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Health Economics Review

REVIEW

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The economic impact of retinal diseases for which gene therapy is emerging: a systematic literature review

Claire Willmington[1*], Ann Kirby[1] and Aileen Murphy[1]

Abstract

Background Retinal disease is one of the leading causes of blindness and vision impairment worldwide, including Europe. With the advent of gene therapy, the treatment landscape for retinal disease is changing and clinical trials are underway investigating the therapeutic potential of gene therapy in both acquired and inherited retinal diseases. Given the high price of innovative medicines, it is essential to consider the current costs associated with retinal diseases to inform economic evaluations early in the life cycle of these forthcoming treatments. These could inform future reimbursement decisions, health budgets and service delivery plans.

Aim This systematic literature review sought to examine the economic burden of retinal diseases, for which gene therapy is emerging for patients in Europe.

Methods Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline, a systematic search was performed using the Medline, CINAHL, EconLit and Embase databases. The searches were restricted to English language articles published after 1st January 2000. Following article selection, data were extracted in a tabular form and a narrative synthesis was performed.

Results A total of 28 research studies were identified and included in the review that varied in terms of disease of interest, size, country setting, methodology, as well as how costs were reported and valued. While many retinal diseases were considered, almost half of the articles related to the costs of neovascular age-related macular degeneration (nAMD). Significant cost variations were observed across the studies as costs ranged from 45 USD to almost 30,000 USD per patient per annum, across all conditions combined.

Conclusion This systematic literature review evidences the heterogeneity among studies analysing the economics of retinal diseases underlying vision impairment. The paucity in the literature, signals the need for further research investigating the costs associated with retinal diseases, for which innovative therapies are expected to enter the market and will be subject to evaluation by decision-makers, whose decisions will have a significant impact on the delivery of these technologies to patients.

Keywords Retinal disease, Acquired retinal diseases, Inherited retinal diseases, Economic impact, Cost-of-illness, Gene therapy

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Background

In Europe alone, around 50 million individuals are affected by vision loss [1]. Retinal diseases, such as age-related macular degeneration (AMD), are one of the main contributors to the prevalence of blindness in adults over 50 [2, 3]. Furthermore, diabetic retinopathy (DR), a complication of diabetes mellitus, is one of the leading causes of blindness amongst the working age population [4, 5]. Another major cause of blindness in the working-age population are inherited retinal diseases (IRDs), which affect 1 in 1,380 individuals and represent a wide variety of conditions resulting from a broad range of genetic mutations [6].

In terms of treatment, the past few decades saw a rise in different modalities in a number of these conditions. Ever since the regulatory approval of pegaptanib for the neovascular form of AMD (also called wet AMD) by the European Medicines Agency in 2006, anti-vascular endothelial growth factors (anti-VEGFs) have revolutionized the treatment landscape for patients in Europe with a range of retinal diseases, including nAMD, diabetic macular oedema (DMO) (a potential complication of DR), as well as macular oedema due to retinal vein occlusion (RVO) and myopic choroidal neovascularisation (mCNV) [4, 7–9]. Despite the effectiveness of anti-VEGF injections in stabilizing and, even in some cases, reversing these conditions demonstrated in clinical trials [10], their high price compounded with their long-term associated care represent a strain on health systems and patients [11–13]. In addition to causing discomfort in patients, the repeated injections can cause potentially serious side effects, such as ocular haemorrhage and endophthalmitis [14]. As for the dry form of AMD, there are currently no treatment options for patients in Europe. Concerning DR without DMO complication, depending on disease presentation, clinicians may lean more towards more traditional modes of treatment, such as laser therapy, over anti-VEGFs to treat both DR forms (proliferative and non-proliferative) [15, 16]. With respect to IRDs, the only treatment currently on the market is a gene therapy, Luxturna (voretigene neparvovec), intended to treat RPE65 mediated Leber congenital amaurosis (LCA) and retinitis pigmentosa, and which was marketed at 450 000 USD per eye injection in the United States [17].

To address either the absence or inadequacies of currently available treatments in retinal diseases, scientists have been investigating gene therapy as a potential solution for a number of these conditions. Table 1 summarises the active clinical trials investigating gene therapy in retinal diseases in 2024. While these technologies could bring immense benefits to patients and society, the high price of innovative medicines means that health systems need evidence regarding not only their health benefits, but also the possible cost savings that their provision would generate, that could be offset against their expected high price. As a step towards estimating the potential cost savings that these technologies could generate for patients and society, this study identifies the current costs associated with retinal diseases for which gene therapy is emerging. Previous literature reviews analysing costs associated with vision impairment and blindness found a high degree of heterogeneity across these studies in terms of size, methodology, as well as the way in which costs were defined and reported [17, 21–23]. This study advances on previous literature by conducting a systematic literature review on the economic burden of retinal diseases in the European region, where gene therapy is expected to have a significant economic and clinical impact in the near future.

Methods

Literature search

A systematic literature review was conducted, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [24], to assess the economic impact of retinal diseases for which gene therapy is possible. The study protocol was registered with the Prospective Register of Systematic Reviews database (PROSPERO identification number CRD42024576511).

An electronic search was performed on 15th July, 2024 using the Medline, CINAHL and EconLit and Embase databases. The searches were restricted to English language journal articles published after 1 st January, 2000 to better reflect current practices and prices which were in large part influenced by the advent of certain technologies, such as anti-VEGFs in the mid-2000s [22, 25]. Search terms were defined according to current literature on retinal diseases for which gene therapy is emerging, as well as the economic burden that these conditions imply.

Search terms included specific retinal diseases for which clinical trials were actively testing gene therapies (see Table 1), as well as those that, although were not directly targeted in any of the clinical trials outlined in Table 1, could equally benefit from certain tested molecules, as it is the case of macular oedema secondary to retinal vein occlusion or myopic choroidal neovascularisation. Given the paucity of research around the economics of IRDs and the likelihood of faster gene therapy development in these conditions (in part due to the monogenetic nature of most IRDs), general terms referring to IRDs, such as "inherited retinal diseases", were also included in the search string. As for search terms pertaining to the economic aspect, their selection reflected the current terminology around costs and the studies that analyse them [26]. A description of the search terms and the relationship between these is provided in Supplementary Table 1.

Table 1 Gene therapies [a] in clinical trial for IRDs and acquired retinal diseases

	Condition	Tested molecule	Clinical trial Phase	Clinical trial sponsor	NCT number
Acquired retinal diseases	nAMD	ADVM-022	Phase 2	Adverum Biotechnologies, Inc	NCT05536973
		RGX-314	Phase 2 Phase 3	Abbvie	NCT04704921, NCT04514653, NCT03999801, NCT05407636
		4D-150	Phase 1/2	4D Molecular Therapeutics	NCT05197270
		EXG102-031	Phase 1	Exegenesis Bio	NCT05903794
		FT-003	Phase 1/2	Frontera Therapeutics	NCT06492863
		KH658	Phase 1/2	Chengdu Origen Biotechnology Co., Ltd.	NCT06458595, NCT05672121, NCT05657301
	Dry AMD and geographic atrophy	OCU410	Phase 1/2	Ocugen	NCT06018558
		GT005	Phase 2	Gyroscope Therapeutics Limited	NCT05481827
	Diabetic retinopathy without macular oedema	RGX-314	Phase 2	AbbVie	NCT04567550
	Diabetic macular oedema	4D-150	Phase 2	4D Molecular Therapeutics	NCT05930561
		SKG0106	Phase 1	Wang Min	NCT06237777
		FT-003	Phase 1/2	Frontera Therapeutics	NCT05916391, NCT06492876
		OCU200	Phase 1	Ocugen	NCT05802329
		JNJ-81,201,887	Phase 2	Janssen Research & Development, LLC	NCT05811351
Inherited retinal diseases (IRDs)	Achromatopsia	CNGB3 or CNGA3	Phase 1/2	MeiraGTx UK II Ltd	NCT03278873
		AGTC-402	Phase 1/2	Applied Genetic Technologies Corp	NCT02935517
		AGTC-401	Phase 1/2	Applied Genetic Technologies Corp	NCT02599922
		rAAV2tYF-PR1.7-hCNGB3 (AGTC-401)	Phase 1/2	Applied Genetic Technologies Corp	NCT02599922
		rAAV.hCNGA3	Phase 1/2	STZ eyetrial	NCT02610582
	Choroideremia	4D-110	Phase 1	4D Molecular Therapeutics	NCT04483440
	Retinitis Pigmentosa (RP)	OCU400	Phase 1/2	Ocugen	NCT05203939
		MCO-010	Phase 2	Nanoscope Therapeutics Inc.	NCT04945772
		QR-1123	Phase 1/2	ProQR Therapeutics	NCT04123626
		Ultevursen	Phase 2/3	Laboratoires Thea	NCT05158296
		VP-001	Phase 1	PYC Therapeutics	NCT05902962
		BS01	Phase 1/2	Bionic Sight	NCT04278131
		GS030-DP	Phase 1/2	GenSight	NCT03326336
		VG901	Phase 1	ViGeneron GmbH	NCT06291935
		CPK850	Phase 1/2	Novartis	NCT03374657
		SPVN06	Phase 1/2	SparingVision	NCT05748873
		rAAV.hPDE6A	Phase 1/2	STZ eyetrial	NCT04611503
	Usher Syndrome	Ultevursen	Phase 2/3	Laboratoires Thea	NCT05158296
		SAR421869	Phase2	Sanofi	NCT02065011
	Stargardt disease	SAR422459	Phase 1/2	Sanofi	NCT01736592
		JWK006	Phase 1/2	West China Hospital	NCT06300476
		OCU410ST	Phase 1/2	Ocugen	NCT05956626
		ACDN-01	Phase 1/2	Ascidian Therapeutics, Inc	NCT06467344
	Retinoschisis	AAV-RS1	Phase 1/2	VegaVect, Inc	NCT02317887
		ZM-01-L/ZM-01-H	Phase 1	Zhongmou Therapeutics	NCT06066008
		LX103	N/A	Shanghai General Hospital	NCT05814952
		ATSN-201	Phase 1/2	Atsena Therapeutics Inc.	NCT05878860

Table 1 (continued)

	Condition	Tested molecule	Clinical trial Phase	Clinical trial sponsor	NCT number
	Leber congenital amaurosis (LCA)	OCU400	Phase 1/2	Ocugen	NCT05203939
		AAV2-hRPE65v2	Phase 1	Spark Therapeutics, Inc.	NCT01208389
		ATSN-101	Phase 1/2	Atsena Therapeutics Inc.	NCT03920007
		rAAV2-CBSB-hRPE65	Phase 1	University of Pennsylvania	NCT00481546
		EDIT-101	Phase 1/2	Editas Medicine, Inc.	NCT03872479
		Sepofarsen	Phase 2/3	ProQR Therapeutics	NCT03913143
		OPGx-001	Phase 1/2	Opus Genetics, Inc	NCT05616793
	Leber Hereditary Optic Neuropathy	scAAV2-P1ND4v2	Phase 1	Byron Lam	NCT02161380
		rAAV2-ND4	Phase 2/3	Huazhong University of Science and Technology	NCT03153293
		NFS-02	Phase 1/2	Neurophth Therapeutics Inc	NCT05820152
		NR082	Phase 1/2	Neurophth Therapeutics Inc	NCT05293626
		NR082	Phase 2/3	Wuhan Neurophth Biotechnology Limited Company	NCT04912843

AMD: age-related macular degeneration; *nAMD*: neovascular age-related macular degeneration; *DR*: diabetic retinopathy; *NPDR*: non-proliferative diabetic retinopathy; *PDR*: proliferative diabetic retinopathy; *DMO*: diabetic macular oedema Information extracted from [18]

[a] : The term "gene therapy" was used throughout the manuscript as a composite term that encompasses both gene and RNA therapies, as it has been adopted in previous literature [19, 20]

Study selection

As described in Table 2, the inclusion and exclusion criteria were defined within a PICOS framework (i.e. population, intervention, comparators, outcomes, study design, setting), which was adapted to the study's aim. Two reviewers (CW and AM & CW and AK) were paired and independently screened article titles and abstracts for eligibility before reviewing the full texts of selected articles. Any disagreement was resolved through discussion until consensus among the three reviewers was reached. The reference lists of key articles and reviews were searched manually for additional articles of relevance. The population of interest consisted of patients diagnosed with IRD or one of the retinal diseases described previously. Studies that focused on screening strategies involving individuals without a retinal disease were excluded.

As the reporting of costs was one of the key inclusion criteria, careful attention was given to their classification. In ophthalmology, as in other disease areas, the research reflects three main categories of costs, including direct (medical and non-medical), indirect and intangible costs [22, 27–29]. In this study, direct medical costs refer to costs related to inpatient/outpatient care and treatment, whereas direct non-medical costs refer to costs related to the use of non-medical resources, such as transportation, formal care and assistive technologies. Moreover, indirect costs pertain to productivity, tax and deadweight loss, as well as informal care, impacting patients, carers and society at large. Productivity loss can result from a reduction in paid activities of patients and caregivers, but also from a reduction in activities that bring value to society, such as volunteering and household duties. Additionally, intangible costs, often expressed as quality-of-life values (i.e. Quality Adjusted Life Years (QALYs), Disability Adjusted Life Years (DALYs)), are generated by the pain and suffering of patients and caregivers in relation to the disability. In this study, we only

Table 2 PICOS framework

Category	Inclusion Criteria	Exclusion Criteria
Population	• Patients diagnosed with IRD or one the following conditions: nAMD; dry AMD and geographic atrophy; DR; DMO; macular oedema due to RVO or mCNV. • Collaterally impacted individuals (i.e. caregivers). • No restriction in terms of patient age.	• Patients with a retinal disease outside of the scope of interest. • Studies involving undiagnosed individuals, such as in screening strategies.
Intervention	Not applicable.	Not applicable.
Comparator	Not applicable.	Not applicable.
Outcome	Costs reported by the studies associated with retinal diseases in patients: • Direct medical and non-medical costs • Indirect costs • Intangible costs	Economic or well-being impact that is not reported in monetary terms.
Study Design	Partial economic evaluations, namely cost analyses and COI studies.	• Reviews of already published economic studies. • Full economic evaluations, such as cost-effectiveness and cost-benefit studies.
Setting	Studies conducted in the European region.	Studies conducted outside the European region.

included studies reporting costs expressed in monetary terms. Concerning study design, we considered partial economic evaluations, namely, cost analyses and cost-of-illness (COI) studies. As for geographical setting, only studies conducted in the European region were included in the final review, where age-related retinal diseases, including AMD and DR, are particularly prevalent [2, 3]. Finally, reviews, conference presentations, case reports, research protocols, and abstracts were excluded from this study.

Data extraction and synthesis

Following article selection, data was extracted in a tabular form to support reporting uniformity and reproducibility, as well as to minimise bias. The following elements were extracted: authors; publication year; study design; geographical setting; patient population; epidemiological approach (prevalence vs. incidence); type of costs; year of costing; estimated costs; method of resource quantification (bottom-up vs. top-down); study perspective; time horizon; cost data sources; and distribution of payer(s) bearing the costs [26]. The use of resources (i.e. inpatient care, outpatient care, medication) included in the estimated costs were also extracted from the studies when sufficient information was provided. To allow for comparability between studies, we reported per person annual costs. We also reported costs for specific subgroups of patients when those were estimated in the studies. Given the heterogeneity between studies in terms of currencies and time periods, costs were inflated and converted to 2024 USD values, using the CCEMG–EPPI Centre Cost Converter web-based tool [30].

Quality appraisal

Both the British Medical Journal Checklist for economic submissions, geared towards COI studies [31, 32] and the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) checklist [33] were used to assess the reporting quality of the results. For each checklist item considered, a rating of "yes" or "no" was given depending on if the study met the criteria.

Results

Study selection and quality assessment

The initial search yielded 5,270 records. Following removal of duplicates, 3,169 articles underwent screening of titles and abstracts, which resulted in 301 articles being selected for full text screening. After which, 28 articles met the inclusion criteria (Fig. 1). Over half of the included articles were related to AMD (55%), followed by DR and DMO (31%), RVO, mCNV and IRD combined (14%). The studies were mainly conducted in Western Europe (90%), followed by Scandinavia (7.5%) and Central Europe (2.5%). The results from the quality appraisal of the 28 studies are described in Supplementary Tables 10 and 11.

Cost component and resource use classification

Costs were categorised based on previously established classifications [22, 27–29] that include direct medical and non-medical costs, indirect costs and intangible costs, as well as the subcategories within these. Figure 2 is a schematic of the taxonomy of the different costs identified and accounted for in this study and Table 3 describes the different resources included in the reported cost estimates across the results.

Cost analysis

Overall significant cost variations were observed across the studies, both within and between conditions. At the patient level, costs ranged from $45 to almost $30,000 per patient per annum, across all conditions. Cost ranges were higher in nAMD and DMO patients ($228 - $28,000 and $370 - $28,000 respectively) than other conditions, including dry AMD ($300 - $3,000), DR without complications ($45 - $4,000) and macular oedema secondary to RVO ($1,800 - $12,000).

1. Costs associated with age-related macular degeneration (AMD)

Sixteen articles considered costs associated with AMD [34–49]. These were further classified into studies examining associated with nAMD [34–43, 45] or Dry AMD [46] alone, or combined [44, 47–49].

a. Costs associated with neovascular AMD (nAMD)

Costs associated with nAMD were described in 12 studies [34–45] (Fig. 3 and Supplementary Table 2), across France (n = 5) [36, 38, 41, 42, 45], Germany (n = 3) [37, 41, 42], Italy (n = 3) [35, 42, 44], Spain (n = 3) [34, 40, 41] and the UK (n = 3) [39, 41, 43]. While most studies concentrated on one country (n = 10) [34–40, 43–45], two studies examined multiple countries in their analysis [41, 42]. As for study design, most were observational [35–45] while one was model-based [34]. In observational studies [34–45], sample size (from 105 to 3879 patients) and patient characteristics varied. Furthermore, three studies focused on patients with bilateral nAMD [40, 41, 43], while five considered both unilateral and bilateral nAMD [34, 38, 39, 42, 44], and four others did not specify the laterality of the condition [35–37, 45]. Whereas most studies took a bottom-up approach (n = 8) [37–40, 42–45], three studies opted for a top-down approach [34–36] and one took both bottom and top-down approaches [41]. A societal perspective was adopted in six studies [34, 39–43], whereas different perspectives were taken

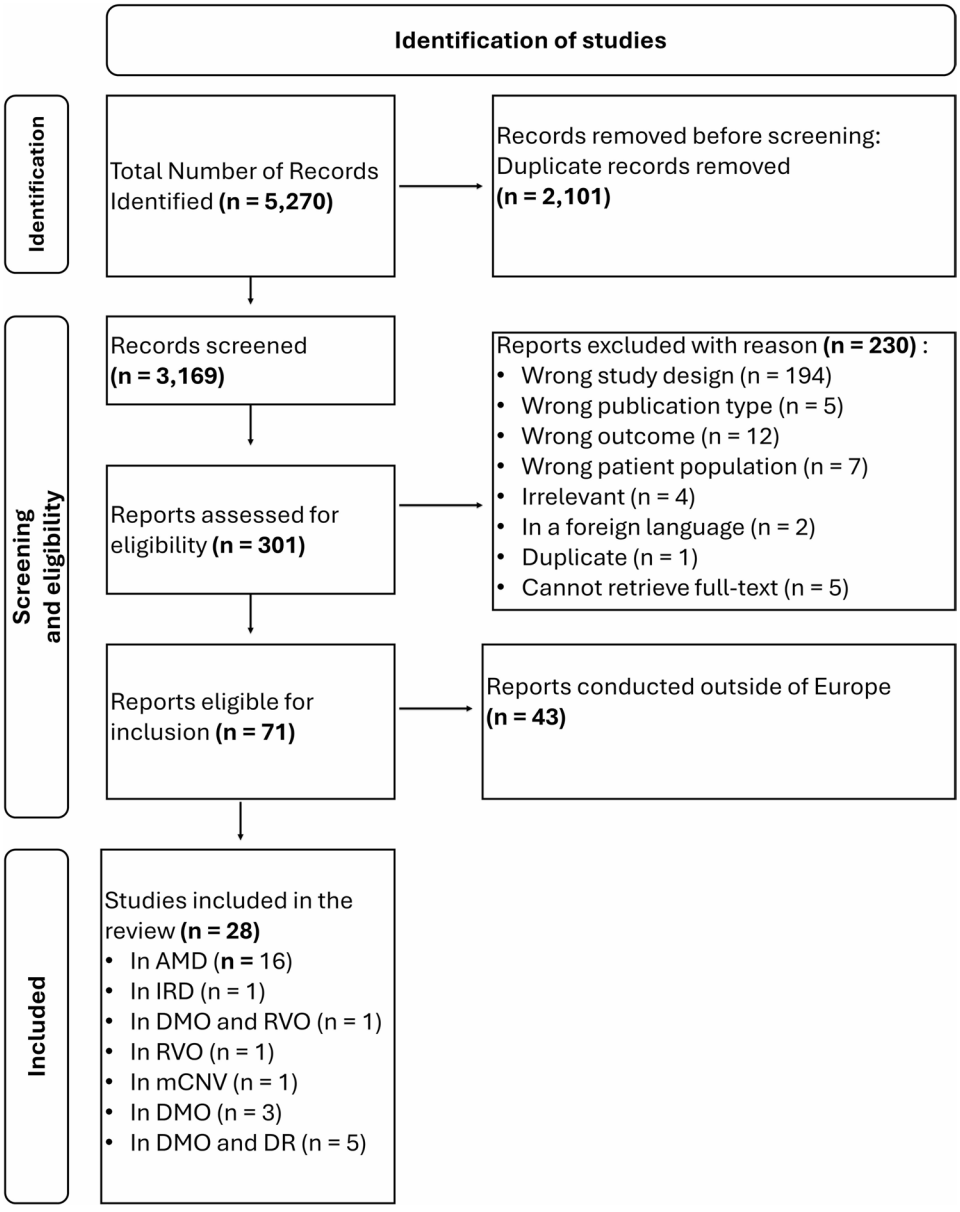


Fig. 1 Study selection

in six others, including national health system [35], payer [36, 45], carer [37], patient [38], and healthcare sector perspective [44]. As for time horizons, most studies assessed the costs over a one-year period (n = 9) [37–45], as opposed to a longer time (from to 2 to 3 years) (n = 3) [34–36]. In terms of cost components, three studies reported direct medical costs only [35, 36, 44], five assessed both direct medical and non-medical costs [40–43, 45], two accounted for both direct and indirect costs [37, 39], one focused on direct non-medical costs only [38], and finally one study examined direct, indirect and intangible costs [34] (Table 3). Additionally, costs were broken down by visual acuity or disease laterality in four studies [37, 41, 42, 45] and age group in one [35].

a.1 Direct medical costs – patient level

Direct medical costs associated with nAMD were described in 11 studies [34–37, 39–45] and ranged from $228 to $12,133 per patient per annum (Fig. 3 and Supplementary Table 2). The direct medical costs reflect the inclusion of different medical resources in each study and disaggregated figures were reported in all 11 studies. Medical resources ranged from ophthalmological care, such as medical exams and treatments, to non-ophthalmological care related to falls and depression (Table 3). While three out of the four studies describing post-2010 direct medical costs explicitly accounted for Anti-VEGF treatment costs [34–36], the seven studies using cost data

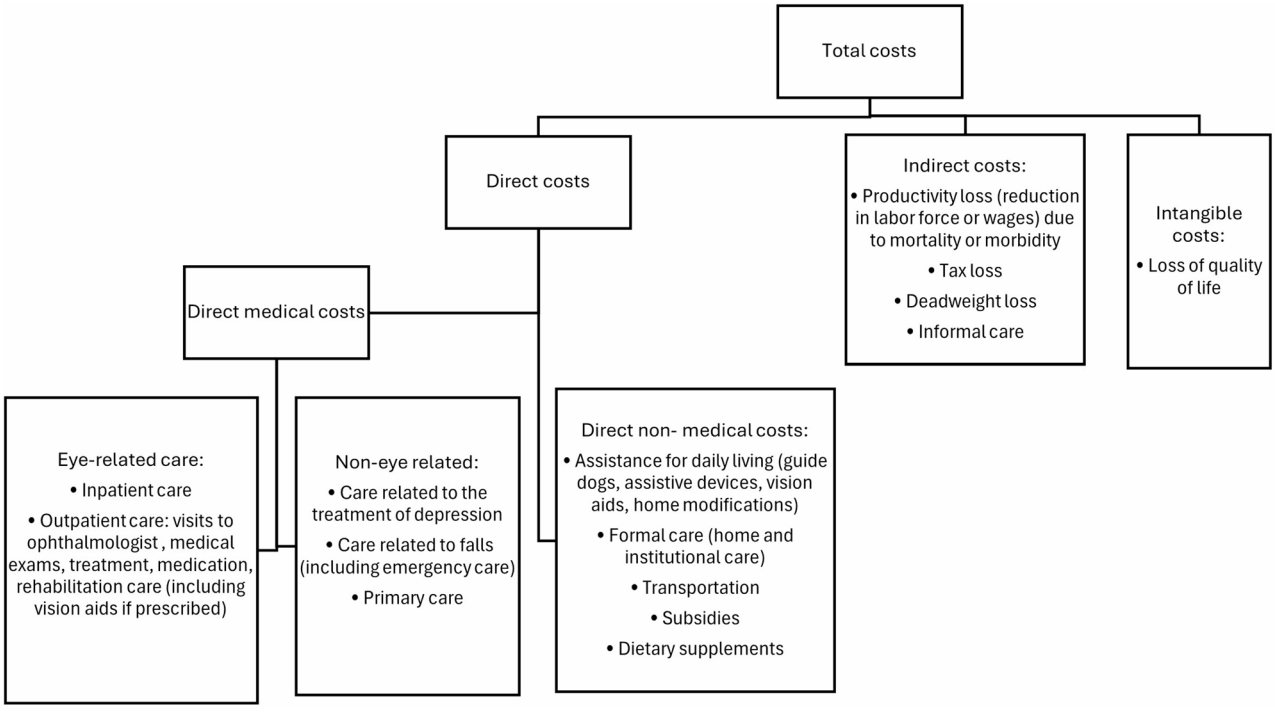


Fig. 2 Taxonomy of the economic burden of retinal disease

prior to 2010 considered the costs of other treatments, including laser therapy (i.e. laser photocoagulation, photodynamic therapy) and intravitreal steroids [39–45]. As for the use of other medical resources, studies using pre-2010 cost data included a wider range of resources than studies with more recent cost data. For instance, non-ophthalmological care costs were included in five [39–42, 45] of the seven studies using pre-2010 data [39–45], as opposed to one [36] among the four studies using more recent data [34–37]. As for annual costs in patients initiating anti-VEGF treatment (n = 2), estimates ranged from \$9,571 to \$14,849 during the first year and declined from 13% to 43% the following year [34, 35] (Supplementary Table 2).

a.2 Direct non-medical costs – patient level

Nine studies [34, 37–43, 45] reported direct non-medical costs per patient per annum, ranging from \$688 to \$15,418 (Fig. 3). The most frequent resources accounted for within direct non-medical costs were formal care [34, 38–43, 45] and assistive technologies [34, 37–39, 41–43, 45], followed by transportation [34, 37–39, 42, 45] and subsidies [40–43] (Table 3). Of note, only three studies using post-2010 cost data reported annual direct non-medical costs [34, 37, 38]. Formal care typically represented the largest share of direct non-medical costs. While annual direct non-medical costs were uniformly lower than direct medical costs in three studies [34, 39, 40] reporting both types of costs, they were higher in other cases [37, 41–43, 45]. For instance, two multi-country studies recorded direct non-medical costs that were higher than direct medical costs in Germany [41, 42] as opposed to other countries. Often, direct non-medical costs increased in line with the severity of vision impairment [37, 41, 42, 45] and in certain instances exceeded direct medical costs in patients with more severe vision impairment [42, 45].

a.3 Indirect and intangible costs – patient and carer level

The loss of productivity, pertaining to the reduction in labour force and wages, among nAMD patients was estimated in two studies [34, 39], and carers in one [37] (Fig. 3). Annual productivity loss in patients ranged from \$23 to \$1,006 [34, 39]. Additionally, annual productivity loss in carers was estimated at \$95.12 in one German study [37]. Of note, two retrospective studies [37, 39] qualitatively noted a minority of subjects (patients or carers) experiencing productivity loss.

In terms of informal care costs, they were estimated in two studies [34, 39], ranging from \$2,508 to \$6,634 per patient per annum. On the other hand, intangible costs related to the impact of the disease on the patient's quality of life and daily activities were estimated annually at the patient level in one model-based study (\$6,185) [34].

Table 3 Resources included in the reported cost estimates

		Direct costs																				Indirect costs				Intangible care
		Direct medical costs												Direct non-medical costs					Productivity loss			Informal care	
		Eye-related care								Non eye-related care																
Article	Condition	Inpatient care	Outpatient care (i.e. general visits)	Outpatient care - medical exams	Treatment - anti-VEGF injections	Treatment other than anti-VEGF injections	Other medication	Rehabilitation care	Not specified	Care for depression	Emergency care (i.e. falls)	Other care (i.e. GP hospitalizations)	Not specified	Assistance for daily living	Formal care	Transportation	Subsidies	Other (i.e. Dietary supplements)	Reduction in labour force participation	Wage reduction	Deadweight loss		
(34)	nAMD		✓	✓	✓									✓	✓	✓		✓		✓		✓	✓
(35)	nAMD	✓	✓		✓		✓																
(36)	nAMD		✓		✓			✓				✓											
(37)	nAMD						✓							✓		✓		✓		✓			
(38)	nAMD													✓	✓	✓		✓					
(39)	nAMD		✓	✓		✓	✓				✓			✓	✓	✓			✓	✓		✓	
(40)	nAMD		✓	✓		✓		✓		✓	✓	✓			✓		✓						
(41)	nAMD		✓	✓				✓		✓	✓			✓	✓		✓						
(42)	nAMD	✓	✓			✓	✓				✓	✓		✓	✓	✓	✓						
(43)	nAMD		✓	✓		✓		✓						✓	✓		✓						
(44)	AMD	✓	✓	✓			✓																
(45)	nAMD	✓	✓	✓		✓		✓				✓		✓	✓	✓							
(48)	AMD			✓	✓	✓																	
(47)	AMD		✓	✓					✓														
(49)	AMD		✓	✓	✓	✓	✓	✓															
(46)	Dry AMD		✓	✓		✓				✓	✓	✓		✓	✓								
(55)	DMO	✓	✓	✓	✓	✓				✓				✓	✓	✓			✓	✓		✓	✓
(56)	DMO		✓	✓	✓	✓				✓							✓			✓			
(57)	DMO, RVO	✓	✓	✓		✓					✓								✓	✓			
(58)	DMO		✓	✓		✓		✓							✓						✓		
(54)	DR, DMO		✓	✓	✓	✓														✓			
(52)	DR, DMO	✓	✓	✓		✓																	
(50)	DR, DMO		✓	✓	✓	✓										✓							
(51)	DR, DMO								✓														
(53)	DR, DMO	✓	✓	✓		✓	✓	✓				✓		✓	✓	✓	✓			✓			
(61)	mCNV	✓	✓	✓							✓	✓		✓				✓	✓	✓			
(60)	RVO	✓	✓	✓		✓	✓	✓															
(59)	IRD																						

StartFragment *AMD*: age-related macular degeneration; *nAMD*: neovascular age-related macular degeneration; *DR*: diabetic retinopathy; *NPDR*: non-proliferative diabetic retinopathy; *PDR*: proliferative diabetic retinopathy; *DMO*: diabetic macular oedema; *IRD*: inherited retinal disease; *RVO*: retinal vein occlusion; *mCNV*: myopic choroidal neovascularisation EndFragment

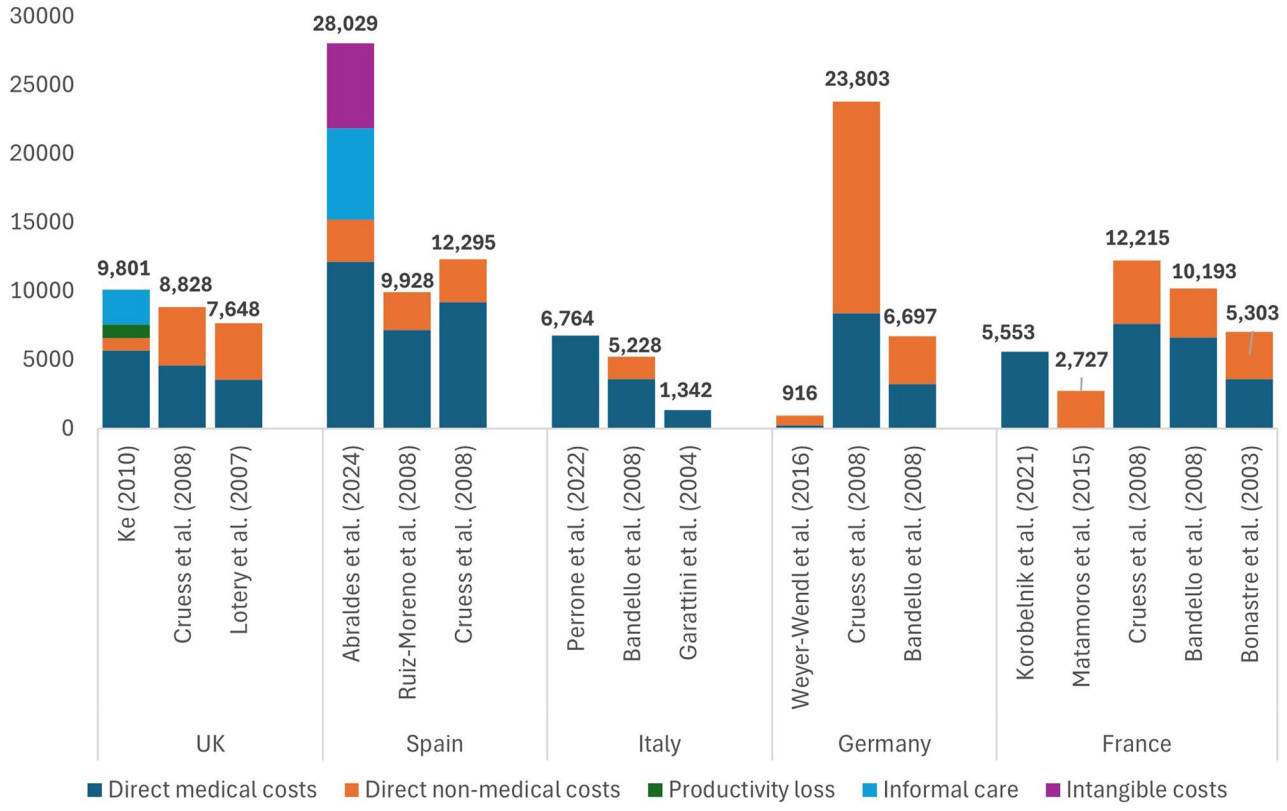


Fig. 3 Total annual costs per person for nAMD across countries (in 2024 USD)

a.4 Disease burden

Total direct costs were projected at the national level in one multi-country study conducted by Cruess et al. in 2008 [41], where annual direct medical costs per patient were extrapolated using published prevalence rates (Supplementary Table 3). These figures ranged from $1.44 billion (Spain) to $6.27 billion (Germany) annually, partly reflecting differences in geographic settings and population sizes.

b Costs associated with dry AMD

Three studies [44, 46, 47] estimated costs associated with dry AMD and more specifically geographic atrophy, the advanced form of dry AMD (Fig. 4 and Supplementary Table 4). While two of these studies were set in the UK and Italy respectively [44, 47], another assessed costs in multiple geographical settings, including the UK, Ireland, Germany and Canada [46]. All three studies opted for an observational study design and had a bottom-up approach to resource quantification. The patient samples used in these studies varied in sizes, ranging from 78 to 725 patients, and included individuals with either bilateral geographic atrophy only [46] or both unilateral and bilateral geographic atrophy [44, 47]. In terms of study perspective, one took a healthcare payer perspective [47], while the other two didn't explicitly state the perspective but healthcare sector perspective is implied [44, 46]. Time horizons over which costs were evaluated tended to be short and varied from one year [44, 46] to two years [47].

b.1 Direct medical costs – patient level

Direct medical costs were reported in all studies [44, 46, 47] and were expressed as mean annual costs per patient in two [44, 46], ranging from $496 to $2,633. While ophthalmological care was accounted for in all studies, costs pertaining to care for depression and falls was explicitly considered in one multi-country study [46]. Of note, direct median medical costs were estimated by laterality of geographic atrophy over two years, ranging from $525 to $700 in a UK study [47]. Given the absence of treatment options for dry AMD at the time of the studies' publication, no treatment cost related to the condition was considered in any of the three studies.

b.2 Direct non-medical costs – patient level

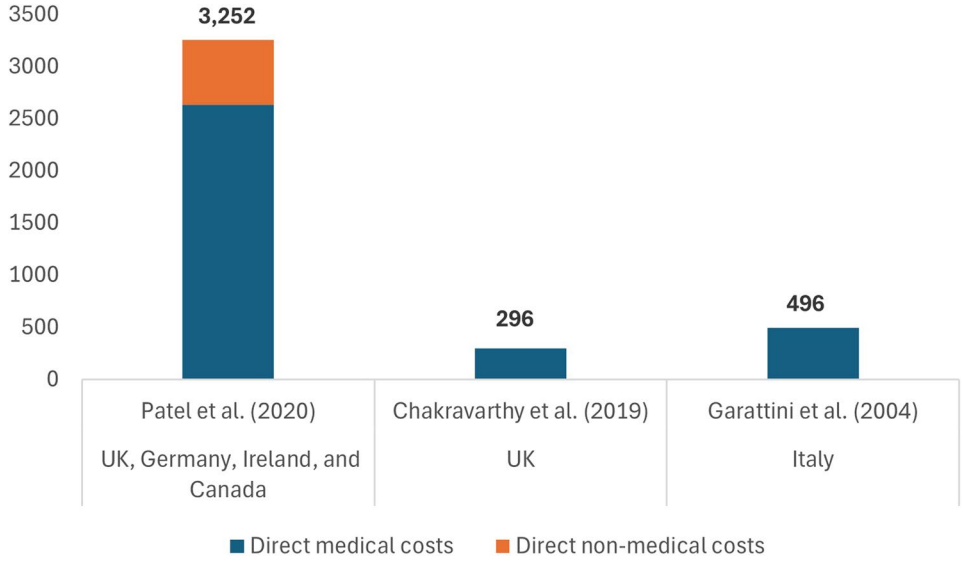


Fig. 4 Total annual costs per person for dry AMD across countries (in 2024 USD)

Direct non-medical costs related to formal care and assistive technologies were estimated at $620 per patient per year in one multi-country study led by Patel et al. [46].

c. Costs associated with AMD (studies combining dry AMD and nAMD patients together)

Three studies reported costs associated with dry AMD and nAMD together: A model-based study with a top-down approach that did not distinguish between dry AMD and nAMD patients in terms of both demographics and costs across four countries [49]; a Spanish observational based study that distinguished between different conditions in terms of demographics but not in terms of costs [48]; and finally a UK observational study that estimated costs in patients with both geographic atrophy and nAMD simultaneously [47] (Supplementary Table 5). The two observational studies adopted a bottom-up approach to resource quantification and used patient samples with sizes that varied from 355 to 1164 individuals [47, 48]. In terms of study perspective, the studies were conducted from either a hospital [48], healthcare payer [47] or payer perspective [49]. As for time horizons used in the studies, they were relatively short and ranged from one [48, 49] to two years [47].

c.1 Direct medical costs – patient level

In the study that did not distinguish between dry AMD and nAMD patients [49], the mean annual ophthalmological care costs ranged from $20,079 to $24,606 per patient in four different countries (France, Germany, Italy and the UK). Furthermore, costs of laser therapy, related to nAMD treatment specifically, were included in this study and represented a major cost driver (Supplementary Table 5). On the other hand, the Spanish study [48] specified the number of patients with either nAMD (87%), dry AMD (1%) or both (12%) within their sample but did not account for these differences in their reporting of the mean annual ophthalmological-related medical costs ($8,475 per patient). It is worth noting that this study also analysed the use and costs of anti-VEGFs by molecule (bevacizumab, ranibizumab and aflibercept) among the sampled patients and suggested that while ranibizumab was used in only 30% of patients, it represented the highest share of the overall anti-VEGF costs across the patient sample, as opposed to the two other anti-VEGF molecules [48]. Furthermore, the UK study that included patients with geographic atrophy in one eye and nAMD in the other [47] estimated the median ophthalmological-related direct medical costs at $1,501 per patient per annum.

c.2 Disease burden

Finally, in the two studies where annual costs were projected at a subgroup level, the level of extrapolation varied from the patient sample [48] to the country level [49] (Supplementary Table 3). While direct medical costs were estimated at $9.87 million for a sample of 1,164 patients in the Spanish cost analysis [48], the cross-county study (France, Germany, Italy and the UK), prevalence rates, estimated that costs ranged from $96.56 million to $190.29 million [49], using published prevalence rates.

2. Costs associated with Diabetic retinopathy (DR)

Nine articles [50–58] considered costs associated with DR and its associated complications (i.e. DMO).These were further classified into studies examining costs associated with DMO alone [55–58] or combined with DR [50–54].

a. Costs associated with non-proliferative diabetic (NPDR) and proliferative diabetic retinopathy (PDR)

Three studies, in Germany [53], Hungary [54] and Sweden [52], estimated costs associated with NPDR and PDR (Fig. 5 and Supplementary Table 6). In terms of study design, two were observational studies [52, 53], whereas the other was model-based [54]. As for the method of resource quantification, one study included bottom-up and top-down approaches [53], whereas the remaining two opted for a top-down approach [52, 54]. In two of the studies that adopted an observational design, patient sample sizes varied from 161 to 3,045 subjects [52, 53]. Study perspective was explicitly specified in two of the three studies - societal and healthcare payer in the German study [53] and health system and patient in the Hungarian study [54] - while a health system perspective was implied in the Swedish study [52]. Additionally, time horizons were restricted to one year in all three studies [52–54]. Annual costs were reported at the patient level in all three studies and projected at the population level by DR subtype in the Hungarian study only [54]. Furthermore, costs were broken down by DR subtype in all three studies and by NPDR severity in the German study [53]. While direct medical costs were reported in all three studies, direct non-medical and indirect costs were reported in only one [53].

a.1 Direct medical costs – patient level

Annual direct medical costs ranged from $45 to $613 in NPDR patients and from $441 to $3,031 in PDR patients (Fig. 5 and Supplementary Table 6), suggesting direct medical costs associated with PDR were about 5.8 times higher than those associated with NPDR. Concerning NPDR, studies varied in terms of how they defined the patient population with this condition. For instance, the German study [53] considered three groups of patients (sizes ranging from 38 to 43 subjects) with varying levels of NPDR severity (from mild to severe) in their cost calculations, which tended to be higher in the case of severe NPDR ($1,178 per patient per annum), as opposed to mild and moderate NPDR ($243 and $478 per patient per annum respectively). On the other hand, the two other studies considered single a NPDR patient population in their analysis [52, 54] and were defined as follows: patients with "referable NPDR" in one [54], and patients with background retinopathy (which is considered the milder form of NPDR) in the other [52]. Although only the German study [53] reported disaggregated costs associated with different uses of specific medical resources (ophthalmological and non-ophthalmological related), the other two studies reported aggregated costs while specifying the ophthalmological care resources they were accounting for in their estimates [52, 54]. All studies included costs of treatment, which encompassed costs of laser therapy [52–54] and vitrectomy [52, 54] (Table 3).

a.2 Direct non-medical and indirect costs – patient level

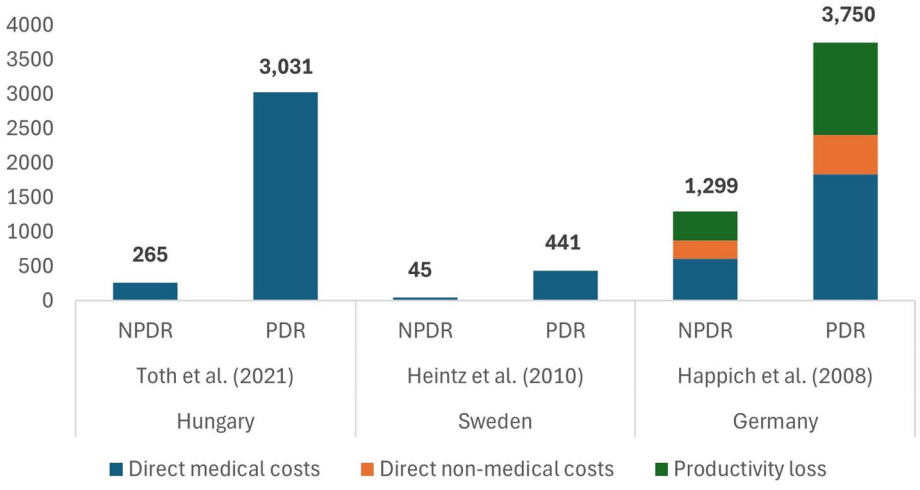


Fig. 5 Total annual costs per person for NPDR and PDR across countries (in 2024 USD)

In terms of direct non-medical and indirect costs, they were estimated at the patient level in the German study [53] and tended to be lower in NPDR patients than PDR patients in both cases: $259 vs. $571 per patient per annum for direct non-medical costs and $427 vs. $1,344 per patient per annum for indirect costs related to the productivity loss in patients (Supplementary Table 6).

a.3 Disease burden

Finally, annual direct medical costs associated with NPDR and PDR were estimated at $2.93 million and $34.32 million respectively in Hungary in the model-based study [54] (Supplementary Table 3).

b. Costs associated with diabetic macular oedema (DMO)

Costs associated with DMO were described in six studies for Spain (n = 2) [55, 57], Hungary [54], Italy [56], Sweden [52] and the UK [58]. All included direct medical costs, at either the patient [52, 55, 57], population level [56, 58], or both [54] (Fig. 6 and Supplementary Tables 3 and 7). While four out of the six studies were model based with a top-down approach to resource quantification [54–56, 58], two opted for an observational design with either a bottom-up [57] or top-down approach [52]. The latter two studies used patient samples with sizes ranging from 255 to 298 patients and with either unilateral and bilateral DMO [57], or unspecified DMO laterality [52]. Furthermore, two model-based studies [55, 56] accounted for patients with both unilateral and bilateral DMO in similar proportions as the Spanish observational study [57]. In terms of study perspective, the Spanish studies took a societal perspective [55, 57], while others took a health and social care provider [58], a health system [52] a health system and societal [56], or a health system and patient perspective [54]. As for time horizons over which costs were assessed, they were restricted to one year in four studies [52, 54, 57, 58] and lengthened to three and five years respectively in the two other studies [55, 56].

b.1 Direct medical costs – patient level

Among the four studies reporting direct medical costs at the patient level, estimates ranged from $370 to $14,642 per annum [52, 54, 55, 57] (Fig. 6 and Supplementary Table 7). While two of these included ophthalmological and non-ophthalmological related medical costs [55, 57], the others estimated ophthalmological-related medical costs only [52, 54] (Table 3). Of note, outpatient visits, treatments and examinations were the most frequently accounted for resources in ophthalmological-related medical costs. As for the costs of treatment at the patient level, two studies considered anti-VEGF injection costs [54, 55], whereas two others considered costs of other treatments only, such as laser therapy (i.e. photocoagulation) and surgery (i.e. vitrectomy) [52, 57] (Table 3). In the Spanish model-based study, costs of dexamethasone (DEX) implants were accounted for in addition to anti-VEGF costs [55]. Furthermore, this study broke down costs by treatment, which were analysed in patients receiving either anti-VEGFs (ranibizumab or aflibercept), or a DEX implant following treatment failure with a three-month course of anti-VEGFs [55]. More specifically, lower costs were reported in patients treated with a DEX implant ($11,607 per patient per annum), as opposed to anti-VEGF injections only ($16,159 per patient per annum). Also, annual costs over three years following diagnosis were estimated and suggested a drop

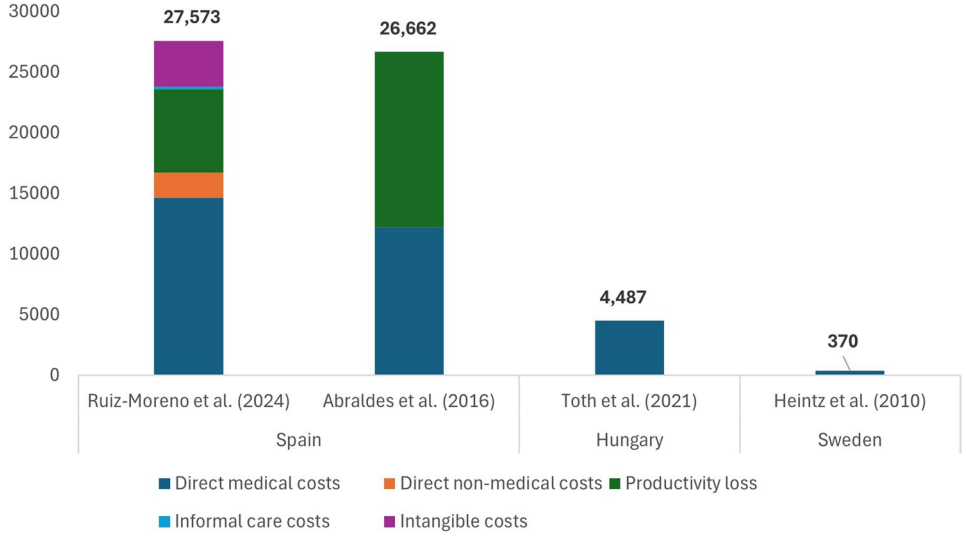


Fig. 6 Total annual costs per person for DMO across countries (in 2024 USD)

in treatment costs from 11.5% to 29% after the first year of patients initiating anti-VEGF injections only and of 47% after a first year of treatment with the anti-VEGFs injections/DEX implant combination [55]. The Hungarian study also accounted for anti-VEGF injections in their annual cost estimates ($4,487 per patient) [54]. Direct medical costs were reported by laterality of the condition in another Spanish study [57], where little difference was found in terms of direct medical costs between patients with unilateral DMO and those with bilateral DMO ($12,187 vs. $12,199 per patient per year).

b.2 Direct non-medical, indirect and intangible costs – patient level

As for direct non-medical costs, reflecting the use of formal care, transportation and vision aids, they were estimated at $2,068 per patient per annum in the Spanish model-based study [55]. Informal care and intangible costs, such as the loss of quality of life and daily activities, were also estimated in the same study at $193 and $3,767 respectively [55].

In terms of productivity losses in patients, they were estimated in only two studies [55, 57]: one combining reduction in labour and working hours in their estimates ($6,903 per patient per annum) [55]; and the other focusing on cost of temporary and permanent occupational disability ($14,471 per patient per annum) [57]. The latter study [57] reported a large gap in terms of productivity loss between patients with unilateral DMO and those with bilateral DMO ($8,501 vs. $23,915).

b.3 Disease burden

Three model-based studies [54, 56, 58] projected costs associated with DMO at the population level (Supplementary Table 3). The patient population sizes varied from 28,300 to 237,602 subjects, in part reflecting differences in geographical settings, as well as stages of DMO considered. For instance, Calabro and al. considered the entire DMO patient population in Italy (237,602 individuals) [56], whereas Tóth et al. considered a more specific DMO patient population consisting of patients with "referable" DMO based in Hungary (28,300 individuals) [54]. All three studies [54, 56, 58] estimated direct medical costs, which ranged from $126.93 million [54] to $1.93 billion [56]. In terms of DMO specific treatment, the UK study focused on laser-based treatments only [58] and the remaining two considered either anti-VEGF injections and DEX implants [56] or anti-VEGF injections and laser therapy [54]. Of note, the Italian study [56] also estimated the costs related to psychological services in addition to ophthalmological care costs (Table 3). In terms of direct non-medical costs, they were described in two studies [56, 58], and varied from $250,241.84 to $18.95 million. As for indirect costs, the Italian study reported productivity losses among DMO patients and carers ($256.78 million and $166.87 million respectively) [56], whereas another reported deadweight loss in England ($26.36 million) [58].

c. Costs associated with DR and its complications combined.

Costs pertaining to DR and its complications (including DMO) were combined in three studies [50, 51, 53], whereas costs in patients affected by both DR and DMO simultaneously were reported in two studies [52, 53] (Supplementary Tables 3 and 8). All four studies had an observational study design and were conducted in Germany [51, 53], Norway [50] and Sweden [52]. While three out of the four studies adopted a top-down approach to resource quantification [50–52], one opted for bottom-up and top-down approaches [53]. Sample sizes varied from 143 to 35,733 subjects. Direct medical costs were reported in all four studies, at the general patient level only [51–53], or combined with the sub-group level as well [50]. As for direct non-medical costs, they were estimated at the patient level in one German study [53], which also estimated total costs at the population level [53]. Three studies specified taking a healthcare payer [51], extended healthcare [50], or a societal and healthcare payer perspective [53]. A health system perspective was implied in the Swedish study [52].

c.1 Patient level costs

Concerning studies that examined costs in patients with DR and its complications altogether [50, 51], one reported aggregated direct medical costs among 35,733 patients identified through the German national insurance database (average of $4,175 per patient per annum) [51], while the other reported direct medical costs combined with transportation costs ($5,036 - $6,351 per patient per annum) in patients identified through Oslo University Hospital's patient registry in Norway [50] (Supplementary Table 8). In terms of treatment costs, the Norwegian study accounted for anti-VEGF injections, DEX implants, laser therapy and surgery (i.e. vitrectomy) in their cost estimates [50], whereas no DR-specific treatment was specified in the German study by Kähm et al. [51] (Table 3).

As for studies examining costs in patients affected by both DR and DMO [52, 53], direct medical costs ranged from $742 to $2,955 per patient per annum. Costs of treatment, such as laser therapy and vitrectomy, were considered in both studies [52, 53]. In terms of direct non-medical costs and loss of productivity, they were

estimated at $1,155 and $2,402 per patient per annum respectively in the German study by Happich et al. [53].

3. Costs associated with inherited retinal diseases (IRDs).

A Danish study was the only study in this review to describe costs associated with IRDs [59]. This observational study with an implied healthcare payer perspective, reported direct medical costs by age group at the patient level [59] (see Fig. 7 and Supplementary Table 9). Danish patients whose IRDs arose in childhood were considered. The direct medical costs accounted for both ophthalmological and non-ophthalmological care and were estimated, on average, at $674 per patient per year, across all age groups combined. As for direct non-medical costs, they pertained to formal care and were estimated at $241 per patient per year.

4. Costs associated with macular oedema due to retinal vein occlusion (RVO) and myopic choroidal neovascularisation (mCNV).

Three studies analysed costs associated with macular oedema secondary to RVO [57, 60] and mCNV [61] (see Fig. 8 and Supplementary Table 9). Two of these were Spanish [57, 61] and one covered multiple countries (Germany France and Italy) [60]. All studies were observational studies with a bottom-up approach to resource quantification and time horizons restricted to one year. In terms of perspective, the two Spanish studies took a societal perspective [57, 61], while the multi-country study opted for a healthcare payer perspective [60]. All costs were reported annually at the patient level [57, 60, 61]. Direct medical costs were estimated in all studies, followed by indirect costs in two Spanish studies [57, 61] and direct non-medical costs in the multi-county study [57].

For RVO, direct medical costs were estimated at $9,018 [57] in Spain, and ranged from $1,785 to $4,085 across Germany, France and Italy in the multi-country analysis [60] (Supplementary Table 9). In terms of medical resource use, both studies accounted for ophthalmological care and more specifically encompassed treatment modalities, including laser therapy (i.e. photocoagulation) [57, 60], surgery (i.e. vitrectomy) [57] and steroid injections [60] (Table 3). Of note, anti-VEGF injections were not considered in neither of the two studies. Furthermore, the multi-country study reported direct medical costs by RVO type, which ranged from $1,361 to $3,395 per patient per annum for branch RVO and from $2,078 to $4,774 per patient per annum for central RVO (Fig. 8.a and Supplementary Table 9). Productivity loss in patients, defined as temporary and permanent occupational disability, was assessed in one Spanish study and estimated at $2,704 per patient per annum [57].

As for costs associated with mCNV, they were examined in only one Spanish study [61] (Fig. 8.b and Supplementary Table 9). Direct medical costs were estimated at $3,859 and accounted for both ophthalmological and non-ophthalmological care resources. However, the treatment costs were not fully accounted for in this study as the authors noted that they were unable to estimate costs associated with pharmacological treatment. Direct non-medical costs, as well as productivity loss in patients, were estimated at $498 and $7,976 per patient per annum respectively.

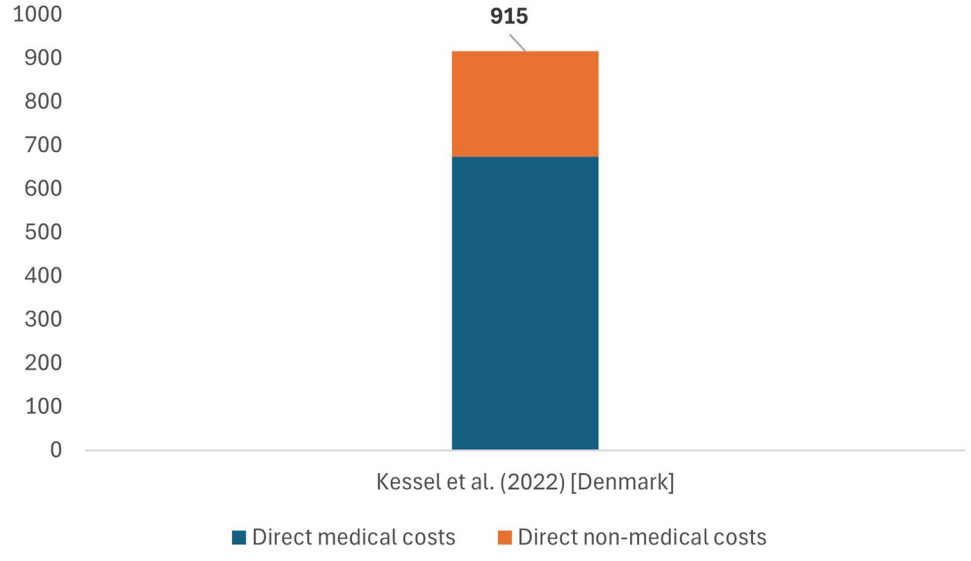


Fig. 7 Total annual costs per person for IRD (in 2024 USD)

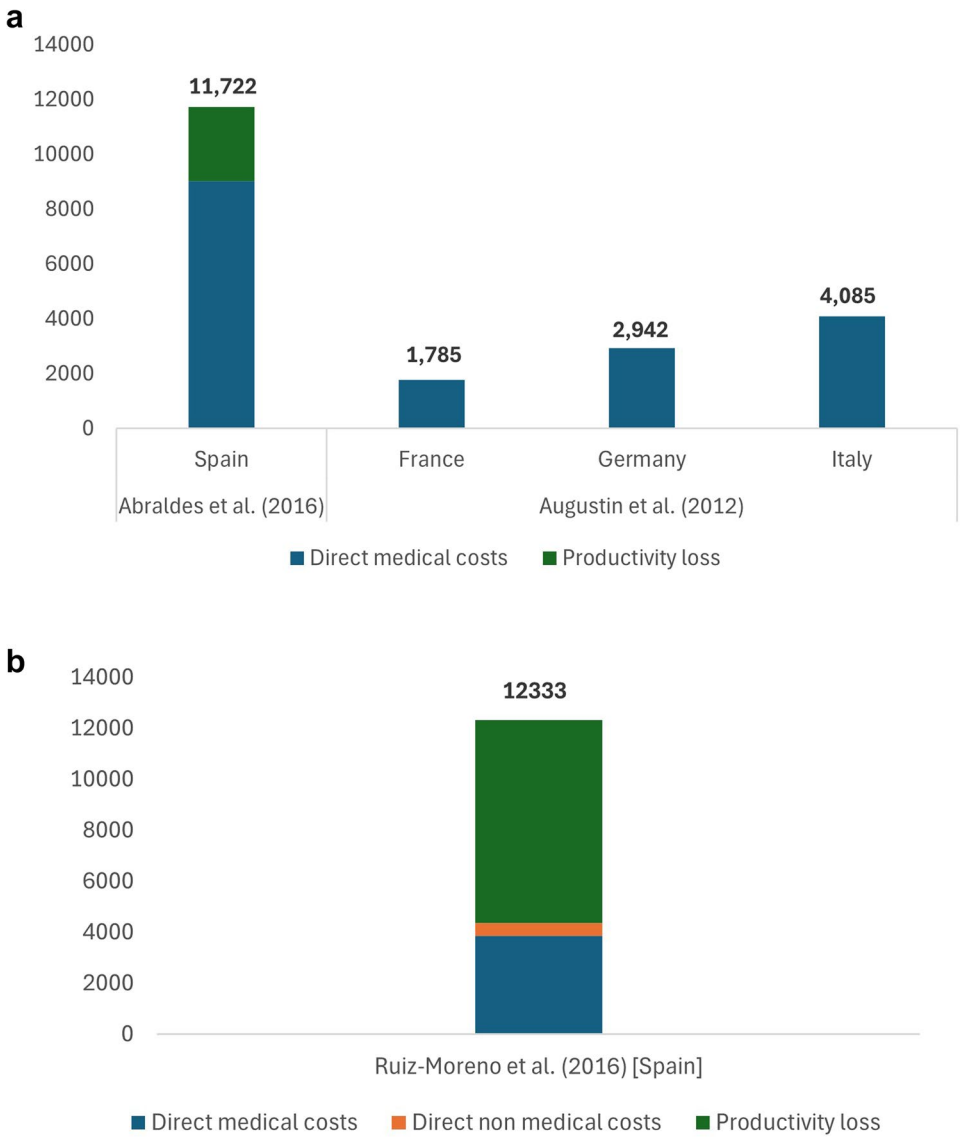


Fig. 8 Total annual costs per person for macular oedema secondary to RVO and mCNV across countries (in 2024 USD). **a** RVO. RVO: retinal vein occlusion. **b** mCNV. mCNV: myopic choroidal neovascularisation]

Discussion

This systematic literature review investigates the economic impact of retinal diseases in Europe, specifically those for which gene therapy is emerging, which will have significant clinical and economic effects. The review identified 28 studies that varied in terms of disease of interest, sample size, methodology, as well as how costs were reported and valued, thus concurring with previous literature that found a high degree of heterogeneity across these types of studies [17, 21–23].

While a large number of retinal diseases were considered, almost half of the articles related to the costs of nAMD. There were less than 5 publications for each of the other conditions individually. Furthermore, only one publication was identified reporting costs of IRD and macular oedema secondary to mCNV respectively. Of note, eight studies [47–53, 59] did not distinguish between costs of different conditions, further hindering the interpretation. Neovascular AMD, being one of the leading causes of vision impairment and blindness in western countries, as well as the first targeted retinal disease by anti-VEGFs, has garnered much attention over the years. Furthermore, the long-term aspect of treatment provision and associated clinical follow-up in nAMD has led to high economic burden. This in turn could be reflected by higher number of economic studies conducted on the subject as opposed to other retinal diseases. Concerning dry AMD, there were significantly fewer studies estimating the costs of this condition, as opposed to its wet counterpart, nAMD (3 vs. 12). Several

reasons could explain the lack of studies in this area. For instance, although 85% of AMD patients have the dry form of AMD, disease progression is typically slower and less likely to lead to blindness as in nAMD [62]. Treatment options for dry AMD have been lacking and preventive measures, such as smoking cessation and adopting a healthy diet, are recommended [62]. Also, although two molecules, pegcetacoplan (Syfovre) and avacincaptad pegol (Izervay), have received FDA market approval in recent years for the treatment of geographic atrophy (the advanced form of dry AMD), they have not yet received regulatory approval from the European Medicines Agency, in large part due to the lack of meaningful clinical benefit found in patients receiving these [63]. The cost variations observed across the studies could be influenced by multiple factors, including the type of cost components included, the time periods at which the studies were conducted, cross-country differences in clinical practices, social and economic settings, as well as how and which uses of resources were estimated and valued in the studies. While the majority of studies reported direct medical costs, a narrow perspective of the medical costs was typically adopted wherein only ophthalmological care resources were included. Non-ophthalmological health care resources were not consistently accounted for, thus potentially underestimating health care resource use and costs amongst patients prone to falls and depression [64–66]. While direct non-medical costs were considered in about half of the studies and generally represented a lower share of the total costs incurred compared to direct medical costs, they mainly pertained to the use of formal care and assistive technologies, and often did not capture other uses of resources, such as transportation. For instance, a number of the conditions for which costs were assessed may be treated with anti-VEGF injections, which require patient to frequently travel to a medical facility and incur substantial costs related to transportation [13]. A systematic and more extensive inclusion of non-medical resources (i.e. transportation, formal care and assistive technologies) should be considered in future studies to help estimate the true economic cost. As for indirect costs, they were estimated in a minority of studies (n = 10 [34, 37, 39, 53–58, 61]), and mainly pertained to productivity losses for patients. Only three studies evaluated the costs related to informal care [34, 39, 55]. Furthermore, intangible costs, related to the patient's loss of quality of life, were estimated in only two studies [34, 55].

Relatedly, inclusion of treatment costs (or exclusion of such) contributes to cost variations. For instance, the general absence of available treatment in dry AMD and almost all IRDs correlates with relatively low direct medical costs identified in this study ($300 - $3,000 per patient per annum) for these conditions. On the other hand, a significant number of conditions, including nAMD, DR, DMO and macular oedema secondary to RVO and mCNV, are conditions for which anti-VEGF based treatments are indicated, but only a minority of this study's results included costs of anti-VEGF injections (n = 9 [34–36, 48–50, 54–56]). For instance, although anti-VEGF injections have been the standard of care in nAMD for over a decade, most studies examining the costs of nAMD used cost data prior to when anti-VEGFs became widely available in Europe and focused on other historically more common forms of treatment, such as laser therapy. This may have impacted the cost estimates associated with nAMD reported in this review, which may not accurately reflect current practices and the true medical costs of treating nAMD in Europe, and therefore signals the need for further studies conducted in this area that fully capture current medical resource utilisation and associated costs, perhaps through the use of clinical registries, thus avoiding misestimating costs. In other cases, studies were unable to assess costs of anti-VEGF treatments used in patients due to lack of information (i.e. dosage and treatment duration) [57, 61]. Of note, three out of the nine studies that included anti-VEGF costs were model-based [34, 54, 55], two of which reported comparatively higher costs per patient (both medical and total) than the other studies included in the results.

Research has suggested that the delivery of anti-VEGF injections is a major cost-driver and is expected to increase over time [12, 50, 67, 68]. For instance, a Norwegian study [50] found that the use of anti-VEGF injections in DR patients with and without DMO replaced other forms of therapy (i.e. laser therapy) and led to higher treatment costs over time. Other studies showed a similar trend regarding the increase in the number of anti-VEGF injections, which is projected to become even greater in the future [12, 68]. While the high price of anti-VEGFs contributes to increasing costs, their long-term associated care – requiring careful follow-up and monitoring from skilled practitioners - is also a financial strain on patients and health systems that is not fully captured by current costing studies [12, 13, 67]. The repeated injections may take a significant toll on the patients' emotional wellbeing and quality of life [11, 69], adversely affecting adherence and potentially leading to under-treatment and deterioration of the condition [70]. Even with optimal adherence, anti-VEGFs' effectiveness can subside in nAMD patients, owing to underlying pathological changes occurring over time, leading to further vision loss [71, 72]. Also, anti-VEGF injections failed to improve or stabilise visual outcomes in over 50% of DMO patients after two years of treatment [73].

Therefore, despite the expected potential of anti-VEGFs, inadequacies and gaps persist. To address these absences and inadequacies of currently available treatments in retinal diseases, longer-acting treatments such

as gene therapy, are sought [74]. The small size, accessibility, confined structure, and immune-privileged status of the eye [74, 75], make it an ideal target for gene therapy, which in turn is less likely to cause excessive inflammatory and immune responses when delivered to this organ [76]. However, despite over three decades of research [19] and a large number of clinical trials testing gene therapy in retinal diseases (Table 1), the provision of such therapy to patients remains uncertain. Furthermore, achieving market authorization for gene therapies (classified as advanced therapy medicinal products (ATMPs)) does not guarantee their immediate uptake or provision by health systems, which are constrained by limited budgets and capacities. Evidence is required to guide and support such clinical and reimbursement decisions. Economic evaluations, within health technology assessments (HTAs), provide decision makers with information on the clinical benefits and cost-savings of these novel and costly therapies. Wherein, data from clinical trials and studies such as those analysed in this review, is incorporated in economic models to assess the value of innovative medicines.

Assessing the cost-effectiveness and economic value of ATMPs is complex [20, 77, 78] and is further complicated by high levels of uncertainty, owing to the lack of data regarding safety (potential adverse events resulting from the delivery procedure and long-term side effects) and effectiveness, as well as suitable comparators for several conditions typically targeted by ATMPs. Of note, future gene therapy may have varying effects on disease progression and visual restoration, even more so if the condition affects both eyes at different levels of severity, which in turn could lead to significant differences in cost savings. As such, these aspects need to be accounted for in economic models through supplementary analyses such as scenario analysis. Additionally, small patient populations, as it is the case for many retinal diseases, such as IRDs, can exacerbate the situation. Current national guidelines on the design for economic evaluations vary and few recommend taking a societal perspective and including indirect costs [79], which could underestimate the economic value of the therapy and hinder or delay their provision. For instance, while this review identified only one original study estimating costs of IRDs in Europe [59] (reporting direct costs of $900 per patient per annum), other international studies suggested that 81% to 90% of the costs associated with IRDs are indirect and intangible [80–84]. As such, if IRD patients received effective gene therapy, substantial indirect and intangible costs may be avoided. However, knowing if these savings would be sufficient to offset the direct medical costs of the therapies requires longer term data, which typically is not captured by current clinical trials.

Also, recommended discounting methods may be ill adapted in the case of gene therapy due to very high upfront costs, and experts have suggested to explore the use of different discount rates in supplementary scenario analyses [20]. Furthermore, one could speculate that the steep cost of gene therapy at market entry may decrease within the following years depending on its patent protection status and potential license agreements surrounding it.

In existing HTA processes, value of interventions typically encompasses benefits that translate into meaningful improvements in patients' everyday functioning, as well as cost-savings. Some argue that other factors may also contribute to the value of ATMPs to patients and society include hope, an unmet need addressed, perceived innovativeness and the intervention's propensity to transform the lives of patients and their carers [78, 85–87]. Uptake of ATMPs by individual European states accelerated over the past few years [88] and the recent EU HTA Regulation on Joint Assessment, which aims to harmonize clinical assessments of health technologies across EU member states, should further assist to support evidence-based decisions, reduce duplication, and improve patient access to innovative treatments [89]. Some argue that more tailored solutions within the framework will be needed to handle the high levels of uncertainty associated with gene therapy [90]. Only time will tell if the aims are achievable, meanwhile robust evidence will be required to inform the assessments [91].

There is growing interest in the types of costs that need to be accounted for in health economics assessments and the ways in which these need to be sourced to accurately capture value [28]. Experts have recognized the importance of adopting a standardized approach when quantifying costs, which ensures adequate comparisons across studies, especially in the case of systematic reviews where the fullness of incurred costs (including direct, indirect and intangible) pertaining to a particular disease area need to be reflected [22, 28, 29]. Additionally, studies have increasingly adopted a societal perspective and included indirect and intangible costs [34, 55], which in turn could aid decision-makers appraise the full extent of the economic burden.

Finally, this review presents several limitations worth noting. First, its geographical scope was restricted to the European region, which could have limited the number of data points considered in the analysis. Second, while this review targeted studies that included patient populations with retinal diseases of interest, it did not distinguish between patients based on level of disease severity nor laterality. Third, an over representation of studies reporting costs associated with nAMD could have made the costs appear higher across retinal diseases than they

actually are, thus potentially inducing bias. Another limitation is that the effects of differences between retinal diseases that occur in older age (i.e. AMD) and those that afflict younger individuals (i.e. DR and IRD) on costs were not examined in this study and are speculated to be substantial, especially in terms of productivity loss.

Conclusion

This systematic literature review evidences the heterogeneity among studies analysing the economics of retinal diseases underlying vision impairment. Several of the studies are outdated and unreflective of the diseases' complexity, especially in terms of current treatment guidelines, varying disease severity, potential treatment failure, out-of-pocket expenditure and indirect costs over time. An oversimplification, driven by the use of models, short time horizons and the aggregation of costs across multiple conditions, may be misestimating the actual costs incurred, which in turn makes interpretation of these results difficult. The paucity in the literature, compounded with the fact that most of the studies were conducted in Western Europe, signals the need for further research investigating the costs associated with these conditions that accurately reflect the diversity of health systems, as well as social and economic settings across the European region. This in turn could facilitate a timely and adequate consideration of costs of future innovative therapies for retinal diseases, as well as the cost-savings they would generate, by national HTA bodies, whose decisions will have a significant impact on the delivery of these technologies to patients.

Abbreviations

Abbreviation	Full name
AMD	Age-related macular degeneration
DR	Diabetic retinopathy
IRD	Inherited retinal disease
nAMD	Neovascular age-related macular degeneration
Anti-VEGF	Anti-vascular endothelial growth factor
DMO	Diabetic macular oedema
RVO	Retinal vein occlusion
mCNV	Myopic choroidal neovascularisation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Cost of illness	COI
Non-proliferative diabetic retinopathy	NPDR
Proliferative diabetic retinopathy	PDR
Dexamethasone implant	DEX implant
Advanced therapy medicinal product	ATMP
Health technology assessment	HTA

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

CW designed the search strategy and performed the search. All authors reviewed articles and interpreted results. CW drafted the manuscript and other authors reviewed and edited the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

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Competing interests

The authors declare no competing interests.

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