



Age-Related Macular Degeneration: A Scientometric Analysis

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ABSTRACT

Age-related macular degeneration (ARMD) is a major cause of central blindness among working aged adults across the world. Systematic research planning on any subject, including ARMD is in need of solid data regarding previous efforts in this field and to identify the gaps in the research. This study aimed to elucidate the most important trends, directions, and gap in this subject.

The data extracted from the Institute for Scientific Information were used to perform a bibliometric analysis of the scientific productions (1993–2013) about ARMD. Specific parameters related to ARMD were analyzed to obtain a view of the topic's structure, history, and document relationships. Additionally, the trends and authors in the most influential publications were analyzed.

The number of articles in this field was found constantly increasing. Most highly cited articles addressed genetic epidemiology and clinical research topics in this field. During the past 3 years, there has been a trend toward biomarker research.

Through performing the first scientometric survey on ARMD research, we analyzed the characteristics of papers and the trends in scientific production. We also identified some of the critical gaps in the current research efforts that would help in large-scale research strategic planning.

KEY WORDS

Age-related Macular Degeneration, Bibliometrics, Historiography, Scientometrics, Citation Analysis

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INTRODUCTION

Age-related macular degeneration (ARMD) is one of the top four causes of blindness in elderly people. ARMD, described more than 80 years ago, is a progressive disease of the central area in the ocular posterior segment (the macula lutea), which leads to a gradual deterioration in central vision and causes severe

disability to affected individuals. In North America, Europe, and Australia, ARMD accounts for up to half of all cases of central blindness, affecting approximately 3% of the general adult population. In the United States, about 12%–15% of people older than 80 years of age were estimated to have ARMD in 2000, and this number is expected to be more than 2.95 million in 2020. People with ARMD have been found to experience reduced



quality of life, depression, and difficulty with the activities of daily living, which pose serious financial burden on their family in terms of high medical and societal costs that are due to increased risk of falling, need for vision enhancing equipment, depression/anxiety treatment, and assistance with activities of daily living (1, 2).

Visual loss in late ARMD can be caused by either of the following two processes that cause photoreceptor dysfunction: geographic atrophy (GA) or choroidal neovascularization. GA refers to the confluent atrophy of the choriocapillaris and associated retinal pigment epithelium (RPE). The RPE is the outermost layer of the retina, which is involved in phagocytosis of the photoreceptor outer segments and biologic maintenance. In choroidal neovascularization, an ingrowth of new vessels occurs from the choriocapillaris invading the retina. These new vessels leak serous fluids beneath and into the neural retina causing fibrous scarring, which defines the late stage of ARMD (exudative, or neovascular) (3). Non-exudative (dry) ARMD is often marked by the formation of drusen, pigmentary changes in the RPE, and atrophy of the RPE. Dry ARMD is more common; in one series of autopsy eyes, ARMD was found in 33% of patients older than 65 years (4, 5).

The incidence of the disease increases with age. Through major breakthrough discoveries made in the last decade in treating the wet form of ARMD, the chance of stabilizing or increasing vision has been increased to 90%. Nonetheless, this improvement is associated with a significant price tag of monthly intravitreal injections (with the ever-present phantom of endophthalmitis and other injection-related adverse events) and uncertainty regarding the duration of treatment (6).

A scientometrics method is one that measures and analyzes scientific publications related to a specific topic regarding the trends in citations, most important content, authors, and journals. A widespread use of scientometric method goes back to 1960s when Eugene Garfield finalized the construction of Science (7). In this article, we performed the first scientometric analysis of the ARMD field to elucidate the most important trends and directions of this subject.

MATERIAL AND METHODS

A bibliometric study was performed on the articles related to “Age-Related Macular Degeneration” published between 1993 and 2013. The Institute for Scientific Information (ISI) web of science available at <http://www.isiknowledge.com> was our main source. Two mesh terms—“Age-Related Macular Degeneration” and “ARMD”—already checked in Pubmed mesh database were used to conduct the search.

Only original articles were selected for further evaluation. These articles were evaluated regarding citation characteristics, contributing role of each author, country, funding agency, institution, journal, and language of published articles. Articles were also evaluated regarding the trend of publication and citation during a selected time and also subject areas covered. Articles that were published in 10 countries with the greatest number of publications on the topic were analyzed separately.

Articles published by each country were evaluated regarding subject areas and publishing journals. Special attention was paid to total citations with and without self-citation, citation per year, and citation per item for journals of each country. Articles that were cited more than 100 times were evaluated regarding year of publication, country of affiliation of the first author, and publishing journal. Number, country, and year of collaborative studies were also considered. All three resources available in the ISI web of science were used for this purpose (Science Citation Index Expanded, Social Sciences Citation Index, The Arts & Humanities Citation Index). For the citation analysis, two parameters were calculated: Local Citation Score (LCS) and Global Citation Score (GCS). LCS listed all papers sorted by citation frequency within the local (the starting bibliography) collection; however, GCS counted citations in the whole collection. For the citation burst analysis, first, 100 key words that generated the citation bursts were extracted, and then non-specific and general key words were omitted.

RESULTS

Annual Publication Number During 1993-2013



A total of 3235 research articles were available on ARMD in the ISI Web of Science during 1993-2013. These papers were drafted by 10,706 authors, 2332 institutions, and 67 countries and were published in 388 journals in 9 languages. Figure 1 demonstrates the growth rate of publications in this field (14.46% per year). The H-index of this subject was 125.

Citation Profile of Articles

The total LCS citations were 29,924 in number and GCS citations were 91,840 in number. The average citation per paper (C/P) was 28.39

Table 1 shows the articles that were cited 100 or more times. Figure 2 shows the trend of citations during the period. Appendix 1 shows the highly cited articles in this field. Figure 1 shows the histogram map of 20 years of research in this field.

Figure 3 shows the key words generating the highest citation bursts and the time periods associated with them. The key words associated with the highest citation bursts included: drusen, choroidal neovascular membranes, subfoveal neovascular membranes, neovascularization, subretinal neovascularization, blindness, fluorescein angiography, retinal pigment epithelium, choroidal perfusion abnormality, indocyanine green angiography, dystrophy, Beaver dam eye, Bruch membrane change, angiography, neovascular membranes, radiation therapy, photocoagulation, videoangiography, indocyanine green videoangiography, occult choroidal neovascularization, choriocapillaris, teletherapy, retinitis pigmentosa, Stargardt disease, mutations, apolipoprotein E, subfoveal choroidal neovascularization, laser photocoagulation, genome-wide scan, susceptibility loci, verteporfin therapy, c-reactive protein, avastin, pegaptanib, ranibizumab, polypoidal choroidal vasculopathy, complement factor H, bevacizumab, optical coherence tomography, polymorphism, endothelial growth factor, and vascular endothelial growth factor.

Subject Analysis of the Most Highly Cited Documents

The most common topics of the top 10 highly cited papers were genetic epidemiology research (40%),

clinical study (surgical or pharmaceutical treatment) (50%), and epidemiologic study (10%) (Table 1). *Languages, Journal Subjects, and Author Profiles of Publications*

Most ARMD articles were in English (3068), followed by German (105) and French (47). In total, the articles were written in nine languages (English, German, French, Portuguese, Hungarian, Spanish, Polish, Serbian, and Slovene). Dr R. Klein, with 80 articles, had the largest number of publications in the field of ARMD research (Table 2). When analyzed based on the number of papers in ARMD, 8 out of top 10 journals were general medical journals (such as the New England Journal of Medicine) and the remaining were ophthalmology journals. But when the same calculation was made based on the citation number (TLCS), seven journals were general medical journals and three were ophthalmology journals. When analyzed based on TGCS, highly cited papers were mostly published in general medical journals (80%), and the remaining 20% were published in Ophthalmology journals (Tables 3). No correlation was found between the impact factor of the most highly influential journals in this field and the total citations they had received for their papers in the field of ARMD.

A majority of the top 10 universities and institutions in the list are from the United States and Australia. The first two of them are the Johns Hopkins University and University of Melbourne in terms of number of documents and Harvard University and University of Wisconsin in terms of number of citations (Table 4).

Geographical Distribution

In general, 67 countries contributed to the promotion of the field of ARMD by publishing articles. The United States, Germany, and the UK had the highest number of documents but they had the highest number of citations to their research papers in the field of ARMD (Table 5).

**Table 1. Articles With Highest Number of Citations**

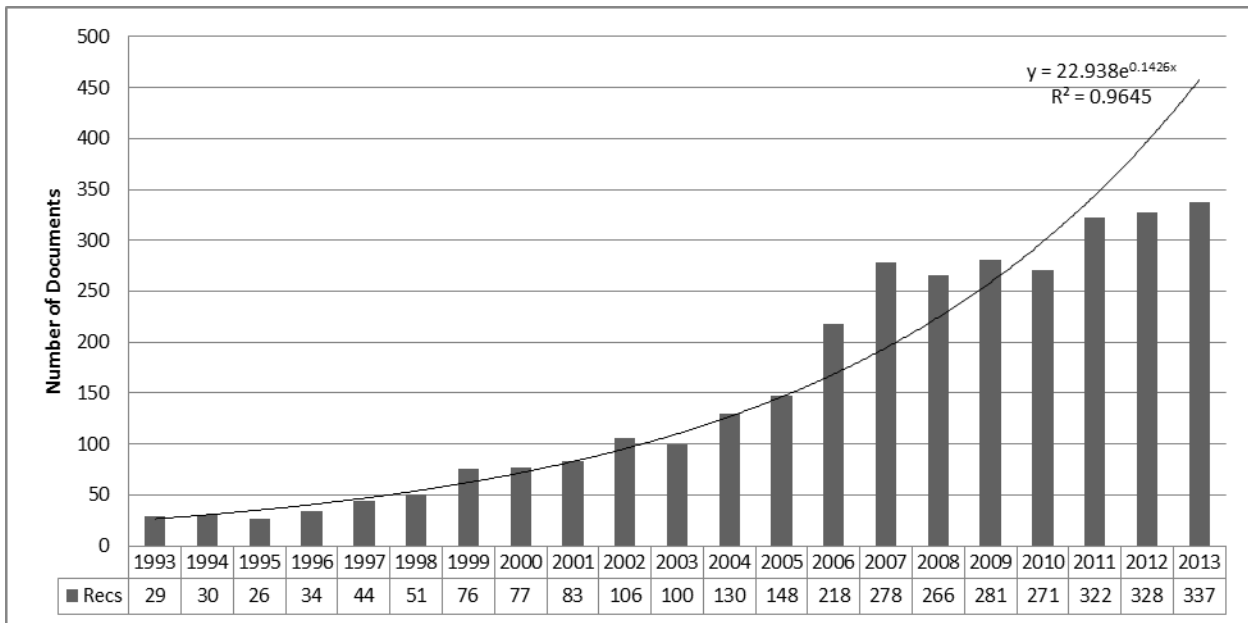
#	<u>Author/ Title / Journal</u>	CITATION
1	Klein Rj, Zeiss C, Chew Ey, Tsai Jy, Sackler Rs, Et Al. Complement Factor H Polymorphism In Age-Related Macular Degeneration Science. 2005 Apr 15; 308 (5720): 385-389	1814
2	Rosenfeld Pj, Brown Dm, Heier Js, Boyer Ds, Kaiser Pk, Et Al. Ranibizumab For Neovascular Age-Related Macular Degeneration New England Journal Of Medicine. 2006 Oct 5; 355 (14): 1419-1431	1662
3	Edwards Ao, Ritter R, Abel Kj, Manning A, Panhuysen C, Et Al. Complement Factor H Polymorphism And Age-Related Macular Degeneration Science. 2005 Apr 15; 308 (5720): 421-424	1173
4	Brown Dm, Kaiser Pk, Michels M, Soubrane G, Heier Js, Et Al. Ranibizumab Versus Verteporfin For Neovascular Age-Related Macular Degeneration New England Journal Of Medicine. 2006 Oct 5; 355 (14): 1432-1444	1161
5	Haines Jj, Hauser Ma, Schmidt S, Scott Wk, Olson Lm, Et Al. Complement Factor H Variant Increases The Risk Of Age-Related Macular Degeneration Science. 2005 Apr 15; 308 (5720): 419-421	1148
6	Gragoudas Es, Adamis Ap, Cunningham Et, Feinsod M, Guyer Dr Pegaptanib For Neovascular Age-Related Macular Degeneration New England Journal Of Medicine. 2004 Dec 30; 351 (27): 2805-2816	1146
7	Kassoff A, Kassoff J, Buehler J, Eglow M, Kaufman F, Et Al. A Randomized, Placebo-Controlled, Clinical Trial of High-Dose Supplementation With Vitamins C And E, Beta Carotene, And Zinc For Age-Related Macular Degeneration And Vision Loss - Areds Report No. 8 Archives Of Ophthalmology. 2001 Oct; 119 (10): 1417-1436	1081
8	Bressler Nm Photodynamic Therapy Of Subfoveal Choroidal Neovascularization In Age-Related Macular Degeneration With Verteporfin - One-Year Results Of 2 Randomized Clinical Trials - Tap Report 1 Archives Of Ophthalmology. 1999 Oct; 117 (10): 1329-1345	1021
9	Friedman Ds, O'colmain B, Tomany Sc, Mccarty C, De Jong Ptv, Et Al. Prevalence Of Age-Related Macular Degeneration In The United States Archives Of Ophthalmology. 2004 Apr; 122 (4): 564-572	970
10	Hageman Gs, Anderson Dh, Johnson Lv, Hancox Ls, Taiber Aj, Et Al. A Common Haplotype In The Complement Regulatory Gene Factor H (Hf1/Cfh) Predisposes Individuals To Age-Related Macular Degeneration Proceedings Of The National Academy Of Sciences Of The United States Of America. 2005 May 17; 102 (20): 7227-7232	929



Table 2. Most Active Authors in the Field of ARMD Research

#	Author	Recs	TLCS	TGCS
1	Klein R	80	2405	6370
2	Bressler Nm	76	3639	10146
3	Mitchell P	63	1300	3350
4	Soubrane G	60	1202	3152
5	Seddon Jm	58	2269	6377
6	Schmidt-Erfurth U	56	1511	4504
7	Holz Fg	55	550	2187
8	Guymer Rh	52	310	855
9	Wong Ty	52	422	1004
10	Bressler Sb	48	2546	6735

Figure 1. Annual Number of Published Papers



The growth rate of 14.6% in the article numbers was observed.



Table 3. Journals with Highest Number of Papers in This Field

#	Journal	Records	Citation	2 year IF	5 year IF
1	Ophthalmology	289	12624	5.563	5.777
2	Investigative Ophthalmology & Visual Science	274	7421	3.441	3.730
3	American Journal Of Ophthalmology	232	8043	3.631	4.292
4	Retina-The Journal Of Retinal And Vitreous Diseases	225	3933	2.825	2.761
5	British Journal Of Ophthalmology	198	4462	2.725	3.023
6	Archives Of Ophthalmology	166	13369	3.826	4.160
7	Graefes Archive For Clinical And Experimental Ophthalmology	125	2550	1.932	2.037
8	Eye	97	1015	1.818	1.883
9	Molecular Vision	73	1210	1.987	2.311
10	Acta Ophthalmologica	65	408	2.345	2.428
11	Ophthalmologica	57	503	1.412	1.236
12	Klinische Monatsblätter Fur Augenheilkunde	49	197	0.699	0.473
13	Ophthalmologe	48	295	0.529	0.681
14	European Journal Of Ophthalmology	46	296	0.912	0.963
15	Journal Francais D Ophtalmologie	45	112	0.438	0.443
16	Japanese Journal Of Ophthalmology	43	234	1.274	1.488
17	PLose One	43	493	3.730	4.244
18	Ophthalmic Surgery Lasers & Imaging	39	634	1.464	0.922
19	Canadian Journal Of Ophthalmology-Journal Canadien D Ophtalmologie	38	398	1.145	1.320
20	Clinical And Experimental Ophthalmology	28	291	1.964	2.047



Table 4. Institutions with Highest Number of Papers

#	Institution	Records	Citations
1	Johns Hopkins Univ	130	7472
2	Univ Melbourne	125	3103
3	Harvard Univ	117	9211
4	Duke Univ	97	4450
5	Univ Wisconsin	97	6462
6	Nei	86	6282
7	Univ Sydney	79	3584
8	Moorfields Eye Hosp	73	2029
9	Univ Penn	73	3241
10	Univ Southern Calif	68	1737
11	Univ Heidelberg	64	1960
12	Univ Miami	57	5242
13	UCL	54	1273
14	Univ Paris 12	53	2140
15	Natl Univ Singapore	51	809
16	Univ Cologne	50	1054
17	Univ Utah	49	2540
19	Univ Iowa	48	3215
20	Univ Bonn	47	1190

DISCUSSION

We analyzed the subject of highly cited papers, dividing them into two broad categories: epidemiology versus clinical research and translational versus basic science research (Appendix 1). Most of the highly cited papers were genetic epidemiology or clinical reports. Although ARMD is a debilitating disease and adversely affects the quality of life and emotional status of subjects, highly cited papers had largely neglected this subject. Highly

cited reports also addressed the following subjects more frequently: (1) association of various genotypes with ARMD, (2) chemotherapy for wet ARMD, including the intravitreal treatment, and (3) effect of diet and vitamins on ARMD. Recently, as Appendix 2 shows, there has been a trend toward more applicable genetic epidemiology and translational research (biomarkers). In cluster analysis for the citations, we found the following three major clusters in the citation histogram map (Figure 1): (1) complement H factor polymorphism in the ARMD (nodes 831, 832, 833, and 842 in the index 1), (2) treatment of subfoveal choroidal neovascularization in ARMD (nodes 386, 402, and 428), and (3) ranibizumab treatment for neovascular ARMD (nodes 1116 and 1117).

Table 5. Countries With Highest Number of Papers in the Field of ARMD

#	Country	Recs	CITATION
1	USA	1338	60915
2	Germany	363	8968
3	UK	340	9990
4	Australia	215	6031
5	Japan	193	3740
6	France	163	4862
7	Peoples R China	144	2486
8	Italy	120	1842
9	Austria	112	3371
10	Unknown	105	2707
11	Canada	97	3205
12	Switzerland	92	2959
13	Netherlands	74	4699
14	Spain	65	1184



Figure 3. Citation Burst Analysis

Keywords	Strength	Begin	End	1992 - 2014
Drusen	12.2823	1992	1998	
Choroidal neovascular membranes	11.1771	1992	2002	
Subfoveal neovascular membranes	4.9606	1992	2001	
Neovascularization	4.4565	1992	2002	
Subretinal neovascularization	4.4497	1992	2005	
Blindness	4.2906	1992	2004	
Fluorescein angiography	4.0001	1992	2000	
Retinal-pigment epithelium	16.5474	1994	2002	
Choroidal perfusion abnormality	3.746	1994	2002	
Indocyanine green angiography	3.6439	1994	2003	
Dystrophy	9.0779	1995	2002	
Beaver dam eye	8.3643	1995	2001	
Bruch membrane change	6.4945	1995	2004	
Angiography	5.8675	1995	2000	
Neovascular membranes	3.3267	1995	2000	
Radiation-therapy	14.3348	1996	2001	
Photocoagulation	9.7554	1996	2004	
Videoangiography	9.2262	1996	2003	
Indocyanine-green videoangiography	5.4875	1996	2002	
Occult choroidal neovascularization	3.5868	1996	1997	
Choriocapillaris	3.5137	1996	2003	
Teletherapy	7.591	1997	2004	
Retinitis-pigmentosa	9.5991	1998	2003	
Stargardt-disease	8.4595	1999	2004	
Mutations	5.4898	1999	2002	
Apolipoprotein-e	4.587	2001	2005	
Subfoveal choroidal neovascularization	16.8328	2003	2006	



Laser photocoagulation	13.8898	2003	2005	
Genomewide-scan	6.2849	2004	2006	
Susceptibility loci	8.7481	2005	2007	
Verteporfin therapy	13.1273	2006	2009	
c-reactive protein	4.2676	2006	2008	
Avastin	15.7886	2008	2010	
Pegaptanib	5.9235	2008	2010	
Ranibizumab	39.5427	2010	2014	
Polypoidal choroidal vasculopathy	7.0762	2010	2014	
Complement factor-h	5.5849	2010	2011	
Bevacizumab	19.7189	2011	2014	
Optical coherence tomography	13.2565	2011	2014	
Polymorphism	3.7394	2012	2012	
Endothelial growth-factor	3.5527	2012	2012	
VEGF	5.228	2013	2014	

Several lines of research have been previously identified as priorities in ARMD research. These include temporal patterns and changing the prevalence of ARMD; improvements of ocular imaging (eg, high-resolution OCT) to allow better phenotype classification of both early and late ARMD; and epidemiologic studies to determine gene-environment interactions for ARMD to identify early modifiable risk factors to prevent ARMD (12). According to the results of our study, several of these areas do not receive enough attention from the experts in the field, and better research strategies should be implemented.

In conclusion, the result of our report as the first scientometric analysis of the research on ARMD can be used as a guideline for authors, researchers, and policy makers to determine the best ways to allocate their financial and workforce resources.

DISCLOSURE

The authors report no conflicts of interest in this work.

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Appendix-1: Top most cited articles in the past 20 years. The numbers before the article indicate the location of the article on the histogram map.

#	Author / Title/ Journal	Citation
1	831 Klein RJ, Zeiss C, Chew EY, Tsai JY, Sackler RS, et al. Complement factor H polymorphism in age-related macular degeneration SCIENCE. 2005 APR 15; 308 (5720): 385-389	1814
2	1116 Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, et al. Ranibizumab for neovascular age-related macular degeneration NEW ENGLAND JOURNAL OF MEDICINE. 2006 OCT 5; 355 (14): 1419-1431	1662
3	833 Edwards AO, Ritter R, Abel KJ, Manning A, Panhuysen C, et al. Complement factor H polymorphism and age-related macular degeneration SCIENCE. 2005 APR 15; 308 (5720): 421-424	1173
4	1117 Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration NEW ENGLAND JOURNAL OF MEDICINE. 2006 OCT 5; 355 (14): 1432-1444	1161
5	832 Haines JL, Hauser MA, Schmidt S, Scott WK, Olson LM, et al. Complement factor H variant increases the risk of age-related macular degeneration SCIENCE. 2005 APR 15; 308 (5720): 419-421	1148
6	786 Gragoudas ES, Adamis AP, Cunningham ET, Feinsod M, Guyer DR Pegaptanib for neovascular age-related macular degeneration NEW ENGLAND JOURNAL OF MEDICINE. 2004 DEC 30; 351 (27): 2805-2816	1146
7	428 Kassoff A, Kassoff J, Buehler J, Eglow M, Kaufman F, et al. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss - AREDS Report No. 8 ARCHIVES OF OPHTHALMOLOGY. 2001 OCT; 119 (10): 1417-1436	1081
8	270 Bressler NM Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin - One-year results of 2 randomized clinical trials - TAP report 1 ARCHIVES OF OPHTHALMOLOGY. 1999 OCT; 117 (10): 1329-1345	1021
9	689 Friedman DS, O'Colmain B, Tomany SC, McCarty C, de Jong PTVM, et al. Prevalence of age-related macular degeneration in the United States ARCHIVES OF OPHTHALMOLOGY. 2004 APR; 122 (4): 564-572	970
10	842 Hageman GS, Anderson DH, Johnson LV, Hancox LS, Taiber AJ, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. 2005 MAY 17; 102 (20): 7227-7232	929
11	58 SEDDON JM, AJANI UA, SPERDUTO RD, HILLER R, BLAIR N, et al. DIETARY CAROTENOIDS, VITAMIN-A, VITAMIN-C, AND VITAMIN-E, AND ADVANCED AGE-RELATED MACULAR DEGENERATION JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION. 1994 NOV 9; 272 (18): 1413-1420	762
12	386 Blumenkranz MS, Bressler NM, Potter MJ, Bressler SB, Mones JM, et al. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin - Two-year results of 2 randomized clinical trials - TAP report 2 ARCHIVES OF OPHTHALMOLOGY. 2001 FEB; 119 (2): 198-207	737
13	988 Avery RL, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration OPHTHALMOLOGY. 2006 MAR; 113 (3): 363-372	654
14	402 Arnold J, Kilmartin D, Olson J, Neville S, Robinson K, et al. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: Two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization-verteporfin in photodynamic therapy report 2 AMERICAN JOURNAL OF OPHTHALMOLOGY. 2001 MAY; 131 (5): 541-560	570
15	156 Allikmets R, Shroyer NF, Singh N, Seddon JM, Lewis RA, et al. Mutation of the Stargardt disease gene (ABCR) in age-related macular degeneration SCIENCE. 1997 SEP 19; 277 (5333): 1805-1807	521
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18	545 Crabb JW, Miyagi M, Gu XR, Shadrach K, West KA, et al. Drusen proteome analysis: An approach to the etiology of age-related macular degeneration PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. 2002 NOV 12; 99 (23): 14682-14687	454
19	103 Kvanta A, Algvere PV, Berglin L, Seregard S Subfoveal fibrovascular membranes in age-related macular degeneration express vascular endothelial growth factor INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE. 1996 AUG; 37 (9): 1929-1934	427
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Appendix-2: Top most cited articles (past 3 years)

#	Date / Author / Journal	GCS
1	Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, et al. Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration The CATT Research Group NEW ENGLAND JOURNAL OF MEDICINE. 2011 MAY 19; 364 (20): 1897-1908	387
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