gutmann’s work often focused on defining the clinical basis for the management of NF1 and its individual characteristics. Some of his works include statements on peripheral nerve sheath tumors, optic gliomas, and cardiovascular manifestations of NF1, [18-20] genetic pathways integral to NF1 disease progression, [21,22] as well as an article identifying the NF1 gene product, NF1GRP [23]. His most cited work at 1017 citations is “The diagnostic evaluation of multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2”, an article that updated management guidelines based on recent evidence in a similar manner to that of the 1988 NIH Conference Statement before it, and the Williams 2009 review article after it [7,14,24]. Research that takes several bodies of work and synthesizes them into one cohesive statement for the most appropriate management of a disease is a springboard for future works, leading to multiple citations according to our findings.

Most articles in the top 100 are published within Cell (Figure 2). Notably, the year that had the most articles within the top 100 for NF1 was 1990 (Figure 1) with ten articles; six of which were from Cell. The cell had 11 articles within the top 100, meaning that these six articles may have had a significant influence not only on Cell’s high amount of top 100 NF1 articles but also 1990’s abundance of articles. It was in 1990 that the NF1 gene was cloned, and sections of its cDNA product were sequenced, resulting in each of these articles focusing on the NF1 gene and its GAP-related protein product [25-30]. These works likely had substantial collaboration, with researchers such as Viskochil, Cawthon, White, and Xu appearing in several publications. The cell is a journal focused on molecular biology, so, understandably, a year with an emphasis on discoveries related to the molecular pathway of NF1 would create a spike in publications of interest in Cell specifically. Besides an NF1 and NF2 update by Mulvihill et al., [31] the other publications in 1990 outside of Cell discussed the pathophysiology of malignant NF1 tumors [32,33] and added more information about the NF1 gene [13]; Of Gutmann’s 13 publications in the top 100, only his work on Cui et al. in 2008 was published in Cell [22].

Despite being highly cited, the majority of the articles found within this study held the GRADE score low. None of the studies in the top 100 most cited held the GRADE high. In the case of Neurofibromatosis 1, citation number is not a good surrogate for a quality paper according to the GRADE system [4-6]. One possible reason for this is the number of basic science articles (36) found within the top 100, which often fail to randomize and blind their studies, as well as a lack of randomized, controlled, and double- or triple-blinded studies.

Our analysis was not without limitations. Total citations and citations per year are not fool-proof methods for calculating publication impact. While total citations can often be skewed due to a more extended period of circulation, the inverse can be said with how our top article based on citations per year was still within its first and most relevant year. H-indices are not a perfect stand-in either, as the metric has potentially skewed results that can ignore the works of researchers who published several moderately successful publications or even a handful of outstanding articles [54]. Self-citations can additionally alter apparent citation counts when authors working together on multiple projects reciprocate references. While collaboration on top NF1 publications was noted, numerous studies of the effect of self-citation find that said citations usually account for less than 10% of citations and do not influence outcomes [55-57].

Conclusions
In this study, we identified, characterized, and analyzed the top 100 most-cited works in NF1. This will serve as a historical point of reference for future research, a jumping point for those not familiar with the topic, and an educational foundation for future NF1 specialists and researchers. Citation count did not correlate with the quality of evidence. We suggest that this study be replicated every five years to assess the progress of NF1 research and to identify historical trends.

Additional Information
Disclosures
Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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