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Trends in Research Payments for Diabetic Macular Edema from 2015 to 2021

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Purpose: To evaluate characteristics of research payments for diabetic macular edema (DME) studies and correlations to current management trends.

Design: Retrospective cross-sectional study.

Subjects: Research payments for DME.

Methods: Studies with keywords of "diabetic macular edema" or "DME" in the title were extracted from the Centers of Medicare & Medicaid Services Open Payments database from 2015 to 2021. Recipients, payors, and payment amounts were identified. Industry funding was compared with public research funding by the National Eye Institute (NEI).

Main Outcome Measures: Trends and total value of industry and public fundings for DME from 2015 to 2021.

Results: From 2015 to 2021, 451 beneficiaries received 6062 industry payments for a total of $120 148 997.41 for DME-related research. The total value of industry funding increased from $8 225 859.08 in 2015 to $50 092 778.45 in 2021. Of the 6062 industry payments, 5367 (88.5%) were reported by male recipients compared with 695 (11.5%) female beneficiaries. Payments to female recipients increased from 60 (7.1%) in 2015 to 335 (13.7%) in 2021. In comparison, public funding for DME-related research from the NEI was comprised of $18 863 266.00 to 17 principal investigators from 2015 to 2021. The total value of public funding increased from $973 590.00 in 2015 to $3 354 376.00 in 2021. Of 59 public research payments, 46 (78.0%) were reported by male recipients and 13 (22.0%) by female recipients. Payments to female recipients increased from 1 (25.0%) in 2015 to 3 (30.0%) in 2021. The most highly invested product by industry were anti-VEGF agents, accounting for $89 955 595.20 (74.9%) of total payment value.

Conclusions: There was an increase in both industry and public-sponsored funding for DME-related research from 2015 to 2021. There seemed to be a possible discrepancy in both industry and public funding based on sex for DME studies during the study period.

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Supplemental material available at www.ophthalmologyscience.org.

Industry investments in ophthalmology research have increased over the past few decades, corresponding with significant advancements in ophthalmic therapies.[1] Biotechnology Innovation Organization reported that therapeutic company venture funding in ophthalmology increased from $330 000 000 in 2015 to $1 542 000 000 in 2021.[2] Numerous recent studies have analyzed trends in venture capital, private equity investment, and government funding for ophthalmology research.[3–5]

In 2015, the United States Centers of Medicare & Medicaid Services (CMS) launched the Open Payments Database (OPD) to increase transparency in financial payments between drug and medical device manufacturers and health care providers.[6] Open Payments Database reports payments for research, consulting fees, meals, gifts, and travel. A recent cross-sectional study examining characteristics of industry payments for ophthalmology research in OPD found that industry funding significantly increased by 203% from $62 924 525 in 2014 to $190 714 508 in 2020.[1]

Diabetic macular edema (DME) is one of the most serious complications of diabetes mellitus (DM) that contributes to preventable blindness. Given recent advancements in pharmaceutical therapies for DME, we examined trends and characteristics of industry-sponsored funding and investments for DME-related therapies using OPD. A secondary aim of this study was to compare industry funding with public funding for DME-related research from the National Eye Institute (NEI). Based on the increasing number of research publications in ophthalmology,[7] we hypothesized that funding for DME-related research,

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particularly anti-VEGF therapy, increased during this time period.

Methods

This investigation was a retrospective cross-sectional study using the CMS OPD and the National Institutes of Health database, adhering to the Declaration of Helsinki. Because data were publicly available, and no patient identifying information were utilized, this study was exempt from the Mayo Clinic institutional review board. The OPD database provides payment information in 3 categories: general payments such as consulting fees, travel and food, research payments, and ownership information.[6] The date of the last search was December 2022, and there was no language restriction. In a previous study for ophthalmology-related industry-sponsored research funding using the OPD from 2013 to 2014,[8] only general payments and ownership information were utilized. In this analysis, research payments without indirect payments for DME-related studies were considered from 2015 to 2021. Further breakdown of research payments was not provided in the database. Among reported payments, DME-related studies were identified using the keywords "diabetic macular edema" or "DME" in the name of the study and product therapeutic area. Extracted data were further filtered for ophthalmic purposes only. Data obtained included recipient, payor (e.g., pharmaceutical company), total amount, payment date, drug name, project name, and brief description of study. The sex of the recipients was added after manual web search of the principal investigator's (PI's) name. After identifying the ophthalmologists who received the top 25% of the payment value in the extracted data, their clinical drug usage in 2020 was obtained using the National Provider Identifier CMS Program Use & Payments database's "Medicare Physician & Other Practitioners − by Provider and Service" tool to investigate associations between industry funding recipients of research payments and clinical prescribing patterns.[9]

Public funding data from the NEI were also extracted for DME-related research. Using the National Institute of Health's "RePORTER" tool,[10] we extracted any projects that included the keywords "diabetic macular edema" or "DME" in the title, terms, or abstracts under ophthalmology department for fiscal years 2015 to 2021. The date of the last search was February 2023, and there was no language restriction. Data included project term, title, description, project number, PI, PI sex, fiscal year, total cost, and funding source. After manual review of descriptions of each project, 1 project was excluded due to inaccurate auto-extraction as the study was evaluating retinal dysfunction in Alzheimer's disease mouse models and not DME.

Total payments were calculated for all identified studies and per PI for each year and the rate of change of all subjects of interest over the 7-year study period. Characteristics were assessed for leading recipients, manufacturers (payors), and distribution of funds. Central tendencies and statistical dispersion were reported by medians and interquartile ranges (IQRs), respectively. Statistical analysis was comprised of linear regression for trend analysis and Mann−Whitney U Test for comparison of industry and public funding. A significance level of P value of < 0.05 was considered statistically significant. Microsoft Excel, version 16.70 (Microsoft Corporation) was used for data analysis.

Results

From 2015 to 2021, 451 beneficiaries received 6062 industry research payments for DME-related research for a total of $120 148 997.41 (Table 1). The mean value per reported industry payment was $19 820.03 (median: $5 815.03, IQR: $1649.35−$18 147.50). The total value increased from $8 225 859.08 in 2015 to $50 092 778.45 in 2021 ($P = 0.04$). However, the total value decreased in 2016 ($4 153 891.19) and 2018 ($1 995 414.30) (Fig 1). Of 6062 industry research payments, 5367 (88.5%) were reported by male recipients and 695 (11.5%) by female recipients. Payments to female recipients increased from 60 (7.1%) in 2015 to 335 (13.7%) in 2021 (Fig 2). The mean value of industry funding per physician was $266 405.76 (median: $88 480.78, IQR: $15 973.55−$275 549.12). Of 451 recipients, the top 25% payment values were received by 9 beneficiaries (2.0%), which accounted for $29 757 055.42 in total and > 2 million dollars each, whereas the bottom 25% payment values were received by 258 beneficiaries, which accounted for $29 994 525.63 with an average of $83 783.59. Of note, the highest-paid recipients received $6 599 771.29 across all years. Meanwhile, 185 recipients (41.1%) received $103 123.29 to $999 468.66 (48.7%), and 238 recipients (52.8%) received $30.00 to $99 790.55 (6.0%). Recipients of industry funding for DME-related research were in 43 states of the United States in OPD. The mean value of payments per state was $2 794 162.73 (median: $1 325 955.79, IQR: $485 400.54−$3 339 240.30). Texas (20.3%, $24 381 311.31), California (13.5%, $16 170 277.95), and Florida (10.3%, $12 385 274.92) received the most payments, accounting for 44.1% of the total payment value. When analyzed by recipient affiliation, there were 413 private clinics (77.5%), 70 academic institutions (13.1%), and 50 research centers (9.4%). Of 6061 total payments, 318 (5.2%) were missing their affiliations. Total payment values were $98 157 420.74 (81.7%) for private clinics, $12 826 873.52 (10.7%) for academic institutions, $8 372 046.81 (7.0%) for research centers, and $792 656.34 (0.7%) not reported.

In comparison, 17 PIs received 59 public research payments for a total of $18 863 266.00 for DME-related from the NEI from 2015 to 2021 (Table 1). The mean value per reported payment was $319 716.37 (median: $358 411.00, IQR: $230 005.50−$408 828.50). The total value of public funding increased from $973 590.00 in 2015 to $3 354 376.00 in 2021 ($P = 0.01$) (Fig 1). Of 59 public research payments, 46 (78.0%) were reported by male recipients and 13 (22.0%) by female recipients. Payments to female recipients increased from 1 (25.0%) in 2015 to 3 (30.0%) in 2021 (Fig 3). The mean value of the public funding per PI across all years was $1 109 603.88 (median: $825 896.00, IQR: $714 210.00−$825 896.00). The top 2 PIs (11.8%) received 23.0% of total public funding ($4 332 130.00). Five PIs (29.4%) received $1 131 592.00 to $1 961 377.00 (43.5%), and 10 recipients (58.8%) received $96 696.00 to $902 782.00 (33.6%). By state, Maryland (19.0%, $3 697 571.00), Illinois (15.5%, $2 929 663.00), and Oregon (13.2%, $1 487 570.00) received the most payments, accounting for 48.3% of the total payment value. For public research funding, all payments were made to 15 academic institutions.

There were 62 industry-funded DME research studies from 2015 to 2021. The most invested product was anti-VEGF, accounting for 74.9% of total payments (Table 2).

Table 1. Characteristics of Industry and Public-Sponsored Payments for Diabetic Macular Edema Related Studies from 2015 to 2021

	Year	Payments, Number (%)	Payments, Dollars (%)	Mean Funding Per Payment (SD) in Dollars	Median Funding Per Payment (IQR) in Dollars	Total Recipients	Female, Number (%)	Male, Number (%)
Industry-sponsored payments	2015	851 (14.0)	8 225 859.08 (6.8)	9661.11 (27 712.7)	2153.90 (555.0–7108.4)	129	12 (9.3)	117 (90.7)
	2016	436 (7.2)	4 153 891.19 (3.5)	9527.27 (17 553.2)	4000.00 (678.1–9902.5)	135	12 (8.9)	123 (91.1)
	2017	810 (13.4)	11 245 503.53 (9.4)	13 883.34 (23 038.9)	5411.32 (768.2–16 771.3)	131	14 (10.7)	117 (89.3)
	2018	208 (3.4)	1 995 414.30 (1.7)	95 953.34 (21 534.6)	3505.00 (679.6–8842.5)	107	14 (13.1)	93 (86.9)
	2019	246 (4.1)	8 457 625.31 (7.0)	34 380.59 (99 214.7)	12 130.33 (1040.1–34 918.8)	134	22 (1.4)	112 (83.6)
	2020	1067 (17.6)	35 977 925.55 (29.9)	33 718.77 (93 685.3)	7480.00 (2917.5–22 145.0)	135	18 (13.3)	117 (86.7)
	2021	2444 (40.3)	50 092 778.45 (41.7)	20 496.23 (39 124.7)	7680.25 (2550.9–22 777.9)	285	40 (14.0)	245 (86.0)
	Total	**6062**	**120 148 997.41**	**19 820.03 (53 369.1)**	**5815.03 (1649.4–18 147.5)**	**451**	**68 (15.1)**	**383 (84.9)**
Public-sponsored payments	2015	4 (6.8)	973 590.00 (5.2)	243 397.50 (144 877.0)	346 813.00 (221 393.5–390 939.0)	4	1 (25.0)	3 (75.0)
	2016	6 (10.8)	1 656 982.00 (8.8)	276 163.67 (149 959.7)	358 411.00 (230 250.0–399 750.0)	6	1 (16.7)	5 (83.3)
	2017	7 (11.9)	2 380 179.00 (12.6)	340 025.57 (111 970.9)	341 800.00 (225 466.0–387 197.0)	7	1 (14.3)	6 (85.7)
	2018	9 (15.3)	3 216 910.00 (17.1)	357 434.44 (105 223.1)	370 471.00 (233 401.5–417 011.0)	9	1 (11.1)	8 (88.9)
	2019	9 (15.3)	2 832 676.00 (15.0)	314 741.78 (14 152.8)	355 118.50 (230 127.8–40 8633.3)	9	2 (22.2)	7 (77.8)
	2020	14 (23.7)	4 448 553.00 (23.6)	317 753.79 (132 613.5)	351 666.00 (227 613.5–393 876.0)	14	4 (28.6)	10 (71.4)
	2021	10 (17.0)	3 354 376.00 (17.8)	335 437.60 (90 193.0)	351 826.00 (229 761.0–399 750.0)	10	3 (30.0)	7 (70.0)
	Total	**59**	**18 863 266.00**	**319 716.37 (121 369.7)**	**358 411.00 (230 005.5–408 828.5)**	**17**	**5 (29.4)**	**12 (70.6)**

IQR = interquartile range; SD = standard deviation.

The highest-funded anti-VEGF products were ranibizumab (29.7%), manufactured by Genentech Inc, followed by brolucizumab (29.7%), manufactured by Novartis Pharmaceuticals Corporation, and aflibercept (15.4%), manufactured by Regeneron Pharmaceuticals Inc (Fig S4, available at www.ophthalmologyscience.org). Over all years, the total payment value of anti-VEGF drug studies increased from $5 825 468.12 in 2015 to $39 462 846.72 in 2021. The second and third-most invested products were faricimab, a novel combined mechanism agent inhibiting both VEGF and angiopoietin-2 manufactured by Genentech Inc ($17 117 317.16; 14.3%) and nesvacumab (anti−angiopoietin-2)/aflibercept ($9 154 261.91; 7.6%) manufactured by Regeneron Pharmaceuticals Inc. When analyzed by research studies, 47.5% of total payment values were reported from 2 clinical trials: "Investigation of delivery method for Ranibizumab"[11] (28.2%) and "Phase III study of efficacy and safety of Brolucizumab VS Aflibercept"[12] (19.3%). When analyzing the clinical billing/usage of the recipients of top 25% of the industry funding values for 2020 using the self-reported CMS Program Use & Payment database, ranibizumab 0.1-mg injection was the most frequently provided service (75.1%), followed by aflibercept 1-mg injection (15.5%) and brolucizumab 1-mg injection (3.2%), as shown in Table S3 (available at www.ophthalmologyscience.org).

In comparison, there were 20 publicly funded DME research studies. The top 3 publicly funded projects by total payment value were "Regulation of diabetic retinopathy by Nrf2,"[13] "Inflammatory Resolution and Vascular Restoration in Diabetic Retinopathy,"[14] and "Wide-field and projection-resolved OCT angiography in diabetic retinopathy,"[15] as shown in Table S4 (available at www.ophthalmologyscience.org).

Five drug manufacturers were identified via the OPD that invested in DME-related research. The largest payor was Genentech Inc ($53 300 773.71; 44.4%), the manufacturer of ranibizumab and faricimab (Table 5). The second greatest payor was Novartis Pharmaceuticals Corporation ($35 886 133.96; 29.9%), the manufacturer of brolucizumab and LKA651. Regeneron Pharmaceuticals Inc, the manufacturer of aflibercept and nesvacumab, was the third largest investor ($27 687 787.88; 23.0%).

Discussion

From 2015 to 2021, there was a 509% increase in total reported payment values for industry-funded DME research, consistent with expanding industry-sponsored research funding in ophthalmology overall.[1] However, there were lower industry payments for DME-related research in 2016 and 2018; these trends were most likely associated with the initiation, progress, and closure of related clinical trials.[11] Similarly, the steady increase from 2018 to 2021 was likely attributable to new clinical trials for each manufacturer's drug and the development of combination treatments, such as the investigation of the port delivery method for ranibizumab.[11]

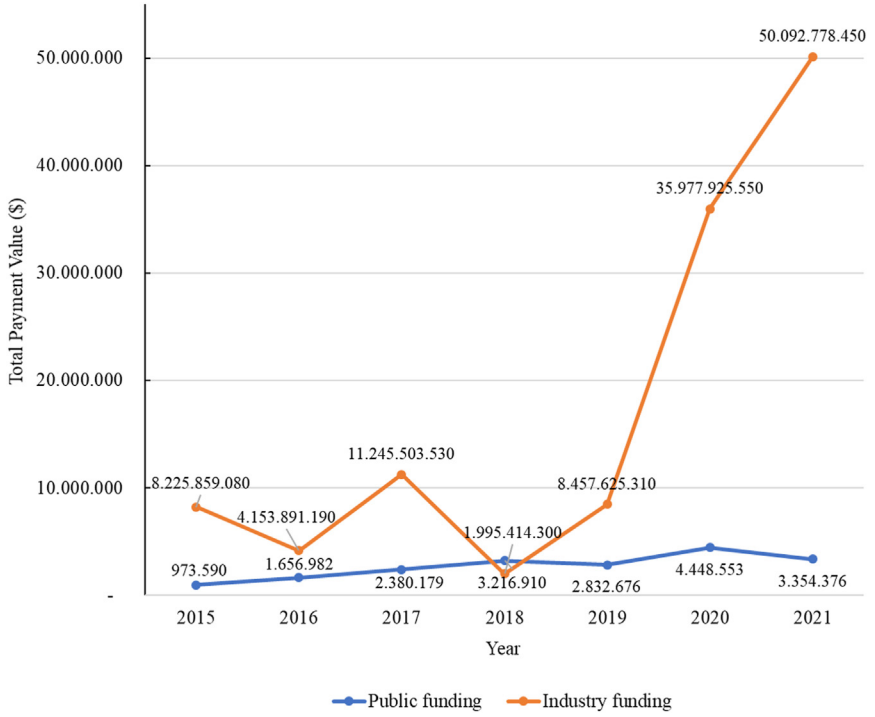

Figure 1. Total payment value of industry and public funding per year from 2015 to 2021. Total payment values of both industry and public-sponsored funding showed an overall increasing trend from 2015 to 2021. However, it also decreased intermittently in 2016 and 2018 for industry funding and in 2019 and 2021 for public funding. *P* value of linear regression was 0.04 for industry funding and 0.01 for public funding. The difference between the total payment value of industry and public funding was significant ($P = 0.02$).

For public funding for DME-related research from the NEI, there was a 245% increase from $973 590.00 in 2015 to $3 354 376.00 in 2021, similar to increasing payment trends of industry funding. However, the total value of public funding for DME was 6.4-times less compared with that of industry funding. Although there were 26.5 times more recipients in industry funding than in public funding, public funding recipients tended to receive higher values of the payments, corroborated by our findings that the mean value per recipient for public funding ($1 109 603.88) was 4.2 times greater than that of industry funding ($266 405.76). Moreover, the distribution of both industry and public funding were skewed, as the top 9 recipients (2.0%) received 24.8% of industry research payments ($29 757 055.42) and top 2 recipients (11.8%) received $4 332 130.00 (23.0%) of public funding. Similarly, a previous retrospective study of overall ophthalmology industry research payment trends using the OPD found that the top 10% of ophthalmologists reportedly received 65.7% of total funding.[1]

When further analyzed by sex, both industry and public research payments to male and female recipients increased during the study period, and sex-related discrepancies seemed consistent. Industry payments to males remarkably increased 908.2% from 208 in 2019 to 2097 in 2021, compared with 778.9% in female industry funding recipients, rising from 38 in 2019 to 334 in 2021. In comparison, public payments to both males and females demonstrated a consistent, stable increase in 2020 followed by a decrease in 2021. These findings suggest a more volatile trend in public funding compared with the significant and consistent growth observed in industry funding. Overall, male recipients received 7.7 times more payments than females in industry funding and 3.5 times more in public funding. In a cross-sectional study examining sex distribution in the San Francisco Match and the American Academy of Ophthalmology database from 2011 to 2019, 43.8% of residents and 42.5% of clinical faculty members were female.[16] Despite the comparable number of female and male ophthalmologists, significant sex disparity in research funding was evident. However, there was a 380% increase in industry payments and 200% in public payments to female recipients from 2015 to 2021, which may be attributed to career advancement and the increasing number of female investigators over the past decade, and this pattern was more evident in industry funding than public funding.[17,18] The sex-related trends in DME-related research funding observed in this study correlate to the sex distribution in publication authorship as well,[19] and a more proactive approach is needed to enhance female representation in both the clinical and research settings, especially in the PI role.

The majority of the industry-funded research payments were made to private clinics (81.7%), followed by academic institutions (10.7%), whereas all public research funding were granted to academic institutions. This can be attributed to the characteristics of the studies. Although most industry-

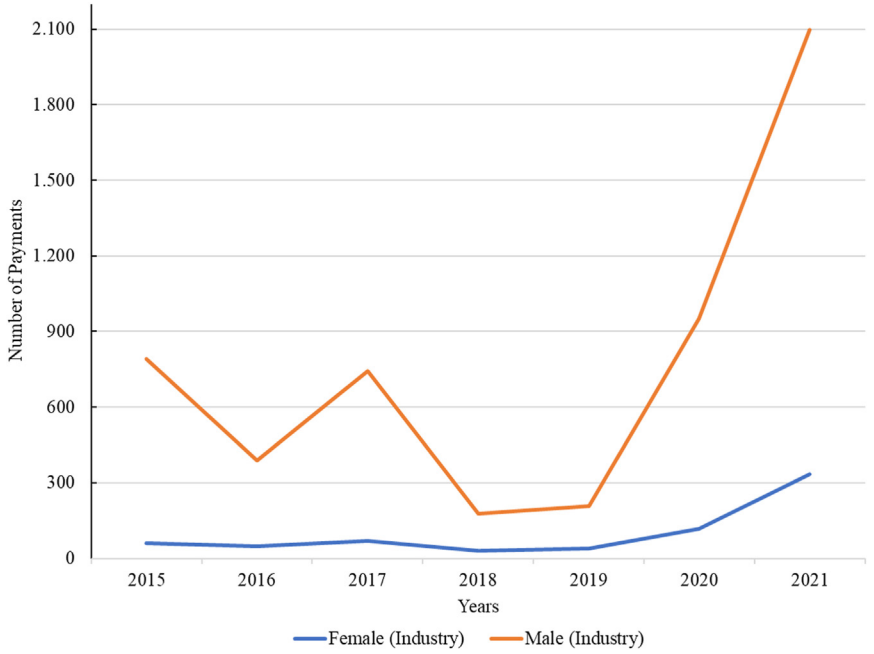

Figure 2. Reported research industry payment number for female and male recipients from 2015 to 2021. The total number of female and male recipients of industry-sponsored funding from 2015 to 2021 are plotted. Although there was fluctuating pattern from 2016 to 2019, the total number significantly increased by 2021. The difference between the number of female and male recipients was significant ($P = 0.04$).

funded research projects were efficacy and safety-related trials of manufacturers' drugs, which could take place in more common settings, such as private clinics, most publicly funded projects were basic science-related, specifically investigation of molecular mechanisms of DME, regulation and restoration of the blood−retina barrier, and imaging technology. These projects are more likely facilitated in academic institutions due to required resources and setting of the experiments. For example, the project that received the most public funding proposed to investigate the molecular basis for Nrf2's protective effect and the cellular context in diabetic retinopathy and DME as a potential therapeutic target.[20]

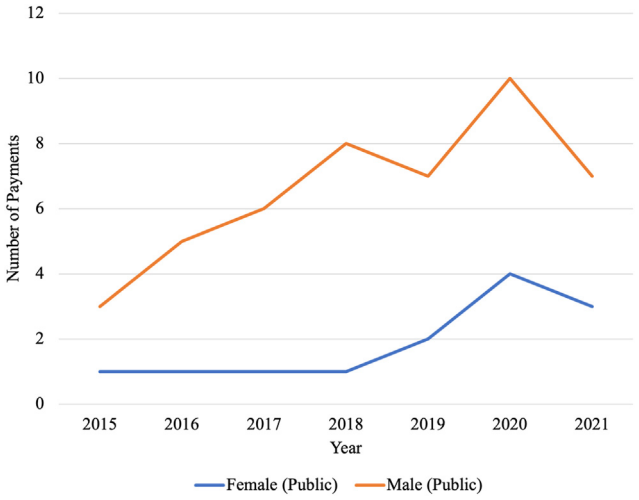

Figure 3. Reported research public payment number for female and male recipients from 2015 to 2021. The total number of female and male recipients of public-sponsored funding from 2015 to 2021 showed a gradually increasing trend. The difference between the number of female and male recipients was significant ($P = 0.001$).

When analyzed by state, the 3 highest payment-receiving states were Maryland, Illinois, and Oregon for public funding. As all public research funding was granted to academic institutions, these states are correlated with the location of the most payment-receiving organizations: Johns Hopkins University, University of Illinois at Chicago, Northwestern University at Chicago, and Oregon Health & Science University. In contrast, Texas, California, and Florida received the highest industry-funded research payments. Private practices, rather than academic institutions, received the highest industry-funded payments in these states. According to the CDC, the percentage of adults aged $\geq$ 18 years with diagnosed DM in Texas and Florida in 2018 were 12.0% and 10.5%, respectively, with the national average of 9.8%.[21] The high prevalence of DM in these states may have contributed to the high industry research payments to these states[21] or perhaps the presence of well-established retina practices with efficient clinical trial teams as well as high population in those states.

Intravitreal anti-VEGF injections are currently the first-line treatments for patients with DME. Similarly, most industry research payments (74.9%) in this retrospective study were for anti-VEGF therapy-related studies. Yearly trends of industry funding for each anti-VEGF treatment were heavily associated with the start and completion of its clinical trials. Studies of ranibizumab received the largest funding and had a substantial increase in payments in 2020

Table 2. Trend of Subject of Study in Reported Research Industry-Sponsored Payments from 2015 to 2021

Subject of Study	Years							
	2015 ($, %)	2016 ($, %)	2017 ($, %)	2018 ($, %)	2019 ($, %)	2020 ($, %)	2021 ($, %)	Total ($, %)
Anti-VEGF	**5 825 468.12 (70.8)**	**393 157.00 (9.5)**	**248 173.90 (2.2)**	**1 159 957.55 (58.1)**	**8 010 077.26 (94.7)**	**34 855 914.65 (96.9)**	**39 462 846.72 (78.8)**	**89 955 595.20 (74.9)**
Ranibizumab	1 571 819.02 (19.1)	101 426.00 (2.4)	—	127 440.00 (6.4)	—	10 899 000.82 (30.3)	23 016 104.88 (45.9)	35 715 790.72 (29.7)
Brolucizumab	—	—	—	780 736.43 (39.1)	7 733 019.98 (91.4)	23 076 468.06 (64.1)	4 103 354.04 (8.2)	35 693 578.51 (29.7)
Aflibercept	4 253 649.10 (51.7)	291 731.00 (7.0)	248 173.90 (2.2)	251 781.12 (12.6)	277 057.28 (3.3)	880 445.77 (2.4)	12 330 687.80 (24.6)	18 533 525.97 (15.4)
Faricimab	—	**1 352 989.86 (32.6)**	**4 554 855.95 (40.5)**	**431 582.51 (21.6)**	**1797.00 (0.0)**	**484 623.16 (1.3)**	**10 291 468.68 (20.5)**	**17 117 317.16 (14.3)**
Nesvacumab + Aflibercept	**389 450.43 (4.7)**	**2 207 089.96 (53.1)**	**6 247 038.23 (55.6)**	**244 911.24 (12.3)**	**65 772.05 (0.8)**	—	—	**9 154 261.91 (7.6)**
Abicipar-Pegol	**1 525 498.93 (18.5)**	**124 569.92 (3.0)**	—	—	—	—	—	**1 650 068.85 (1.4)**
RO7200220	—	—	—	**17 510.00 (0.9)**	**123 838.10 (1.5)**	**616 722.84 (1.7)**	**302 507.01 (0.6)**	**1 060 577.95 (0.9)**
Dexamethasone	**485 441.60 (5.9)**	**18 991.00 (0.5)**	**7500.00 (0.1)**	—	**192 082.40 (2.3)**	**20 454.90 (0.1)**	**34 080.00 (0.1)**	**758 549.90 (0.6)**
Nonpharmacologic study	—	—	—	**141 453.00 (7.1)**	**59 648.50 (0.7)**	—	**1874.24 (0.0)**	**202 975.74 (0.2)**
LKA651	—	—	**187 935.45 (1.7)**	—	**4410 (0.1)**	**210.00 (0.0)**	—	**192 555.45 (0.2)**
PF-04634817	—	**57 093.45 (1.4)**	—	—	—	—	—	**57 093.45 (0.1)**
Unspecified multiple anti-VEGFs	—	—	—	—	—	—	**12 701.80 (0.0)**	**12 701.80 (0.0)**
Total	**8 225 859.08**	**4 153 891.19**	**11 245 503.53**	**1 995 414.30**	**8 457 625.31**	**35 977 925.55**	**50 092 778.45**	**120 148 997.41**

and 2021 when Genentech expanded a new port delivery study.[11] Moreover, based on the self-reported CMS Program Use & Payment database, ranibizumab injection was the most frequently used clinical treatment by the recipients of the top 25% industry payments in 2020, although each usage was not specified for its indication. It is difficult to assess the impact of physician financial incentives on choice of anti-VEGF agent; transparency of potential conflicts of interest is paramount and should be discussed with patients before treatment.[22] Aflibercept was another heavily studied DME pharmacotherapy. Most industry payments for aflibercept in 2015 were part of the VISTA and VIVID trials, which demonstrated the superiority of aflibercept over macular laser photocoagulation.[23] Furthermore, aflibercept was frequently used as a comparator drug in several clinical studies conducted by other manufacturers. More recently, there was an expansion of trials evaluating the efficacy and safety of high dose aflibercept, which led to a 287.8% increase in payments in 2020 compared with the previous year and an additional 92.9% increase in payments in 2021. Brolucizumab is an anti-VEGF therapy that was recently approved by the Food and Drug Administration in 2022. In this study, brolucizumab was the second-most invested drug, and the payments significantly increased every year since 2018 as Novartis launched a clinical trial of brolucizumab in comparison to aflibercept. However, due to higher rates of intraocular inflammation in the brolucizumab group, it was less preferably used in clinical practice compared with other anti-VEGF agents.[24] Lastly, faricimab, a new anti-VEGF/anti−angiopoietin-2 agent developed from 2016 to 2021, was the fourth-most invested drug in our analysis. Faricimab showed noninferiority to aflibercept in the YOSEMITE and RHINE studies, and eyes receiving faricimab had visual and anatomic improvement with adjustable dosing up to every 12 to 16 weeks for DME, allowing for longer injection intervals for patients.[25] Similarly, the increasing trend of anti-VEGF therapy-related studies is also evident in overall ophthalmology research as funding increased 268.7% from 2014 to 2020.[1]

Other management options for DME include corticosteroids and laser photocoagulation. Corticosteroid injection is a second-line DME treatment and accounted for 0.7% of total industry payments[26]; payments were for multiple short-term studies of dexamethasone intravitreal implant (both monotherapy and combination therapy with aflibercept) and triamcinolone acetonide in combination with laser photocoagulation in 2019 and 2020. Lastly, in this study, no payments were made for laser photocoagulation as monotherapy.[23,27]

There were several limitations of this study. The OPD is a collection of data based on industry self-reporting and only includes companies producing products that are covered by government-sponsored programs such as CMS according to the Sunshine Act.[28] Thus, data were likely underreported and only account for a portion of the total industry−physician financial transactions. To analyze research payments only, other general or indirect payments such as consulting fees, travel, and food were excluded. Additionally, the further breakdown of research payment

Table 5. Manufacturers of Study Subject Reporting Research Industry Payments from 2015 to 2021

Manufacturers of Study Subject	Payment Number (%)	Payment Value in Dollars (%)
Genentech, Inc	**2847 (50.0)**	**53 300 773.71** (44.4)
Ranibizumab	1438 (23.7)	34 907 201.06 (29.1)
Faricimab	196 (21.4)	17 117 317.16 (14.3)
RO7200220	102 (1.7)	1 060 577.95 (0.9)
Nonpharmacologic study	4 (0.1)	202 975.74 (0.2)
Unspecified multiple anti-VEGFs	7 (0.1)	12 701.80 (0.0)
Novartis Pharmaceuticals Corporation	**514 (8.5)**	**35 886 133.96 (29.9)**
Brolucizumab	496 (8.2)	35 693 578.51 (29.7)
LKA651	18 (0.3)	192 555.45 (0.2)
Regeneron Pharmaceuticals, Inc	**2132 (35.2)**	**27 687 787.88 (23.0)**
Aflibercept	1322 (21.8)	18 533 525.97 (15.4)
Nesvacumab/Aflibercept	810 (13.4)	9 154 261.91 (7.6)
Allergan Inc	**409 (6.8)**	**2 408 618.75 (2.0)**
Abicipar-Pegol	309 (5.1)	1 650 068.85 (1.4)
Dexamethasone	100 (1.7)	758 549.90 (0.6)
Pfizer Inc	**160 (2.6)**	**865 683.11** (0.7)
Ranibizumab	152 (2.5)	808 589.66 (0.7)
PF-04634817	8 (0.1)	57 093.45 (0.1)
Total	**6062**	**120 148 997.41**

was not reported, and information on the actual usage of the payments was limited. Moreover, some data entries were incomplete, such as recipient sex and organization/affiliation. As a result, some project descriptions were truncated, and manual search for the full description was needed to complete the data analysis. For missing or incorrect data in the OPD, reported physicians can review and update possible errors, but revised data were unknown.[29] Lastly, industry payments were oftentimes assigned to a single representing physician in a private practice or academic institution, and further distribution within the institution could not be identified, which likely contributed to the skewed distribution of the payments in this study and overestimation of payments for a single physician instead of the actual payment distribution within the practices.[1]

In summary, ophthalmologists received a total of $120 148 997.41 of industry funding for DME-related research from 2015 to 2021, and industry funding tremendously increased during this study period. This pattern was supported by the development of several novel anti-VEGF injections and further expansion of clinical trials of existing pharmacotherapy, which correlated to the utilization of anti-VEGF as the first-line treatment of DME in clinical practice. In comparison, public funding was overall less than industry funding but similarly demonstrated an increasing trend from 2015 to 2021. Additionally, a significant sex gap remains for both industry and public funding. As the prevalence of DM continues to rise, research payments for DME-related research from both industry and public payors similarly increased. Understanding trends in research payments is paramount to provide transparency on how potential prescribing patterns might be affected by financial relationships between manufacturers and prescribers.

Footnotes and Disclosures

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No animal subjects were used in this study.

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Conception and design: Lee, Xu, Starr

Data collection: Lee, Xu, Starr

Analysis and interpretation: Lee, Xu, Starr

Obtained funding: Lee, Xu, Starr

Overall responsibility: Lee, Xu, Starr

Abbreviations and Acronyms:
CMS = Centers of Medicare & Medicaid Services; **DM** = diabetes mellitus; **DME** = diabetic macular edema; **IQR** = interquartile range;

NEI = National Eye Institute; **OPD** = Open Payments Database; **PI** = principal investigator.

Keywords:
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