

The Top 100 Most-Cited Papers on Intravitreal Injections: A Bibliographic Perspective

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Purpose: To analyze the top 100 most-cited papers on pars intravitreal injections.

Methods: Literature search using the bibliographic databases of the ISI Web of Knowledge for all types of publications on intravitreal injections published between 1965 and 2019 in peer-reviewed journals.

Results: Eighty-three of the top 100 papers on intravitreal injections were published in ophthalmology journals, their majority in the top five Q1 leading journals in the field. They originated from 16 different countries, predominantly from the USA (n=52), and were all published in English. These manuscripts cover a wide spectrum of topics but were mostly focused on retinal diseases (n=60) and the use of anti-VEGF or steroid agents (n=75).

Discussion: This bibliographic study provides a unique perspective on the evolution and assimilation of intravitreal injections, from their introduction, through their present role as the most common therapeutic procedure in ophthalmology, to future developments.

Keywords: bibliography, citation, historical, intravitreal injection

Introduction

Intravitreal injections are currently an integral part of the practice of ophthalmology, and are a widely accepted method for intraocular drug delivery. Until only 15 years ago, this procedure was performed much less frequently, and was reserved for delivering antibiotics in cases of endophthalmitis¹ or steroids in patients with macular edema.^{2,3} Following the introduction of anti-Vascular Endothelial Growth Factor (VEGF) agents, the use of intravitreal injections increased exponentially, and they quickly became the most commonly performed procedure in ophthalmology.⁴

The first anti-VEGF agent to be approved by the FDA was pegaptanib sodium (Macugen, Pfizer), which was effective in improving visual acuity in patients with neovascular age-related macular degeneration (AMD),^{5,6} but as it only inhibited one isoform of VEGF-A it is no longer used. Soon after ranibizumab (Lucentis, Genentech) was developed, and demonstrated excellent results in treating neovascular AMD in the seminal MARINA and ANCHOR studies.^{7,8} Other anti-VEGF agents in common use are bevacizumab (Avastin, Genentech), which is extensively used off-label for economic reasons,⁹ and aflibercept (Eylea, Regeneron). The efficacy and excellent safety profile of anti-VEGF agents administered by intravitreal injections has been demonstrated in numerous large-scale randomized controlled trials, for a wide variety of retinal diseases, including neovascular AMD, diabetic macular edema (DME), and retinal vein occlusions (RVOs).

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The introduction of anti-VEGF agents has led to no less than a revolution in the practice of ophthalmology. Not only has the procedure changed from a rarely performed technique to the standard of care in numerous retinal diseases, it also achieved much greater success in visual improvement and maintenance than previously available treatment modalities, such as macular laser and photodynamic therapy (PDT), which became almost obsolete. The purpose of this study was to review the literature on intravitreal injections, identify the 100 most-cited papers on this topic, and provide a bibliographic-historic perspective on this important technique which has had an enormous effect on the practice of ophthalmology.

Methods

A comprehensive search of the bibliographic databases of the ISI Web of Knowledge databases (Web of Science core collection and Medline) was performed for the purpose of this study, by an expert medical librarian. The search was performed using the combination of “intravitreal injection” as the keywords. The search included all peer-reviewed journals, and was not limited to the field of ophthalmology. The search included all publications from 1965 (the earliest year available in the databases) to the present (it was conducted on June 1st 2019). All types of publications were included.

The gross results of the search were then analyzed for their type, journal and year of publication, country of origin and language. The results were listed according to the number of total citations, and were then reviewed individually by the authors. The authors read the abstracts and if additional information was required then the manuscripts were reviewed in full. Manuscripts were excluded if they were found not to focus on intravitreal injections or have any relevance to ophthalmology. For example, a paper in which intravitreal injections of a labeling agent was used as a technique for a neuroscience experiment was not included.¹⁰ Included manuscripts had to focus on intravitreal injection as a therapeutic technique, therefore studies in which intravitreal injection was only used as a technique to create a model were also excluded. For example, a study in which intravitreal injections of ouabain were used to induce retinal damage in zebrafish that were later followed for spontaneous regeneration was excluded.¹¹ Using these criteria, a list of the 100 most-cited manuscripts on intravitreal injections was achieved. For each of the manuscripts on the list, the following details were recorded: overall number of citations, mean

citations per year since publication, journal name, year of publication, names of first and last authors, number of authors, country of origin, type of manuscript, number of patients/eyes included, the main topic, and the agents used in the intravitreal injection. Manuscript types were categorized into clinical studies, animal studies, laboratory experiments, reviews, meta-analyses, and case reports.

Correlations between continuous variables were analyzed using Pearson's correlation coefficient, and T-tests and Analysis of Variance (ANOVA) were used to analyze associations between categorical parameters. A *P*-value of 0.05 was used to determine statistical significance. Data was analyzed using SPSS for Windows version 20.

Results

The overall search results yielded 5486 published manuscripts. Of these, the top 100 manuscripts on intravitreal injections were identified following the analysis and inclusion criteria detailed above.

Overall Literature on Intravitreal Injections

Between January 1, 1965 and June 1, 2019, a total of 5486 manuscripts were published on the topic of intravitreal injections. These papers had a total of 113,588 citations, with a mean of 20.69 citations per paper. The number of publications was very low until 2004, and since that year the number of publications on intravitreal injections and their citations have increased significantly and continuously (Figure 1).

Almost two-thirds (63.7%) of the manuscripts were published in Ophthalmology journals, with 82.9% of them being original articles and 7.5% reviews. 95.5% of the manuscripts were published in English, 2.5% in German, and 1.3% in French. About a third (32.1%) of the manuscripts originated from the USA, followed by China, Japan, and Germany. Details of this gross distribution are presented in Figure 2.

The Top 100 Manuscripts on Intravitreal Injections

The top 100 papers on intravitreal injections are listed in order of descending number of citations in Table 1. The mean number of citations was 235 ± 136 , with a median of 173 citations and a range of 128 to 960 citations.

Of the top 100 papers on intravitreal injections, 83 were published in ophthalmology journals. These journals

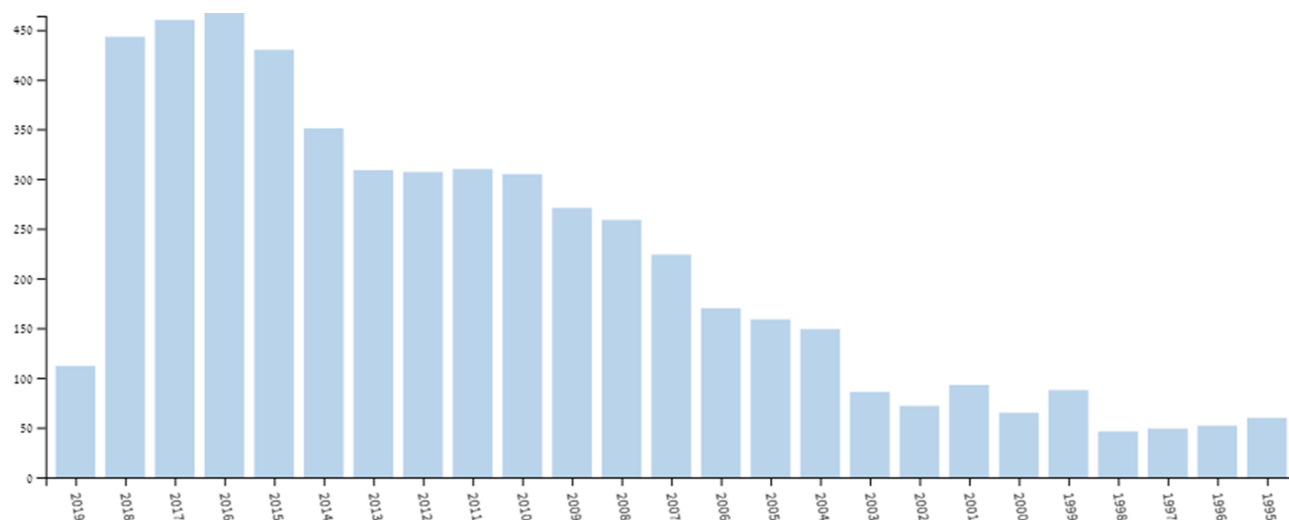


Figure 1 The number of publications on intravitreal injections per year between 1995–2019. Note the significant increase starting in 2004.

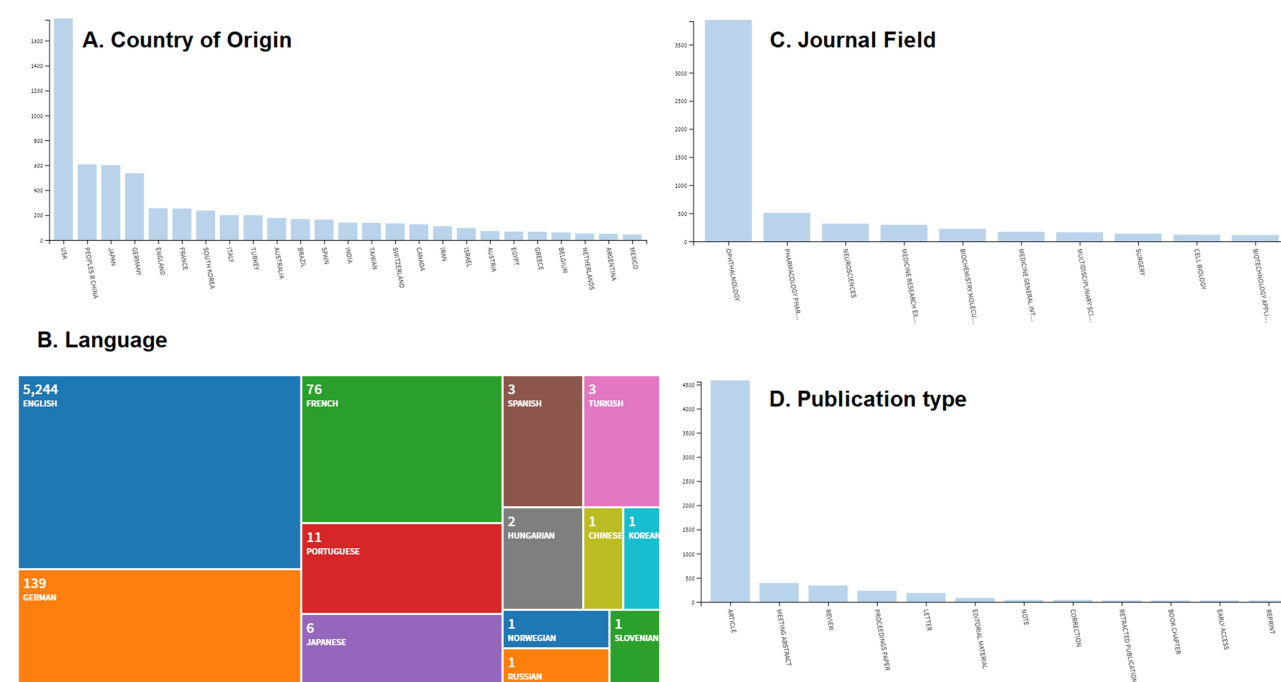


Figure 2 Distribution of the top 100 publications on intravitreal injections, by country of origin (A), language (B), journal field (C), and publication type (D).

include *Ophthalmology* (n=17), *Retina* (n=17), *American Journal of Ophthalmology* (n=12), *Investigative Ophthalmology and Visual Science* (n=12), *Archives of Ophthalmology* (n=9), *British Journal of Ophthalmology* (n=5), *Ophthalmic Surgery and Lasers* (n=2), *Survey of Ophthalmology* (n=2), *Australian and New Zealand journal of Ophthalmology* (n=2), *Graefe's Archive for Clinical and Experimental Ophthalmology* (n=1), *Eye* (n=1), *Experimental Eye Research* (n=1), *Clinical and Experimental Ophthalmology* (n=1), and *Current Opinion*

in Ophthalmology (n=1). Two-thirds (67) of the papers were published in five of the leading Q1 (at the time of publication) journals in Ophthalmology – *Ophthalmology*, *Retina*, *American Journal of Ophthalmology*, *Investigative Ophthalmology and Visual Science*, and *Archives of Ophthalmology*. All papers were written in English. Additionally, 15 of the papers were also presented at international meetings registered at the ISI Web of Knowledge databases, most often at the AAO or ARVO annual conferences.

Table 1 The Top 100 Most-Cited Manuscripts on Intravitreal Injections, Included in This Study. Manuscripts are Listed in Order of Descending Number of Total Citations Since Publication. The Average Citations per Year for Each Manuscript are Also Provided

Title	Authors	Source Title	Publication Year	Total Citations	Average per Year
Suppression of retinal neovascularization in-vivo by inhibition of vascular endothelial growth-factor (VEGF) using soluble VEGF-receptor chimeric proteins	Aiello, LP; Pierce, EA; Foley, ED; Takagil, H; Chen, H; Riddle, L; Ferrara, N; King, GL; Smith, LEH	<i>Proceedings of the National Academy of Sciences of the United States of America</i>	1995	960	38.4
Intravitreal triamcinolone for refractory diabetic macular edema	Martidis, A; Duker, JS; Greenberg, PB; Rogers, AH; Puliafito, CA; Reichel, E; Bauman, C	<i>Ophthalmology</i>	2002	661	36.72
Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin (R)) for neovascular age-related macular degeneration	Rosenfeld, PJ; Moshfeghi, AA; Puliafito, CA	<i>Ophthalmic Surgery Lasers & Imaging</i>	2005	650	43.33
Multiple growth-factors, cytokines, and neurotrophins rescue photoreceptors from the damaging effects of constant light	Lavail, MM; Unoki, K; Yasumura, D; Matthes, MT; Yancopoulos, GD; Steinberg, RH	<i>Proceedings of the National Academy of Sciences of the United States of America</i>	1992	575	20.54
Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration	Spaide, RF; Laud, K; Fine, HF; Klancnik, JM, Jr; Meyerle, CB; Yannuzzi, LA; Sorenson, J; Slakter, J; Fisher, YL; Cooney, MJ	<i>Retina —The Journal of Retinal and Vitreous Diseases</i>	2006	497	35.5
Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration	Ferrara, N; Damico, L; Shams, N; Lowman, H; Kim, R	<i>Retina — The Journal of Retinal and Vitreous Diseases</i>	2006	497	35.5
Vascular endothelial growth factor-induced retinal permeability is mediated by protein kinase C in vivo and suppressed by an orally effective beta-isoform-selective inhibitor	Aiello, LP; Bursell, SE; Clermont, A; Duh, E; Ishii, H; Takagi, C; Mori, F; Ciulla, TA; Ways, K; Jirousek, M; Smith, LEH; King, GL	<i>Diabetes</i>	1997	483	21
Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a nonhuman primate	Adamis, AP; Shima, DT; Tolentino, MJ; Gragoudas, ES; Ferrara, N; Folkman, J; D'Amore, PA; Miller, JW	<i>Archives of Ophthalmology</i>	1996	460	19.17
Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy	Avery, RL; Pearlman, J; Pieramici, DJ; Rabena, MD; Castellari, AA; Nasir, MA; Giust, MJ; Wendel, R; Patel, A	<i>Ophthalmology</i>	2006	455	32.5
Pharmacokinetics of intravitreal bevacumab (avastin)	Bakri, SJ; Snyder, MR; Reid, JM; Pulido, JS; Singh, RJ	<i>Ophthalmology</i>	2007	428	32.92

Intravitreal injection of triamcinolone for diffuse diabetic macular edema	Jonas, JB; Kreissig, I; Sofker, A; Degenring, RF	Archives of Ophthalmology	2003	396	23.29
Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection	Beer, PM; Bakri, SJ; Singh, RJ; Liu, WG; Peters, GB; Miller, M	Ophthalmology	2003	355	20.88
Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin (R)) for macular edema from central retinal vein occlusion	Rosenfeld, PJ; Fung, AE; Puliafito, CA	Ophthalmic Surgery Lasers & Imaging	2005	354	23.6
Intravitreal bevacizumab (Avastin) treatment of macular edema in central retinal vein occlusion – A short-term study	Iturralde, D; Spaide, RF; Meyerle, CB; Klancnik, JM.; Yannuzzi, LA; Fisher, YL; Sorenson, J; Slakter, JS; Freund, KB; Cooney, M; Fine, HF	Retina – The Journal of Retinal and Vitreous Diseases	2006	343	24.5
Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage	Spaide, RF; Fisher, YL	Retina – The Journal of Retinal and Vitreous Diseases	2006	342	24.43
Intravitreal triamcinolone acetonide in exudative age-related macular degeneration	Danis, RP; Ciulla, TA; Pratt, LM; Anliker, W	Retina – The Journal of Retinal and Vitreous Diseases	2000	339	16.95
Intravitreal triamcinolone for uveitic cystoid macular edema: An optical coherence tomography study	Antcliff, RJ; Spalton, DJ; Stanford, MR; Graham, EM; Flytche, TJ; Marshall, J	Ophthalmology	2001	313	16.47
Basic fibroblast growth-factor and local injury protect photoreceptors from light damage in the rat	Faktorovich, EG; Steinberg, RH; Yasumura, D; Matthes, MT; Lavault, MM	Journal of Neuroscience	1992	312	11.14
Intraocular injection of crystalline cortisone as adjunctive treatment of diabetic macular edema	Jonas, JB; Sofker, A	American Journal of Ophthalmology	2001	307	16.16
Intravitreal triamcinolone acetonide for diabetic diffuse macular edema - Preliminary results of a prospective controlled trial	Massin, P; Audren, F; Haouchine, B; Erginay, A; Bergmann, JF; Benosman, R; Caulin, C; Gaudric, A	Ophthalmology	2004	304	19
Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes	Stalmans, P; Benz, MS; Gandorfer, A; Kampik, A; Girach, A; Pakola, S; Haller, JA	New England Journal of Medicine	2012	301	37.63
Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema	Haritoglou, C; Kook, D; Neubauer, A; Wolf, A; Priglinger, S; Strauss, R; Gandorfer, A; Ulbig, M; Kampik, A	Retina – The Journal of Retinal and Vitreous Diseases	2006	293	20.93
Treatment of intraocular proliferation with intravitreal injection of triamcinolone acetonide	Tano, Y; Chandler, D; Machemer, R	American Journal of Ophthalmology	1980	283	7.08

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Table 1 (Continued).

Title	Authors	Source Title	Publication Year	Total Citations	Average per Year
A Phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema	Scott, IU; Edwards, AR; Beck, RW; Bressler, NM; Chan, CK; Elman, MJ; Friedman, SM; Greven, CM; Maturi, RK; Pieramici, DJ; Shami, M; Singerman, LJ; Stockdale, CR	<i>Ophthalmology</i>	2007	280	21.54
Intraocular pressure after intravitreal injection of triamcinolone acetonide	Jonas, JB; Kreissig, I; Degenring, R	<i>British Journal of Ophthalmology</i>	2003	279	16.41
Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Avastin)	Shahar, J; Avery, RL; Heilwell, G Barak, A; Zemel, E; Lewis, GP; Johnson, PT; Fisher, SK; Perlman, I; Loewenstein, A	<i>Retina – The Journal of Retinal and Vitreous Diseases</i>	2006	279	19.93
Safety and efficacy of intravitreal triamcinolone for cystoid macular oedema in uveitis	Young, S; Larkin, G; Branley, M; Lightman, S	<i>Clinical and Experimental Ophthalmology</i>	2001	268	14.11
Acute endophthalmitis following intravitreal triamcinolone acetonide injection	Moshfeghi, DM; Kaiser, PK; Scott, IU; Sears, JE; Benz, M; Sinesterra, JP; Kaiser, RS; Bakri, S; Maturi, RK; Belmont, J; Beer, PM; Murray, TG; Quiroz-Mercado, H; Mieler, WF	<i>American Journal of Ophthalmology</i>	2003	267	15.71
Treatment of the adult retina with microglia-suppressing factors retards axotomy-induced neuronal degradation and enhances axonal regeneration in vivo and in vitro	Thanos, S; Mey, J; Wild, M	<i>Journal of Neuroscience</i>	1993	261	9.67
A randomized clinical trial of a single dose of intravitreal triamcinolone acetonide for neovascular age-related macular degeneration - One year results	Gillies, MC; Simpson, JM; Luo, W; Penfold, P; Hunyor, ABL; Chua, W; Mitchell, P; Billson, F	<i>Archives of Ophthalmology</i>	2003	245	14.41
Comparisons of the intraocular tissue distribution, pharmacokinetics, and safety of I-125-labeled full-length and Fab antibodies in rhesus monkeys following intravitreal administration	Mordenti, J; Cuthbertson, RA; Ferrara, N; Thomsen, K; Berleau, L; Licko, V; Allen, PC; Valverde, CR; Meng, YG; Fei, DTW; Fourre, KM; Ryan, AM	<i>Toxicologic Pathology</i>	1999	243	11.57
Intravitreal bevacizumab for the management of choroidal neovascularization in age-related macular degeneration	Bashshur, ZF; Bazarbachi, A; Schakal, A; Haddad, ZA; El Haibi, CP; Nouredin, BN	<i>American Journal of Ophthalmology</i>	2006	240	17.14
Intraocular pressure elevation after intravitreal triamcinolone acetonide injection	Jonas, JB; Degenring, RF; Kreissig, I; Akkoyun, I; Kamppeiter, BA	<i>Ophthalmology</i>	2005	238	15.87

Gene therapy with brain-derived neurotrophic factor as a protection: Retinal ganglion cells in a rat glaucoma model	Martin, KRG; Quigley, HA; Zack, DJ; Levkovitch-Verbin, H; Kielczewski, J; Valenta, D; Baumrind, L; Pease, ME; Klein, RL; Hauswirth, WW	Investigative Ophthalmology & Visual Science	2003	231	13.59
Exudative macular degeneration and intravitreal triamcinolone: 18 month follow up	Challa, JK; Gillies, MC; Penfold, PL; Gyory, JF; Hunyor, ABL; Billson, FA	Australian and New Zealand Journal of Ophthalmology	1998	227	10.32
Testing intravitreal toxicity of bevacizumab (Avastin)	Manzano, RPA; Peyman, GA; Khan, P; Kivilcim, M	Retina – The Journal of Retinal and Vitreous Diseases	2006	227	16.21
Primary intravitreal bevacizumab (Avastin) for diabetic macular edema – Results from the Pan-American Collaborative Retina Study Group at 6-month follow-up	Arevalo, JF; Fromow-Guerra, J; Quiroz-Mercado, H; Sanchez, JG; Wu, L; Maia, M; Berrocal, MH; Solis-Vivancol, A; Farah, ME	Ophthalmology	2007	224	17.23
Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy	Arevalo, JF; Maia, M; Flynn, HW, Jr; Saravia, M; Avery, RL; Wu, L; Farah, M; Eid, Pieramici, DJ; Berrocal, MH; Sanchez, JG	British Journal of Ophthalmology	2008	222	18.5
Combined photodynamic therapy with verteporfin and intravitreal triamcinolone acetate for choroidal neovascularization	Spaide, RF; Sorenson, J; Maranan, L	Ophthalmology	2003	220	12.94
Neurotrophic factors cause activation of intracellular signaling pathways in Muller cells and other cells of the inner retina, but not photoreceptors	Wahlin, KJ; Campochiaro, PA; Zack, DJ; Adler, R	Investigative Ophthalmology & Visual Science	2000	213	10.65
Safety of an intravitreal injection of triamcinolone – Results from a randomized clinical trial	Gillies, MC; Simpson, JM; Billson, FA; Luo, W; Penfold, P; Chua, W; Mitchell, P; Zhu, MD; Hunyor, ABL	Archives of Ophthalmology	2004	213	13.31
Intraocular pharmacokinetics of bevacizumab after a single intravitreal injection in humans	Krohne, TU; Eter, N; Holz, FG; Meyer, CH	American Journal of Ophthalmology	2008	208	17.33
N-methyl-D-aspartate (NMDA)-induced apoptosis in rat retina	Lam, TT; Abler, AS; Kwong, JMK; Tso, MOM	Investigative Ophthalmology & Visual Science	1999	205	9.76
Ciliary neurotrophic factor and stress stimuli activate the Jak-STAT pathway in retinal neurons and glia	Peterson, WM; Wang, Q; Tzekova, R; Wiegand, SJ	Journal of Neuroscience	2000	197	9.85

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Table 1 (Continued).

Title	Authors	Source Title	Publication Year	Total Citations	Average per Year
Penetration of bevacizumab through the retina after intravitreal injection in the monkey	Heiduschka, P; Fietz, H; Hofmeister, S; Schultzeiss, S; Mack, AF; Peters, S; Ziemssen, F; Niggemann, B; Julien, S; Bartz-Schmidt, KU; Schraermeyer, U	<i>Investigative Ophthalmology & Visual Science</i>	2007	192	14.77
Photodynamic therapy with verteporfin combined with intravitreal injection of triamcinolone acetonide for choroidal neovascularization	Spaide, RF; Sorenson, J; Maranan, L	<i>Ophthalmology</i>	2005	190	12.67
Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients	Boyer, DS; Faber, D; Gupta, S; Patel, SS; Tabandeh, H; Li, X-Y; Liu, CC; Lou, J; Whitcup, SM	<i>Retina-the Journal of Retinal and Vitreous Diseases</i>	2011	186	20.67
Efficacy of intravitreal bevacizumab for polypoidal choroidal vasculopathy	Gomi, F; Sawa, M; Sakaguchi, H; Tsujikawa, M; Oshima, Y; Kamei, M; Tano, Y	<i>British Journal of Ophthalmology</i>	2008	182	15.17
Noninfectious endophthalmitis associated with intravitreal triamcinolone injection	Roth, DB; Chieh, J; Spirn, MJ; Green, SN; Yarian, DL; Chaudhry, NA	<i>Archives of Ophthalmology</i>	2003	176	10.35
Maximum tolerated dose of a humanized anti-vascular endothelial growth factor antibody fragment for treating neovascular age-related macular degeneration	Rosenfeld, PJ; Schwartz, SD; Blumenkranz, MS; Miller, JW; Haller, JA; Reimann, JD; Greene, WL; Shams, N	<i>Ophthalmology</i>	2005	173	11.53
Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature	Falavarjani, KG; Nguyen, QD	<i>Eye</i>	2013	173	24.71
Adenovirus-mediated gene transfer of ciliary neurotrophic factor can prevent photoreceptor degeneration in the retinal degeneration (rd) mouse	Cayouette, M; Gravel, C	<i>Human Gene Therapy</i>	1997	172	7.48
Intravitreal triamcinolone acetonide for exudative age related macular degeneration	Jonas, JB; Kreissig, I; Hugger, P; Sauder, G; Panda-Jonas, S; Degenring, R	<i>British Journal of Ophthalmology</i>	2003	172	10.12
Meta-analysis of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents causative organisms and possible prevention strategies	McCannel, CA	<i>Retina – The Journal of Retinal and Vitreous Diseases</i>	2011	171	19
MicroRNA-200b regulates vascular endothelial growth factor-mediated Alterations in diabetic retinopathy	McArthur, K; Feng, B; Wu, Y; Chen, S; Chakrabarti, S	<i>Diabetes</i>	2011	171	19

Association of endothelin-1 with normal-tension glaucoma – clinical and fundamental studies	Sugiyama, T; Moriya, S; Oku, H; Azuma, I	Survey of Ophthalmology	1995	170	6.8
Exudative macular degeneration and intravitreal triamcinolone – A pilot study	Penfold, PL; Gyory, JF; Hunyor, AB; Billson, FA	Australian and New Zealand Journal of Ophthalmology	1995	170	6.8
Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment – Three-month efficacy and safety results of a prospective, randomized, double-masked, placebo-controlled clinical trial	Sutter, FKP; Simpson, JM; Gillies, MC	Ophthalmology	2004	170	10.63
Long-term protection of retinal structure but not function using RAAV/CNTF in animal models of retinitis pigmentosa	Liang, FQ; Aleman, TS; Dejneka, NS; Dudas, L; Fisher, KJ; Maguire, AM; Jacobson, SG; Bennett, J	Molecular Therapy	2001	168	8.84
Intravitreal triamcinolone acetate in eyes with cystoid macular edema associated with central retinal vein occlusion	Park, CH; Jaffe, GJ; Fekrat, S	American Journal of Ophthalmology	2003	166	9.76
Anti-vascular endothelial growth factor therapy for subfoveal choroidal neovascularization secondary to age-related macular degeneration – Phase II study results	Fish, G; Haller, JA; Ho, AC; Klein, M; Loewenstein, J; Martin, D; Orth, D; Rosen, RB; Sanislo, S; Schwartz, SD; Singerman, LJ; Williams, G; Adamis, AP; Blumenkranz, M; Goldberg, M; Gragoudas, ES; Miller, JW; Yannuzzi, L; Guyer, DR; O'Shaughnessy, D; Patel, S	Ophthalmology	2003	165	9.71
Intravitreal injection of dexamethasone – treatment of experimentally induced endophthalmitis	Graham, RO; Peyman, GA	Archives of Ophthalmology	1974	163	3.54
Intravitreal injection of crystalline cortisone as adjunctive treatment of proliferative diabetic retinopathy	Jonas, JB; Hayler, JK; Sofker, A; Panda-Jonas, S	American Journal of Ophthalmology	2001	163	8.58
Corticosteroids inhibit VEGF-induced vascular leakage in a rabbit model of blood-retinal and blood-aqueous barrier breakdown	Edelman, JL; Lutz, D; Castro, MR	Experimental Eye Research	2005	162	10.8
Ultrastructural findings in the primate eye after intravitreal injection of bevacizumab	Peters, S; Heiduschka, P; Julien, S; Ziemssen, F; Fietz, H; Bartz-Schmidt, KU; Schraermeyer, U	American Journal of Ophthalmology	2007	161	12.38
Macular edema	Tranos, PG; Wickremasinghe, SS; Stangos, NT; Topouzis, F; Tsinopoulos, L; Pavesio, CE	Survey of Ophthalmology	2004	159	9.94
AAV-mediated expression of CNTF promotes long-term survival and regeneration of adult rat retinal ganglion cells	Leaver, SG; Cui, Q; Plant, GW; Arulpragasam, A; Hishah, S; Verhaagen, J; Harvey, AR	Gene Therapy	2006	159	11.36

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Table 1 (Continued).

Title	Authors	Source Title	Publication Year	Total Citations	Average per Year
Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema	Campochiaro, PA; Brown, DM; Pearson, A; Ciulla, T; Boyer, D; Holz, FG; Tolentino, M; Gupta, A; Duarte, L; Madreperla, S; Gonder, J; Kapik, B; Billman, Kn; Kane, FE	<i>Ophthalmology</i>	2011	158	17.56
In vivo protection of photoreceptors from light damage by pigment epithelium-derived factor	Cao, W; Tombran-Tink, J; Elias, R; Sezate, S; Mrzsek, D; McGinnis, JF	<i>Investigative Ophthalmology & Visual Science</i>	2001	154	8.11
Potential role of microglia in retinal blood vessel formation	Cecchin, D; Sennhaub, F; Levassasseur, E; Leduc, M; Chemtob, S	<i>Investigative Ophthalmology & Visual Science</i>	2006	154	11
Intravitreal bevacizumab (Avastin) for persistent new vessels in diabetic retinopathy (IBEPE Study)	Jorge, R; Costa, RA; Comt, DC; Cintra, LP; Scott, IU	<i>Retina – The Journal of Retinal and Vitreous Diseases</i>	2006	153	10.93
Intravitreal triamcinolone acetonide as treatment of macular edema in central retinal vein occlusion	Jonas, JB; Kreissig, I; Degenring, RF	<i>Graefes Archive for Clinical and Experimental Ophthalmology</i>	2002	152	8.44
Pharmacokinetics of bevacizumab after topical, subconjunctival, and intravitreal administration in rabbits	Nomoto, H; Shiraga, F; Kuno, N; Kimura, E; Fujii, S; Shinomiya, K; Nugent, AK; Hirooka, K; Baba, T	<i>Investigative Ophthalmology & Visual Science</i>	2009	152	13.82
Serum concentrations of bevacizumab (Avastin) and vascular endothelial Growth factor in infants with retinopathy of prematurity	Sato, T; Wada, K; Arahori, H; Kuno, N; Imoto, K; Iwahashi-Shima, C; Kusaka, S	<i>American Journal of Ophthalmology</i>	2012	152	19
Intravitreal injection of bevacizumab (Avastin) for treatment of stage 3 retinopathy of prematurity in zone I or posterior zone II	Mintz-Hittner, HA; Kuffel, RR	<i>Retina – The Journal of Retinal and Vitreous Diseases</i>	2008	151	12.58
Aflibercept therapy for exudative age-related macular degeneration resistant to bevacizumab and ranibizumab	Bakall, B; Folk, J C; Boldt, HC; Sohn, EH; Stone, EM; Russell, SR; Mahajan, VB	<i>American Journal of Ophthalmology</i>	2013	149	21.29
Intravitreal injection of crystalline cortisone as adjunctive treatment of proliferative vitreoretinopathy	Jonas, JB; Hayler, JK; Panda-Jonas, S	<i>British Journal of Ophthalmology</i>	2000	148	7.4

Encapsulation of dexamethasone into biodegradable polymeric nanoparticles	Gomez-Graete, C; Tsapis, N; Besnard, M; Bochot, A; Fattal, E	2007	146	11.23
Intravitreal triamcinolone acetate inhibits choroidal neovascularization in a laser-treated rat model	Ciulla, TA; Criswell, MH; Danis, RP; Hill, TE	2001	144	7.58
Neuroprotective effect of (-)-Delta(9)-tetrahydrocannabinol and cannabidiol in N-methyl-D-aspartate-induced retinal neurotoxicity – Involvement of peroxynitrite	El-Remessy, AB; Khalil, IE; Matragoon, S; Abou-Mohamed, G; Tsai, NJ; Roon, P; Caldwell, RB; Caldwell, RW; Green, K; Liou, G	2003	143	8.41
Intravitreal triamcinolone for the treatment of macular edema associated with central retinal vein occlusion	Ip, MS; Gottlieb, ML; Kahana, A; Scott, IU; Altaweel, MM; Blodi, BA; Gangnon, RE; Puliafito, CA	2004	143	8.94
Anti-vascular endothelial growth factor for neovascular age-related macular degeneration	Solomon, SD; Lindsley, R; Vedula, SS; Krzystolik, MG; Hawkins, BS	2014	142	23.67
Endotoxin-induced uveitis in the rat – the significance of intraocular interleukin-6	Hoekzema, R; Verhagen, C; Vanharen, M; Kijlstra, A	1992	141	5.04
Peroxisome proliferator-activated receptor-gamma ligands inhibit choroidal neovascularization	Murata, T; H, SK; Hangai, M; Ishibashi, T; Xi, XP; Kim, S; Hsueh, WA; Ryan, SJ; Law, RE; Hinton, DR	2000	141	7.05
Intravitreal injection of erythropoietin protects both retinal vascular and neuronal cells in early diabetes	Zhang, J; Wu, Y; Jin, Y; Ji, F; Sinclair, SH; Luo, Y; Xu, G; Lu, L; Dai, W; Yanoff, M; Li, W; Xu, GT	2008	141	11.75
Evaluation of the retinal toxicity and pharmacokinetics of dexamethasone after intravitreal injection	Kwak, HW; Damico, DJ	1992	140	5
Role of intravitreal methotrexate in the management of primary central nervous system lymphoma with ocular involvement	Smith, JR; Rosenbaum, JT; Wilson, DJ; Doolittle, ND; Siegel, T; Newelt, EA; Pe'er, J	2002	140	7.78
Intravitreal injection of corticosteroid attenuates leukostasis and vascular leakage in experimental diabetic retina	Tamura, H; Miyamoto, K; Kiryu, J; Miyahara, S; Katsuta, H; Hirose, F; Musashi, K; Yoshimura, N	2005	138	9.2
CNTF promotes survival of retinal ganglion cells after induction of ocular hypertension in rats: the possible involvement of STAT3 pathway	Ji, JZ; Elyaman, W; Yip, HK; Lee, VWH; Yick, LW; Hugon, J; So, KF	2004	136	8.5
Outcome of intravitreal triamcinolone in uveitis	Kok, H; Lau, C; Maycock, N; McCluskey, P; Lightman, S	2005	136	9.07

(Continued)

Table 1 (Continued).

Title	Authors	Source Title	Publication Year	Total Citations	Average per Year
Intravitreal anti-VEGF for diabetic retinopathy: hopes and fears for a new therapeutic strategy	Simo, R; Hernandez, C	<i>Diabetologia</i>	2008	135	11.25
Incidence of endophthalmitis related to intravitreal injection of bevacizumab and ranibizumab	Fintak, DR; Shah, GK; Blinder, KJ; Regillo, CD; Pollack, J; Heier, JS; Hollands, H; Sharma, S	<i>Retina-the Journal of Retinal and Vitreous Diseases</i>	2008	134	11.17
Diabetes-enhanced tumor necrosis factor- α production promotes apoptosis and the loss of retinal microvascular cells in type 1 and type 2 models of diabetic retinopathy	Chin, HS; Park, TS; Moon, YS; Oh, JH	<i>Retina – The Journal of Retinal and Vitreous Diseases</i>	2005	133	8.87
Regression of iris neovascularization after intravitreal injection of bevacizumab in patients with proliferative diabetic retinopathy	Oshima, Y; Sakaguchi, H; Gomi, F; Tano, Y	<i>American Journal of Ophthalmology</i>	2006	133	9.5
Complications of intravitreal injections	Sampat, KM; Garg, SJ	<i>Current Opinion in Ophthalmology</i>	2010	133	13.3
Biodegradable microspheres for vitreoretinal drug delivery	Herrero-Vanrell, R; Refojo, MF	<i>Advanced Drug Delivery Reviews</i>	2001	132	6.95
Triple therapy for choroidal neovascularization due to age related macular degeneration – Verteporfin PDT, bevacizumab, and dexamethasone	Augustin, AJ; Puls, S; Offermann, I	<i>Retina –the Journal of Retinal and Vitreous Diseases</i>	2007	132	10.15
Electrophysiologic findings after intravitreal bevacizumab (Avastin) treatment	Maturi, RK; Bleau, LA; Wilson, DL	<i>Retina – The Journal of Retinal and Vitreous Diseases</i>	2006	131	9.36
Rapid improvement of rubeosis iridis from a single bevacizumab (avastin) injection	Davidorf, FH; Mouser, J; Derick, RJ	<i>Retina – The Journal of Retinal and Vitreous Diseases</i>	2006	129	9.21
Posterior vitreous detachment induced by microplasmin	Gandorfer, A; Rohleder, M; Sethi, C; Eckle, D; Welge-Hussen, U; Kampik, A; Lutbert, P; Charteris, D	<i>Investigative Ophthalmology & Visual Science</i>	2004	128	8

Table 2 Authors Who Had More Than One First or Last Authorship on a Paper in the Top 100 List

Author Name	Number of First/Last Authorships
Jonas, JB	8
Degenring, RF	4
Spaide, RF	4
Billson, FA	3
Gillies, MC	3
Puliafito, CA	3
Rosenfeld, PJ	3
Tano, Y	3
Aiello, LP	2
Arevalo, JF	2
LaVail, MM	2
Lightman, S	2
Maranan, L	2
Panda-Jonas, S	2
Schraermeyer, U	2
Scott, IU	2

The top 100 manuscripts originated from 16 different countries, with about half of them (52 manuscripts) originating from the US. Other countries of origin included Germany (n=15), Japan (n=6), Australia (n=6), the UK (n=4), Canada (n=3), France (n=2), China (n=2), Spain (n=2), Venezuela (n=2), and Belgium, Brazil, Israel, Lebanon, the Netherlands, and South Korea (n=1 each).

The mean number of authors was 6.1 ± 3.4 , with a median of 5 and a range of 1–21. Only one manuscript was published by a single author. There were 16 authors who had more than one first or last authorship on a paper in the top 100 list. These authors are listed in Table 2.

The top 100 manuscripts on intravitreal injections were published between 1974 to 2014. When further divided by decades, there were only two manuscripts published before 1990, 14 manuscripts were published between 1990–1999, 74 manuscripts were published between 2000–2009, and 10 were in 2010 or later. There was no correlation between year of publication and the total number of citations, but a significant correlation was found between later year of publication and a higher mean number of citations per year ($P=0.0004$).

Almost half (49) of the top 100 manuscripts on intravitreal injections were clinical studies which were conducted on human patients. Of these, 32 (65%) were prospective studies, 14 (29%) were retrospective studies, and three (6%) were observational studies. The number of eyes/patients analyzed in these clinical studies varied between 1–26,905, with a median of 26. Nine (18%) of the studies

Table 3 The Topics of the Top 100 Most-Cited Manuscripts on Intravitreal Injections Included in This Study, in Descending Order of Frequency

Topic	Number of Papers
Diabetic Retinopathy	23
Age Related Macular Degeneration	20
Complications of Intravitreal Injections	9
Pharmacokinetic Studies	9
Cytokines and pathways (not anti-VEGF/steroids)	8
Retinal Vascular Occlusion	5
Retinal Ischemia and Retinopathy of Prematurity	5
Uveitis	4
Glaucoma	3
Drug Mechanism of Action	3
Vitreomacular Traction	2
Proliferative Vitreoretinopathy	2
Drug Delivery Techniques	2
Gene Therapy	2
Polypoidal Choroidal Vasculopathy	1
Retinitis Pigmentosa	1
Lymphoma	1

included 100 or more eyes/patients, while eight (16%) included fewer than 10 eyes/patients. Another 38 manuscripts were basic science papers, conducted on animal eyes or tissues under laboratory settings. The remaining 13 manuscripts included seven reviews, two meta-analyses, and four case reports.

The top 100 manuscripts on intravitreal injections covered a wide variety of topics. Most (60) of the manuscripts were focused on retinal diseases, including diabetic retinopathy (DR) and DME (n=23), neovascular AMD (n=20), RVOs (n=5), retinal ischemia and retinopathy of prematurity (ROP) (n=5), vitreomacular traction (VMT) and macular hole (MH) (n=2), proliferative vitreoretinopathy (PVR) (n=2), polypoidal choroidal vasculopathy (PCV) (n=1), retinitis pigmentosa (RP) (n=1), and lymphoma (n=1). There were also four manuscripts on uveitis and three manuscripts on glaucoma. Nine manuscripts were focused on complications of intravitreal injections, such as intraocular pressure elevation and endophthalmitis. The remaining 24 manuscripts focused on topics other than the injections themselves or specific clinical conditions, such as pharmacology and pharmacokinetic studies on intravitreally injected drugs (n=9), research on the effect of pathways and cytokines other than anti-VEGF and steroids

($n=8$), mechanisms of action of intravitreally injected drugs ($n=3$), novel drug delivery techniques ($n=2$), and gene therapy ($n=2$). These topics are presented in Table 3.

The agents studied in the top 100 manuscripts on intravitreal injections were numerous, but the majority of the manuscripts (75 of them) included anti-VEGF agents (pegaptanib, bevacizumab, ranibizumab, or aflibercept; $n=38$) or steroids (dexamethasone, triamcinolone, or fluocinolone; $n=37$). The most common anti-VEGF agent was bevacizumab ($n=27$; 71%), and the most common steroid was triamcinolone acetonide ($n=29$, 78%). The remaining 25 manuscripts included other intravitreally injected agents, such as ciliary neurotrophic factor ($n=6$), ocriplasmin ($n=2$), methotrexate ($n=1$), and other factors and antibodies that are not in clinical use.

Discussion

Over the past 15 years, intravitreal injections have become a mainstay in the practice of ophthalmology in general, and especially in the treatment of retinal diseases. Their excellent safety and efficacy profiles proved them to be superior to previous treatments, and they have very rapidly gained popularity and became the most commonly performed procedure in ophthalmology.⁴ This is the first bibliographic study focused on intravitreal injections, although it should be noted similar works have been done on macular imaging by optical coherence tomography (OCT)¹² and pars plana vitrectomy.¹³ However, in contrast to these two key techniques that have also revolutionized the practice of ophthalmology, the evolution and acceptance of intravitreal injections has been much more rapid.

All manuscripts in the top 100 list were in English, and most of them were published in leading Q1 journals in Ophthalmology ($n=67$), with the most common country of origin being the USA ($n=52$). These findings are comparable with previous bibliographic works in ophthalmology.^{12–15} This is not surprising, as the leading journals are based in the USA and published in English, and their manuscripts are likely to be more cited.

The majority of the top 100 manuscripts on intravitreal injections were published in the decade between 2000–2009 ($n=74$), with relatively few published prior to 1999 ($n=16$) or after 2010 ($n=10$). The first explanation for this finding is that the 2000–2009 decade was the time in which the pivotal studies that established the clinical efficacy of intravitreal injections of anti-VEGF agents (as well as steroids) were published. The works

that introduced agents such as bevacizumab, ranibizumab, and triamcinolone acetonide as therapeutic modalities for numerous retinal conditions became landmark papers, with a high rate of citation. This is also reflected in the fact that most of the top 100 manuscripts included these drugs ($n=75$). A second explanation for this finding is related to the timing of publication. Relatively few studies published before 1999 have focused on these issues, and most of the works from that time that made it into the top 100 list are laboratory experiments, animal studies or small series, that have laid the base for the larger clinical trials of the 2000–2009 decade. Additionally, it is possible that older papers that are expected to have more citations, may have been under-cited as they became common knowledge, forgotten, or refuted.¹⁶ In our study, there was no correlation between year of publication and total number of citations, indicating that older papers were not necessarily quoted more frequently than newer ones. Studies published after 2010 require a very high rate of citations per year in order to be included in the top 100 list, as is reflected by the significant correlation between the year of publication and mean number of citations per year ($P<0.001$). This is compatible with the fact that to achieve a high number of citations comparable to older publications, newer publications have to be cited more often each year since their publication, a phenomenon that was also reported in previous works.^{13,15}

Most of the top 100 manuscripts were focused on retinal diseases ($n=60$), the most common being AMD, DR, and DME. Also, half of them were clinical studies including human patients. These findings are not surprising, and intravitreal injections are primarily used for the treatment of these common retinal diseases, and have had a huge clinical impact for countless patients with numerous conditions. On the other hand, it is important to note that a significant portion of the top 100 manuscripts is focused on other diseases, novel drug delivery techniques, gene therapy, as well as new therapeutic agents administered by this route, indicating that intravitreal injections are not only integral to the current practice of ophthalmology, but also to ongoing research and development, and will likely continue to be an essential part of ophthalmology in the future.

There are several limitations to this study. We acknowledge that using different databases and search-engines, with different limitations and search definitions, would have resulted in a different list of 100 most cited

manuscripts. Our search methodology included all publication types, as citation rates apply to both original research articles as well as reviews, meta-analyses, and other publication types. We also note that the number of citations is not an objective measure of a paper's quality, accuracy, or validity, but rather of its influence and acceptance in the field. This concept also has its limitations, as newer papers take time to accumulate a high citation rate, and older papers may become less cited with time as they become common knowledge or irrelevant.¹⁶ Therefore, we emphasize that this is our list of the 100 most cited papers on intravitreal injections, and not necessarily the best 100 papers. Another limitation is that self-citation was not excluded, as it would have been very complicated to determine this separately for each author in the 100 most cited papers. This is not a significant limitation, as self-citation has been reported to have a low influence on the total citation rate.¹⁷

This bibliographic analysis depicts the rapid evolution of intravitreal injections and their effect on ophthalmology, as they transformed from a relatively rare procedure to the most common therapeutic modality in ophthalmology, matching the introduction and rapid prevalence of anti-VEGF agents administered by this route. The list includes many landmark papers and papers by leaders in the field, that have together driven the development of this technique that has truly revolutionized the practice of ophthalmology.

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