

A systematic review of teleophthalmological studies in Europe

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Abstract

• A systematic review of the recent literature regarding a series of ocular diseases involved in European telemedicine projects was performed based on the PubMed, Google Scholar and Springer databases in June 2017. Literature review returned 44 eligible studies; among them, emergency ophthalmology, diabetic retinopathy, glaucoma, age-related macular disease, cataract and retinopathy of prematurity. The majority of studies indicate teleophthalmology as a valid, reliable and cost-efficient method for care-provision in ophthalmology patients which delivers comparable outcomes to the traditional examination methods.

• **KEYWORDS:** teleophthalmology; telemedicine; Europe; glaucoma; cataract; diabetic retinopathy

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INTRODUCTION

Tele is a Greek word that means “distance” and ophthalmology is a discipline of medicine dealing with the anatomy, functions, pathology and treatment of the eye^[1]. Therefore, according to the etymology of the word, teleophthalmology means ophthalmology from a distance. Teleophthalmology is a method which contributes to the examination, investigation, monitoring and treatment of patients’ eye-related problems with the care provider and the patient located in different geographical areas^[1].

The advances of medical technology and of telecommunications have allowed the introduction of telecare. One of the first applications of telemedicine to ophthalmology took place in 1987 as part of a project, which aimed to monitor retinal vessels during flights into space. To confirm its efficacy, the Johnson Space Center in Houston developed a system, which

could transmit real-time fundus images that were taken by a portable video fundoscope^[1].

Teleophthalmology can contribute to the examination of a variety of eye-related problems. Among the most common are diabetic retinopathy (DR) and glaucoma, which are the most frequent causes of blindness in Europe. Aiming at the reduction of blindness by these diseases, major European initiatives [United Kingdom (UK), Denmark, Germany, Czech Republic] were merged and created tele-ophthalmological services-citizen-centred applications (TOSCA)^[2]. In fact, TOSCA project, a study supported by European Union (EU), aimed to estimate the feasibility of a telescreening procedure for DR at different locations of Europe, the quality assurance procedure and the satisfaction of patients and healthcare professionals (retinal photographers and graders). The telescreening has been tested in South Wales (UK), Aarhus County (Denmark), Trier/Bavaria (Germany), Dublin (Ireland) and Prague (Czech Republic)^[2].

Increased life expectancy nowadays multiplies the need of ageing populations for eye-care services and puts pressure on healthcare systems to provide rural and remote populations with adequate care. Without any intervention, it is expected that the number of blind people worldwide will increase from 44 million in 2000 to 76 million in 2020. Internet-based eye care (teleophthalmology) is considered to be a solution for this problem by which eyecare services can be available to everyone at a low cost^[3]. In order to improve the eye health of the UK and prevent avoidable sight loss by 2020, “VISION 2020: The Right to Sight” was established in 1999 via the collaboration of organisations^[4].

According to published literature, teleophthalmology could be a suitable and efficient method, especially in diseases, in which a digital imaging system is useful for diagnosis and intervention. With the contribution of teleophthalmology, “the information travels instead of the patient”^[1], because it provides the rural and remote population with the opportunity to be examined by eye specialists. In this way, it plays a considerable role in ophthalmic disease screening and supports preventive medicine.

Additionally, teleophthalmology covers many medical activities, including making diagnosis, treatment, prevention, research, distant learning and continuing education^[1,3]. Specialists have the possibility to give consultations with flexible timetables and locations, even from their home. Furthermore, teleophthalmology makes significant savings in

Table 1 Studies' design

Studies	Comparative studies	Descriptive studies	Prospective studies	Retrospective studies
References	6-8,10,12-18,27-28,35,37-40,45,53-54	9,11,19-26,34,36,41-44,46-52	7-8,10,18-22,27,35	12-14,43
No. of studies	21	23	10	4

time and travel expenses^[3]. As a result, the acceptance by the examined population is remarkable. In addition to the tele-eye care application, advantages of digital imaging systems include short examination time, electronic medical images and the ability of non-ophthalmologists to screen for diseases^[1]. Teleophthalmology provides secondary specialist advice in the diagnosis and management of difficult cases^[5]. It also supports real-time surgical telementoring by which complex eye-care procedures are taught^[3].

However, there are a series of conditions that have to be addressed in order to broaden the application of teleophthalmology^[1]. Among them are the lack of teleconsultation infrastructure, the cost of the necessary equipment, the competence of medical and non-medical instruments to make accurate measurements and take images of high quality, the need for training of suitable staff, the deficiency of guidelines and protocols and the effort to preserve personal data safe and private during their transfer *via* the internet.

Within this context, primary objective of this study is to review the recently published literature regarding teleophthalmology in Europe, describe screening methods and equipment depending on the examined eye disease and evaluate cost-effectiveness, patients' compliance with treatment and satisfaction about telemedicine services.

SUBJECTS AND METHODS

A systematic search for relevant studies was performed based on the PubMed, Google Scholar and Springer databases using the following search terms: teleophthalmology AND Europe, teleglaucoma, teleophthalmology AND diabetic retinopathy AND Europe, telemedicine AND hypertensive retinopathy, telemedicine AND cataract. The search was conducted in June of 2017. Search filters and language restrictions were not used in this initial search. The results of this search were checked and only articles with a relative to the subject title were selected. Afterwards, the abstracts and full texts of these selected articles were reviewed thoroughly and the following data were extracted and assessed: examined eye-related problem, country, staff, screening method, equipment, comparison with traditional system, cost-effectiveness, patients' compliance, patients' and staff's satisfaction, and image quality. Both comparative and descriptive studies in adults, adolescents and infants were included in this review. Articles not available in English, German or Spanish language were excluded. When the eligible articles were not available in full text, abstracts were used as a source of information.

Studies' Design The present review included 23 descriptive studies and 21 comparative studies (Table 1)^[6-54]. Among them 10 were prospective studies^[7-8,10,18-22,27,35] and 4 retrospective^[12-14,43], while there was not any relative statement in the rest of the studies. Eleven^[6-8,10,12-18] of the comparative studies dealt with glaucoma patient examination, while two studies^[27-28] compared conventional with telemedical examination of infants for possible retinopathy of prematurity (ROP). Eight^[35,37-40,42,53-54] of the studies compared different methods of teleophthalmological screening for DR, while the rest of the comparative studies referred to telemedical evaluation of cataract patients^[45] and examination of patients with hypertensive retinopathy^[53-54].

Staff The majority of studies indicate that a variety of specialties is necessary for the normal function of teleophthalmological services. The most common medical or paramedical staff is ophthalmologists (consultants and/or residents)^[6,10,16,18-19,21,27,39-43,45-49,54], optometrists^[6-9,12-15,17], trained nurses^[8,15,18-19,28,34-36,44,46-47], general practitioners (GPs)^[9,16,21,39,42-43,49,54], technicians (who mainly collect data)^[14,16,18,34,36,46], clerks^[19], and ophthalmic photographers^[35,39]. One or more of these specialties were involved in each project. In some studies^[27-28], which dealt with ROP screening, neonatal nurses were responsible for image capture and/or image grading. Regarding ophthalmologists' responsibilities, they were multiple. For example, they evaluated^[40-43,49] or graded^[48] photos, made further assessment of patients, if it was necessary^[46], had a teleconsultation^[47] with patients or they participated in studies in order to compare their examination results with the results of GPs^[54].

Screening Methods Screening methods in published studies depend primarily on the examined eye-related problem (Table 2).

RESULTS

Glaucoma It is known that increased life expectancy will put pressure on ophthalmological care-delivery systems. Moreover, it is probable that these systems will depend increasingly on teleglaucoma, although the capabilities of current technologies for diagnosis and monitoring will not meet the goals of the teleglaucoma projects from the beginning.

Since the end of the 90s, some studies which compared costs of monitoring patients with glaucoma by ophthalmologists in hospitals and community optometrists^[6-7] were published and examined the outcome of care offered by these two types of monitoring^[8].

Table 2 Screening methods

Screening methods	References
Ophthalmic slit-lamp examination (anterior segment or fundus)	7,12-13,15-16,44,47-48,53
Binocular dilated indirect ophthalmoscopic examination	8-9,27
Gonioscopy	15-16,18
Fundus photography (nonmydriatic or mydriatic)	14-18,27-28,34-43,46,49-50,53-54
Taking video pictures (fundus video photography or anterior segments photography)	10,16,18,44-45,47-49
IOP measurement (GAT)	7-9,12-13,15-18,42,46,50
IOP measurement (Perkins hand Held-contact applanation tonometry)	9
IOP measurement (air tonometry)	18
RNFL imaging	16-17,50
Visual field testing (automated Humphrey or Octopus)	7-9,12-16,18,46,50
Ultrasound pachymetry	15
Videoconference	10,16,23,44-45,47-48
Online help by telephone	21,46
Snellen or logMAR visual acuity examination	8,15,18
Focimetry	15
Eye monitoring camera snapshot	23,52
Amsler test	42
OCT (fundus: DR, ARMD, glaucoma)	50
Fluorescein angiography	50

IOP: Intraocular pressure; GAT: Goldmann applanation tonometry; RNFL: Retinal nerve fibre layer; logMAR: Logarithm of the minimum angle of registration; OCT: Optical coherence tomography; DR: Diabetic retinopathy; ARMD: Age-related macular degeneration.

Henson *et al*^[9] reported the primary results of a referral refinement scheme, which was designed aiming the reduction of the number of false-positive referrals to the hospital, and its financial costs to the National Health Service (NHS). Patients with suspicion of glaucoma were referred to community optometrists. Depending on whether or not they met the referral criteria, they referred directly to a special eye hospital or they were returned to the referring optometrist, respectively. A 40% reduction in the number of new glaucoma referrals to the hospital eye service (false-positive referrals) and a cost saving of £17 per patient was reported.

Crowston *et al*^[10] dealt with the comparison between the examination of trabeculectomized eyes *via* slit-lamp and the teleophthalmological examination. For this reason, a prospective randomized study was conducted, which concluded that although both methods could evaluate reliably the operated eyes, telemedical examination was inferior as regards evaluation of bleb height and bleb wall thickness. The comparison agreement was good for bleb leak, but any of these techniques could not sufficiently evaluate bleb morphology and microcysts.

Schargus *et al*^[11] assessed a variety of types of secure medical data exchange methods [internet, Universal Serial Bus (USB) stick and smartcard] in some countries of Europe (UK, Germany) in order to create an electronic patient record system for glaucoma (GlaucoCard system), which could contribute

to storage and transfer of data. These data can be valuable for referrals or for teleconsultation of specialists. As a result, treatment of glaucoma patients and generally quality of their medical care would be improved, and healthcare costs caused by unnecessary repeated examinations would be diminished.

Ang *et al*^[12] performed a retrospective study, in which the quality of the glaucoma referrals from the community optometrists in the northeast of Scotland before and after the introduction of the new general ophthalmic services (GOS) contract in April 2006 in Scotland was estimated. After the implementation of this contract, true-positive referrals were remarkably increased, while a reduction of false-positive referrals was noticed.

Another study which examined the efficiency of community optometrists was conducted by Trikha *et al*^[13], who presented a refinement scheme as an example of practice-based commissioning led by a glaucoma consultant. Refinement schemes could intensify the positive predictive rate in glaucoma diagnosis, glaucoma suspect or ocular hypertension, prevent expenses in healthcare costs and result in more effective provision of healthcare.

Wright and Diamond^[14] reported results of a web-based electronic patient record aiming the assessment of a virtual specialist supervision of glaucoma patients. This is the largest tele-glaucoma study reported so far about 4000 patients (24 257 reviews) underwent testing and clinical examination.

Optometrists examined patients, classified them into five categories (“normal”, “stable”, “low risk”, “unstable” and “high risk”) and uploaded data to a web-based electronic patient record in order for them to be reviewed by a glaucoma specialist. There was an agreement between clinic optometrists and glaucoma specialists in 87% of cases. Of 13 patients were assessed as high risk of blindness by the glaucoma specialist but not by the optometrist. The glaucoma specialist reduced the number of review appointments that were decided by optometrists, by 2.4%.

Keenan *et al*^[15] described glaucoma screening in 1733 individuals between 2010 and 2013, who were assessed clinically by an optometrist at a remote area. The applied screening methods were Goldmann applanation tonometry (GAT), pachymetry, monoscopic colour optic disc photographs and automated Humphrey visual field testing. Optometrists decided whether patients had glaucoma or were suspect and whether they should be examined further at a hospital or they would be a false positive referral. A hospital optometrist and consultant ophthalmologist subsequently reviewed virtually all data. This screening program was proved to be a successful method of glaucoma referral evaluation and very useful for the reduction of false-positive referrals for glaucoma to a hospital.

Tuulonen *et al*^[16] conducted a pilot study, in which a control group consisted of 41 patients with glaucoma underwent eye examination at a university eye clinic and one year later 29 glaucoma patients were examined in a rural healthcare center. Rural health center patients were examined by ophthalmic resident and GP. Both patients groups had equal satisfaction with the ophthalmic service. Of 96% teleophthalmologically examined patients wanted to have their next visit in their own healthcare center instead of the university clinic mainly because of reduction in traveling (96%), costs (92%) and time (92%). Comparing teleophthalmology and conventional visits the costs were equal, but reduced traveling saved \$55 per visit. However, the remote center provided images of poorer quality compared with the university clinic.

de Mul *et al*^[17] reported the results of a glaucoma screening study. A total of 1729 patients were screened with a nerve fiber analyzer by 10 optometrists and the images were then further assessed by trained technicians at a hospital. The quality of the images was satisfactory in 89% of cases and there was a high (81%) agreement between optometrists and the hospital about normal or suspect test results. Eighty patients were diagnosed for first time with glaucoma. Additional testing at the hospital was necessary for only 27% of the patients and 11% of them consulted an ophthalmologist.

Labiris *et al*^[18] carried out a three-year prospective study from 1999 to 2001 in order to estimate the quality of medical services which were provided to patients with glaucoma in remote locations. Five remote areas in Greece were visited by

an appropriately equipped mobile medical unit (fourwheel-drive vehicle), where in total 1205 patients were examined, of whom 230 were found with glaucoma. Apart from the traditional examination by the unit's medical staff, consultants at a hospital in Athens examined 56 glaucoma patients telemedically. Remarkably high proportions of reduced awareness of glaucoma (77%, in comparison with urban patients: 20%), low compliance (68%, urban: 23%) and high intraocular pressure (IOP) (21%, urban: 5%) were observed. However, in 13 of the 56 telemedical examinations a poor telephone connection led to technical difficulties.

Twelve months after the beginning of the telemedical project, each care provider (medical and paramedical staff) answered a 10-item questionnaire aiming the assessment of their opinion about telehealth services, their motivation and their experience^[19]. Nurses proved to have the lowest motivation about telemedical services. Regarding the most important factor that determined the efficient use of telemedicine, all members of the staff agreed that in the first place was the lack of readiness of residents in rural areas. In addition, the department was evaluated as capable of adequately efficient teleophthalmological care by the consultants, the inhabitants and the clerks.

Labiris and Petounis^[20] developed a framework in order to evaluate telemedical care for patients with glaucoma who live in remote locations. Researchers used seven performance indices (three of efficiency and four of quality). According to the results of this framework, there was a significant likelihood that isolated communities suffer the complications of glaucoma more than urban populations. Additionally, there were gaps both in the efficiency of services and in the quality. The efficiency gaps indicated that future change is crucial and gaps in the quality revealed the dissatisfaction of isolated populations with the provision of care.

Furthermore, the same group of researchers^[21-22] conducted a prospective eight-year study in order to evaluate the efficiency of internet-based counseling offered to remote patients and make the internet-based service reliable. Concerning the term “remote patient”, the writer explained that it does not only refer to patient in remote areas or indicate that local healthcare resources are not adequate (physical remoteness), but also it refers to the creation of remote patients even in urban areas due to poverty, social isolation, ethnic discrimination, prejudice, cultural ethics and religion (non-physical remoteness). Consequently, internet-based counseling can improve patient compliance and support preventive medicine.

LiveCity e-Health constitutes a research program in Europe, which tries to improve provided treatment and follow-up of patients with glaucoma at their home, *via* telemonitoring with high definition video-to-video (v2v) communication from a hospital. Moreover, this program aims to decrease the cost of health and reduce visits to the hospital^[23].

Diamantopoulos *et al*^[24] carried out a work that presents the LiveCity platform for e-Health. This work described two e-health use-cases. The first one was based on the use of v2v for remote glaucoma patients telemonitoring, while the other one evaluated the advantages of v2v for emergency cases. A future plan was the analysis of the results. As regards remote telemonitoring of glaucoma patients, this telemedicine platform provides two applications, one for the doctor and one for the patient. Both of them are user-friendly. By using “Doctor Telemedicine plugin”, the doctor is able to have a direct v2v communication with the patient and take a snapshot if additional information is necessary for the examination. In contrast, in case a patient needs help, “patient telemedicine plugin” provides the doctor with the possibility of an immediate notification *via* this application or a short message service (SMS).

Another work that presents the LiveCity platform for e-Health took place by Alonistiotis *et al*^[23]. This project performed the development of a user-friendly software application, which can be easily used by old patients at home and can facilitate keeping of medical history and digital data. A web camera, which could take high quality snapshot eye photos, was used. The improvement of training, reminding and correct application of eye drops, namely compliance to therapy, were some direct aims of the project. Although only two patients were entered into the project, more patients are planned soon to be enrolled in the study.

According to Stamatelatos *et al*^[25], one of the aims of LiveCity project is the improvement of medical services by using high quality v2v. In this publication, the related concepts, the e-Health scenario and the pilot set for the tele-monitoring service fulfillment, deployment and provision were referred. Specifically, this paper focused on daily medical treatment of glaucoma while the patient stays at home and GP and/or doctor specialist and/or nurse keeps in touch with the patient.

Molnar and Weerakkody^[26] assessed factors that might affect the long range adoption of a teleglaucoma project in a greek hospital. Various factors arose from the study (technical, usability, process, institutional support, ethics and privacy, clinicians' fear of change and patients' demography related factors). Both the benefits and problems of video based remote treatment of glaucoma were analyzed and it was explained that network connectivity, quality of the video communication, reliability and usability of the application played a pivotal role in the achievement of study's success.

Retinopathy of Prematurity Acute ROP is a disease of premature infants, which influences the postnatal maturation of the blood vessels of retina and can threaten the sight^[27]. New chances to improve ophthalmic care and support scientific research are created with the contribution of digital wide-angle photography combined with telemedicine.

Castillo-Riquelme *et al*^[28] examined five screening strategies, which can contribute to the identification of ROP in prematures. The common strategy was binocular indirect ophthalmoscopy (BIO). However, alternatively some other strategies were recommended based on digital photography (use of a digital colour fundus camera by non-ophthalmologist professionals, *i.e.* neonatal or specialist visitor nurses and grading by the nurses or remote ophthalmologists). Cost-effectiveness of each strategy was evaluated. It was found that alternatively to direct visualization by ophthalmologists, a cost-effective solution was screening by specialist visitor nurses, who had been trained to capture and interpret images with the use of portable digital cameras.

Lorenz *et al*^[27] performed the results of a 6-year study, which referred to wide-field digital imaging based telemedicine (WFDI telemedicine) and aimed to decrease the risk for vision loss from ROP. The installation of wide-angle digital fundus cameras took place in five neonatal intensive care units in Germany, where all prematures at risk of ROP were screened with WFDI and subsequently were examined with BIO by the local ophthalmologists. Overall, 1222 babies at risk born prematurely underwent screening. The total incidence of clinically relevant ROP (CR-ROP, *i.e.* any ROP up to mid-peripheral zone III) was similar to ROP incidences that are reported in other West European countries (27.6%). All suspected treatment-requiring ROP (STR-ROP) stages were detected (100% sensitivity).

Diabetic Retinopathy DR is the most important cause of blindness in working age adults^[29]. Although guidelines for recommended eye examinations are well-established^[30-31], more than half of patients with diabetes mellitus (DM) are not examined regularly by an ophthalmologist. The main reasons for poor compliance are lack of visual symptoms in the early stages of DR, socio-economic reasons, geographic limitations and lack of patient and provider education about the importance of regular retinal examination for DR^[32]. Teleophthalmology could play a determinant role in the improvement of the quality of patient care. It could improve the co-operation between diabetologists and ophthalmologists and support screening for DR^[33].

Ophthalmology Diabetes Telemedicine (OPHDIA[®])^[34] in France described DR screening in 13 777 known diabetic individuals (2004-2006). DR was detected in 23.4% (3350) of patients. The grading of retinal photographs of at least one eye was not possible in 9.7% of patients. Undiagnosed severe non-proliferative DR (NPDR) or proliferative DR (PDR) and/or macular edema were found in 777 (5.6%) patients requiring urgent referral to an ophthalmologist for laser treatment. After the screening examination, 3478 (25.2%) patients were referred to an ophthalmologist for different reasons, including DR, cataract, and/or non-gradable photographs. Therefore, although

fundus photography (FP) cannot replace the examination by an ophthalmologist, it should be an alternative method that could be combined with teleophthalmology and improve the annual screening of DR.

Vujosevic *et al*^[35] emphasized the reliability of used nonmydriatic (NM) techniques and confirmed how important digital images during ophthalmoscopic examination were in screening and grading of DR. Sensitivity and specificity were 82% and 92% for detecting referable DR and 83% and 97% for referable diabetic macular edema (DME) for three NM fields fundus photos and remarkably lower (lower than 80%, which is the requested target of the British Diabetic Association necessary for an effective screening) for one field fundus photo. It was concluded that three colour 45-degree NM fundus fields can detect sufficiently critical levels of DR and DME, and suggest specialist referral, while one central 45-degree image could effectively estimate if DR and DME are present or absent, but not grade them.

In Padova^[36] was done a telematic screening program for DR, whose data were collected between 2005 and 2015 and were consisted of 17 344 screening exams of 9347 patients with DM. The follow-up of patients was determined according to the National Guidelines for Screening of DR. A reevaluation within 12mo was recommended to patients without DR or with mild NPDR, whereas patients with moderate NPDR are recommended a rescreening within 6-10mo and patients with severe NPDR or PDR or with maculopathy were referred to the DR Clinic in order to undergo a complete ophthalmic examination [optical coherence tomography (OCT) and fluorescein angiography, if necessary]. The conclusion of the authors was that a two-and-a-half-year screening for DR is safe in low risk patients [type 2 diabetes mellitus (T2DM) and duration <10y] without DR at first examination. Nevertheless, when other risk factors coexist, a more frequent follow-up is required.

Scarpa *et al*^[37] performed another pilot screening program in Ponzano in 2012 aiming the assessment of the feasibility of a future larger application compared with the "no prevention" strategy. Patients with "positive" fundus photographs obtained with a NM fundus camera were referred for further ophthalmological examination. Three colour, 45-degree, digital retinal photographs were taken by trained nurses and each of them was centred on the macula, optic disc, and midperipheral superior-temporal field, respectively. Sensitivity of three-field NM images was 82%, and specificity was 92% for detecting DR. The authors evaluated also the economic impact of the telematic screening and reported that this program was significantly important because a substantial saving was observed in comparison with the "no prevention" strategy (costs that avoid blindness and direct costs absorbed by the Regional Healthcare Service).

Invernizzi *et al*^[38] reported the 1-year (2012-2013) results of an observational study conducted in Milano. From an economic point of view, the significant cost saving of telemedicine in comparison with slit-lamp fundus examination (included reading center staff evaluating images, fundus camera and the cost of the standard funduscopic examination) was emphasized. In particular, this study compared slit-lamp fundoscopic examination (SFE) with semiautomatic three-field FP DR screening during a remote routine examination of 1281 adults with T2DM. During FP DR screening, 71% and 15% of captured images could not be graded before (BPD) and after pupil dilation (APD), respectively. Specificity of FP was 79% with APD, but only 25% with BPD. Among the subjects that were screened with FP APD, 18.7% had unreadable images, 64.3% had no DR, and 17% were found to have DR. The results from the completion of a questionnaire showed that 98% of patients had a positive attitude towards FP screening.

Luzio *et al*^[39] conducted a study within the TOSCA project. A macular and a nasal digital retinal image per eye were taken and sent to a central server. Officially recognized graders graded images remotely and sent the results back to the referring center. The percentage of gradable photographs was 99%. The majority of patients and healthcare providers (photographers and graders) were satisfied with the screening procedures. Only 6% of patients in one center was dissatisfied. The mean time needed for grading of each patient was found to be 5min. It was concluded that the feasibility of establishing teleophthalmological digital screening for DR using TOSCA system was significant.

In Norway, Johansen *et al*^[40] compared digital monochrome images with colour slides by screening 20 patients for DR with both methods. The agreement between the two methods was 0.95 and 0.89, with respect to disease or no disease. However, the agreement (k) between the two independent ophthalmologists, who graded the colour slides and the digital images, was 0.47 when colour slides were employed and 0.61 when digital monochrome images were employed. The researchers resulted that digital red-free monochrome images are a superior screening method for DR.

Martínez *et al*^[41] performed a descriptive, cross-sectional study, where 2435 diabetic patients were examined from 1 February 2006 to 1 February 2009, in order to estimate the prevalence of DR and evaluate their experience in DR screening. Three 45-degree fundus images of both eyes were captured, sent to the Department of Ophthalmology through the intranet of the hospital and assessed by two retina specialists ophthalmologists. DR was found in 17.90% of the total number of subjects; among them, 80.73% had mild-moderate PDR, 12.16% severe NPDR, 2.29% PDR, and 4.82% diabetic maculopathy associated with any level of DR. Quality of the retinographies was low in 1.69% of patients (41 patients).

A systematic review of teleophthalmological studies in Europe

Recently, an observational randomized study was conducted by Rodríguez *et al*^[42] aiming the identification of the prevalence (12.1%) and risk factors of DR in rural areas, the analysis of diagnostic accuracy among primary care physicians, of the agreement with ophthalmologists and of cost savings. From January 2010 to January 2015, 394 patients underwent an examination. It was mentioned that the risk of DR was higher when patients had hemoglobin A1c (HbA1c) >7.68% or when they were treated both with insulin and oral antidiabetic drugs. Moderate or severe DR was exhibited in 43.3% of patients who were correctly referred to specialists. Additionally, incorrect referrals to ophthalmologists increased from 91.7% in 2010 to 98.6% in 2014. The total saving of the program was estimated to be €152550.45.

Pareja-Ríos *et al*^[43] reported a retrospective study, in which the results of a DR screening program carried out in a primary care area were described. Data from 42 339 diabetic patients collected between 1 January 2007 and 31 December 2015. Regarding the ability of family doctors to correctly interpret fundus photographs, an increase of retinal images classified as normal from 55% in 2007 to 68% in 2015 was observed. Non-evaluable retinographies declined to 7% in 2015 due to the use of tropicamide in case of inadequate images. Severe cases detected have decreased from 14% with severe NPDR and PDR in 2007 to 3% at the end of the study period.

Emergency teleophthalmology Kulshrestha *et al*^[44] performed the results of a 2-year study (2007-2008), in which the teleophthalmological management of 22 emergency patients at a hospital in north Wales took place. A decrease in the need for emergency ambulance transfer was the result of the use of telemedicine.

Age-related Macular Degeneration Additionally, Kulshrestha *et al*^[44] described the use of videoconferencing equipment for a case presentation in order to improve managers' and clinicians' awareness of the intravitreal lucentis service for wet age-related macular degeneration (ARMD) in west Wales, and facilitate the discussion about regional service planning.

Cataract A case report was published by Smith *et al*^[45], in which the review of twelve postoperative cataract surgical patients *via* teleophthalmology was examined in order to evaluate the reliability and possibility of missing pathological data. The reliability of examination by video telelink was relatively good in detection of edema at the central cornea. Nevertheless, detection of edema at the corneal section or anterior chamber flare was not consistent and a complete failure of detection of folds in Descemet's membrane or anterior chamber cells was observed. Patients' experience of telemonitoring was enjoyable and reassuring.

Studies examining different eye disorders Some studies examined more than one ocular diseases^[46-54]. For instance,

Table 3 List of tele-ophthalmology studies in Europe

Eye disorder	Country	No. of studies	References
Glaucoma	UK	11	6-15,47
	Finland	2	16,46
	Netherlands	1	17
	Greece	9	18-26
	Spain	2	49-50
	Germany	2	51-52
ROP	UK	1	28
	Germany	1	27
DR	Finland	1	46
	France	1	34
	Germany	3	51-53
	Italy	4	35-38
	UK	1	39
	Norway	1	40
Emergency eye care	Spain	6	41-43,49-50,54
	UK	1	44
Cataract	UK	2	45,47
Hypertensive retinopathy	Germany	1	53
	Spain	2	49,54
ARMD	Spain	2	49-50
	Germany	2	51-52
	UK	1	44
Miscellaneous	UK	1	48
	Spain	1	49
	Greece	2	21-22

ROP: Retinopathy of prematurity; DR: Diabetic retinopathy; ARMD: Age-related macular degeneration.

glaucoma, DR, ROP, ARMD, trauma, emergency eye care, external eye diseases, diseases of anterior segment, hypertensive retinopathy, retinal vein or arterial occlusion, sequel of retinal detachment surgery, pigmentary epithelium alterations and other sight-threatening conditions (Table 3).

Cost-effectiveness Many studies examined if teleophthalmology is profitable for the NHS of each country or burdens economically the healthcare system without offering an equivalent profit to health.

Gray *et al*^[8] mentioned that the range of annual cost per patient for optometrists was from £68.98 to £108.98, while the range of cost for ophthalmologists in hospital was from £14.50 to £59.95. However, it was analyzed that the higher cost for community optometrists is explained by the fact that the follow-up interval for optometrists was 6mo, while for hospital was 10mo. If the interval between follow-up by optometrists was similar to that of the hospital services, the annual cost of visits to optometrists would be £46.31.

Henson *et al*^[9] found that referrals to the eye hospital were reduced by 40% (328 patients not referred-savings: £55 per visit, total saving: £42 033) and 780 visits to GPs took place

(saving of £15 per visit). In total, the cost saving was estimated to be about £17/patient.

Schargus *et al*^[11] mentioned that the storage of digital data in the GlaucoCard system could be used both for referrals and teleconsultation of glaucoma specialists. As a result, the treatment of glaucoma and generally the quality of glaucoma care would be improved and costs due to unnecessary repeated examinations could be decreased.

Wright *et al*^[14] predicted that annual glaucoma review visits in England would be reduced by 2.4% (57 600 fewer appointments). In this way, the NHS would save about £3 million. Nevertheless, no cost-benefit analysis was included in this study and cost-benefit of a virtual clinic for glaucoma in comparison with traditional in-hospital care could not be evaluated.

Tuulonen *et al*^[16] found that teleophthalmological glaucoma examination and conventional visits cost equal amount of money. However, the diminished traveling saved \$55 per appointment.

Referring to ROP, Lorenz *et al*^[27] explained that a blind person in Germany receives 300 000€ overall for a period of 50y as a direct pension. Therefore, the great cost of diagnosis and treatment failure emphasizes the pivotal role of the support of screening and treatment programs. According to the writer, despite the difficulty in evaluation because of the undoubted complexity of factors that are involved, teleophthalmology seems to have lower cost than BIO. Nevertheless, no formal analysis on the cost-effectiveness of this program has been conducted yet.

According to Castillo-Riquelme *et al*^[28], who evaluated cost-effectiveness in management of ROP in UK, teleophthalmology, in which visiting nurses undertake both image capture and grading (£172 per infant examined), and teleophthalmology, in which visiting nurses undertake image capture, while image grading takes place by remote ophthalmologists (£201 per infant examined), would be the most cost-effective strategies in comparison with traditional bedside ophthalmoscopy (£321 per infant examined). However, more research is necessary for the evaluation of the accuracy of trained nurses for image grading.

From a financial standpoint, the study of Scarpa *et al*^[37] demonstrated that screening program contributed to a considerable saving compared to the "no prevention" strategy. In particular, it was estimated that the presented screening program could reduce the annual prevalence of blindness as a result of DR in the examined area of Italy by 6 cases and save €271 543.32.

Invernizzi *et al*^[38] observed a substantial cost saving through telemedicine compared to ophthalmic slit-lamp fundus examination. Specifically, DR screening with FP saved €801.25.

Satisfaction Patient satisfaction is a factor that plays a pivotal role in the effective implementation of teleophthalmology. For this reason, it was assessed in a great number of telemedical studies^[7-8,16,21,39,45,47]. Patients' satisfaction was evaluated usually by a questionnaire which collected information about travel costs, time spent at appointments/waiting time or their opinion about the quality of services. For instance, after a cataract surgery, many patients find the telemedicine procedure reassuring because they see and interact with their surgeon teleophthalmologically^[45].

A further assessment of telemedical services in some studies^[19,39] was performed by the care providers. In more detail, the members of staff evaluated their perceptions of the efficacy of telemedical services by answering questions about working environment or information technology (familiarization of staff with telemedical applications or preparation of rural communities for teleophthalmology). Undoubtedly, the attitude of staff and their motivation determine the success or failure of a teleophthalmological project. Nevertheless, only two studies in this review were found to examine care providers' attitudes to telemedicine^[19,39].

DISCUSSION

Teleophthalmology is the use of electronic communication and information in order to provide a series of eye care services^[1]. In this review, all major published teleophthalmological studies in Europe were assessed. Their contribution in the diagnosis and screening of the most common eye diseases, namely DR, glaucoma and ROP was evaluated. Additionally, teleophthalmology's contribution in the diagnosis and monitoring of ARMD, trauma and cataract was evaluated, as well.

The examined studies were classified and presented according to the eye disease examined and the country, which supported and funded the telemedicine programs. Both descriptive^[9,11,19-26,34,36,41-44,46-52] and comparative^[6-8,10,12-18,27-28,35,37-40,45,53-54] studies were included in the review.

With regard to the procedure, there are two basic models of care provision. One model pertains to the development of a mobile ophthalmological unit which provided ophthalmological services to rural and remote areas^[18-19,46], while the other refers to primary ophthalmological care by optometrists or other care providers in order to reduce the patients' volume in integrated ophthalmological centers^[6-9,12-15,17,27-28,34,36-44,47,53-54]. In some comparative studies, teleophthalmological outcomes of remote populations were compared to the ones by conventional examination methods; in other studies, telemedical screening by optometrists was compared to conventional screening by consultants. All published studies indicated that telemedicine provides comparable outcomes when compared to the conventional examination methods of hospital settings.

Regarding data provision, teleophthalmology uses two methods to transmit image data and sound. Either the eye-care specialist conducts an ophthalmological examination by telemedical means in a real-time mode^[10,16,18-19,21,23-26,44-45,47-48] or patient's medical data, which are collected by remote ophthalmologists, GPs, optometrists, nurses or technicians, are stored and forwarded to a specialist center, where the consultant reviews them and provides counseling in a second phase^[6-9,11,13-15,17,27-28,34,36-43,46,49-54].

Specifically for glaucoma screening and follow-up, the majority of studies demonstrated a high level of agreement between optometrists who used telemedical methods and conventional glaucoma examination^[12,14-15,17] with an increase of true-positive and reduction of false-positive referrals^[9,12,15]. Within this context, overall cost reduction was significant for both patients and healthcare system. Another important aspect of the disease, which might be addressed by telemedicine, is the limited awareness of glaucoma and low compliance of patients. Therefore, in order to enhance compliance to therapy, some pilot studies^[23-26] were conducted and presented the function of a platform designed for e-Health. *Via* this platform, doctors in hospital can have a high definition v2v communication with patients at their home environment with telemonitoring services.

Concerning ROP screening, the application of WFDI telemedicine was described in some studies^[27-28]. Digital fundus cameras were installed in neonatal intensive care units for prematures at risk of ROP. Conventional BIO by ophthalmologists was compared with fundus digital photography evaluation by nurses, which proved to provide comparable outcomes. Cost-effectiveness of each strategy was evaluated indicating that the most cost-effective strategy was screening by specialist visitor nurses, who had been trained to capture and interpret images with the use of portable digital cameras. Nevertheless, further studies are required in order to generalize the conclusions.

DR is among the primary diseases that traditionally telemedicine attempts to address. It is known, that annual fundus examination is performed in less than 50% of patients with DM; therefore, diabetes-related vision loss remains the major cause of blindness in western populations^[55]. Primary objectives of DM-related telemedicine studies were: 1) evaluation of the efficacy of remote detection and grading of patients with DR; 2) evaluation of the necessity of the three fields fundus photo for remote detection against single-field photography; 3) evaluation of the necessity for mydriasis for remote detection and staging; 4) comparison of red-free versus monochrome remote imaging. Specifically, the majority of studies indicated FP as a valid means to remotely detect DR. Specifically, Vujosevic *et al*^[35] suggested NM imaging as sufficient, while three colour 45-degree NM fundus fields

were superior against single-field in detecting and grading of DR and DME. According to Invernizzi *et al*^[38], remote grading of DR was easier with dilated pupils since image precision was higher. On the other hand, Johansen *et al*^[40] indicated the superiority of digital red-free monochrome images versus full-colour images for screening of DR. Some researchers^[36] indicated that screening for DR every 2.5y is sufficient in T2DM patients with DM<10y (low risk patients). However, in co-existing morbidities, follow-up should take place more frequently. Other researchers suggested, as a rule of thumb, that patients with HbA1c>7.68% and combined treatment (both insulin and oral antidiabetic drugs) should be considered as high-risk ones^[42].

Aforementioned outcomes suggest that specific guidelines for telemedicine screening of DR are yet to be established. According to the guidelines of American telemedicine association (ATA) and ocular telehealth special interest group established in 2004 for DR telescreening program, it is recommended that equipment used in telemedicine should comply with the local requirements and that the technology should be in accordance with the digital imaging and communication in medicines (DICOM)^[56]. With regard to pupil dilation, some programs perform fundus imaging with mydriatic fundus cameras and dilated pupils, while others use NM fundus cameras and undilated pupils^[57]. Although NM cameras are more common in telescreening, mydriasis increases the number of gradable images. It is recommended that mydriasis should be performed when visual acuity (VA) is <20/40 and/ or patient's age>59y. Moreover, mydriasis should be performed in cases when NM photographs are not sufficient for remote diagnosis^[56]. ATA suggests that images with poor quality that excludes diagnosis and staging of DR should be considered as pathologic and a new set of images should be obtained. In case of recurrent inability to obtain images with sufficient quality, patients should be referred to a specialized center for conventional examination^[57].

Consequently, ocular telemedicine programs should establish protocols in order to assess evaluation rates, gradeability of photographs, quality of grading, and follow-up of screen-positive individuals. Photographers and graders should be continuously educated and certified^[55]. In addition, cooperation of expert teams plays a pivotal role in provision of telemedical care with comparable quality to conventional clinical settings^[57]. Concerning the screening tools used worldwide for teleophthalmology, there is a great variety of fundus cameras, including traditional fundus cameras, miniature tabletop fundus cameras, integrated adaptor-detector based handheld ophthalmic cameras, and smartphone based ophthalmic cameras^[55,58]. Additionally, the use of a robotic slit-lamp^[59] and an automatic refractometer for provision of telemedical services is reported^[60]. No studies about the application of

handheld and smartphone based ophthalmic cameras, of robotic slit-lamps, and automatic refractometers in Europe could be retrieved in our research. For this reason, further research in this domain of teleophthalmology is required.

One question that arises is whether or not the healthcare system is financially burdened by teleophthalmology. To evaluate this, some factors have been taken into account (particularly in UK studies). Among them, the reduction of transportation costs, the decrease of annual visits to the hospital, the reduction of unnecessary repeated examinations which all lead to an overall reduction in the cost of ophthalmic care. Additionally, the cost of blindness of undetected or mis-detected ophthalmic diseases and the general improvement of the quality of life [quality-adjusted life years (QUALY)] are some parameters that should be also taken into consideration.

In conclusion, teleophthalmology could be introduced in the ophthalmic care provision network since it is a reliable method both for screening and follow-up of patients. This review describes the application of a variety of teleophthalmological projects in Europe and examines some important factors which play a significant role in the proper function of teleophthalmology, like the screening methods used in the examination of each eye disorder, the appropriate and necessary equipment, cost-effectiveness and satisfaction of both staff and patients. Our review suggests that the next goal for European countries is the integration of teleophthalmology into the national healthcare system as a regular service of in care provision.

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CORRIGENDUM

Safety threshold of intravitreal clonidine in rabbit's eyes

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Correction to: The superscript of third author

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The superscript of third author was written incorrectly by the author as superscript 1,3 at acceptance, so hereby superscript 3 is the corrected affiliation in this paper.

The authors apologize for any inconvenience caused by this error.