THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PH.D)

A SIMPLE, FAST AND LOW-COST APPROACH TO SCREENING FOR COMMON EYE DISEASES

by

Greg Russell, M.Phil.

Supervisors:

Prof. Goran Petrovski, MD, PhD, Dr habil

Dr. Beáta Éva Petrovski, PhD

UNIVERSITY OF SZEGED
DOCTORAL SCHOOL OF
CLINICAL MEDICINE
DEPARTMENT OF OPHTHALMOLOGY

SZEGED, 2021

to my mother and late father, Alexandra and Ivan

Contents

Abbreviations

AAO	American Academy of Ophthalmology
AMD	Age-related Macular Degeneration
BSI	Backside Illuminated
CCD	Charge Coupled Device
C/D	Cup-to-Disc Ratio
CE	European Certificate
CLAHE	Contrast Limited Adaptive Histogram Equalization
DM	Diabetes Mellitus
DR	Diabetic Retinopathy
DR	Dynamic Range
DSLR	Digital Single Lens Reflex
FDA	Federal Drugs Administration
FFA/FA	Fundus / Fluorescein Angiography
HE	Histogram Equalization
IOP	Intra Ocular Pressure
IQR	Interquartile Range
ISO	International Standards Organization
M0,1	Maculopathy Grade
MA	Microaneurysms
NHS EDESP	National Health Service English Diabetic Eye Screening Programme
NVD	New Vessel growth at the Disc
NVE	New Vessel growth Elsewhere in the retina
OCT	Optical Coherence Tomography
OAG	Open Angle Glaucoma
P0,P1	Photocoagulation Grade
R0,1,2,3A,3S	Retinopathy Grade
PACG	Primary Angle Closure Glaucoma

POAG	Primary Open Angle Glaucoma
PRP	Panretinal Laser Photocoagulation
RGB	Red Green Blue
RNFL	Retinal Nerve Fiber Layer
ROG	Referral Outcome Grade (er)
ROI	Regions of Interest
SES	Socioeconomic Status
SLR	Single Lens Reflex
STDR	Sight Threatening Diabetic Retinopathy
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
EXR	Extended Range

MAGYAR NYELVŰ OSSZEFOGLALO

A glaukoma (GL) szűrésére irányuló korai diagnosztikai és prognosztikai stratégiák csökkenthetik a társadalom költségeit a világ minden egyes régiójában, mint ahogy ez megfigyelhető a diabéteszes retinopátia (DR) szűrővizsgálatoknál. Az optikai koherencia tomográfiához (OCT) képest az alacsonyabb költségű digitális fundus kamerák hozzáférhetőségének növekedése, csökkentheti a GL-hoz kapcsolódó egyéni terheket, úgy mint a vakságtól való félelem, a látás elvesztéséből adódó lelki egészség és fizikai állapot. Továbbá csökkentheti a kettős (GL/DR) szűrővizsgálatokra beutaltak számát, ami nagyon időigényes a betegek számára és a betegség progressziójához vezethet; egy standardizált keretet nyújthat a növekvő aggodalomra, hogy a GL detektálására az alapellátásban az optometristák a goniszkópot használják; a pontos pozitív predikciós érték szintjére emeli a szűrés szenzitivitását és specificitását. A diabéteszes betegek ellátása a diabetológusok, dietetikusok, szemészek, optometristák, háziorvosok és népegészségügyi szakemberek multidiszciplináris feladata. Mindannyian felelősek azért, hogy a pácienseknek életviteli tanácsot nyújtsanak, valamint ösztönözzék őket az alapvető szűrővizsgálatokon való részvételre.

Míg az OCT technológia rohamosan fejlődik a látóideg és az elülső szegmentum értékelésének területén, a növekvő egészségügyi költségek és a technológiai hozzáférés hiánya, megnyitja az alternatív képelemzési formák iránti igényt a GL területén.

A DR-szűrés jelenlegi állapotát tekintve, a páciensek nem reálisan értékelik a szövődmények kockázatát és elhanyagolják az ajánlott szűrővizsgálatokon való részvételt.

Továbba, a pácienseknek szükségük van egy gyors, könnyű és pontos funduskamerás szemfenék vizsgálatra, a hagyományos, időigényes és „nem megfelelő” szemfenék-vizsgálat alternatívájaként.

Összegzésképpen, bemutatunk egy alternatív, alacsony költségű módszert a GL és DR jövőbeni detektálására és menedzselésére. GL értékelési módszert használunk a digitális képelemzés során kapott volumetrikus, geometriai és szegmentációs adatok felhasználására, amelyek jól megfelelnek a nagyfelbontású OCT képalkotással nyertekkel. Ezek a stratégiák azt eredményezik, hogy a DR már nem lesz a vakság egyik vezető oka a munkaképes korú lakosság körében, és nincs értelme megkérdőjelezni a DR és a GL szűrőrendszerek egységét. Világszerte további kutatások szükségesek a vakság megelőzésére és korai felismerésére, a DR és a GL értékelésnek automatizálására.

2020).

1. Introduction

Diabetic retinopathy (DR) and glaucoma (GL) are the two most common forms of blindness in the working age population (Vision Loss and Age | CDC, 2021), Beside them, age-related macular degeneration is another leading cause of vision loss in the elderly, with its onset being generally slow and progressive (Pathogenic Mechanisms | www.amdbook.org, 2021). Both DR and GL can result in a rapid onset of vision loss and become hard to manage, manifesting some observable diagnostic features which can easily be detected (Chalakkal, Abdulla and Hong, 2020).

Diagnosis from 2D images can however be challenging (Chapter 12 Perceiving 3D from 2D Images, 2021). especially where final diagnosis is going to be dependent on data obtained from multi-modal testing (Glaucoma Diagnosis, 2021). There are existing and effective methods for automated diagnosis of DR, which at the time of the writing this Thesis, two United States Food and Drug Administration (FDA) approved systems could be located: EyeArt from Eyenuk Inc., Los Angeles (Home - Eyenuk, Inc. ~ Artificial Intelligence Eye Screening, 2021), and Digital Diagnostics, Coralville, Iowa (Digital Diagnostics | AI The Right Way, 2021). EyeArt's FDA mark is unique as it can determine bilateral DR changes/diagnosis, and can determine severity as more than mild DR (MTMDR) as well as sight-threatening DR (STDR). This breakthrough paves the way for the ability to do stratified deployment of such systems.

At the time of writing this Thesis, no automated FDA approved, CE class IIa or above products could be found for the diagnosis of GL, one of the challenges being that the observations of glaucomatous changes are much more detectable via a multi-modal approach than for DR screening (Weinreb and Kaufman, 2011), which can be detected and graded from 2D images obtained by a cheaper, non-mydriatic 45-degree field of view cameras. GL presents present a challenge due to 3D visualization shortcomings of a 2D fundus image of the retina, and even where stereo fundus photography imaging exists, image exposure can interfere with human interpretation (Ittarat et al., 2017). Fundus photography, and portable anterior photography imaging is far cheaper in the delivery of a screening service than optical coherence tomography (OCT), visual field tests, tonometry, pachymetry, confocal and polarized imaging.

GL is classified as a group of diseases with progressive damage to the optic nerve. It can be divided into primary open angle GL (POAG), primary angle closure GL (PACG) and secondary GL. The most recognized risk factor for glaucomatous progression is increased intraocular pressure (IOP), which occurs in eyes with an imbalance between aqueous humor production and drainage through the angle. In this matter, the angle drainage becomes essential, and the angle anatomy becomes a doubtlessly important factor for assessment in GL management. Worldwide, the prevalence of POAG shows variation which can be attributed to multiple factors including, among others, ethnicity. Meta-analysis has revealed a prevalence of POAG of 1.4% in Asians, 2.0% in Caucasians, and 4.2% in the African population (Rudnicka et al., 2006). In contrast, PACG occurs more frequently in Asians than in Europeans with estimates of 1.5% and 0.04%, respectively (He et al., 2006), (Klein, Klein and Jensen, 1994).

The burden of blindness from GL is challenged not only by the increasing number of cases, but also by the difficulties to recognize the affected population. GL is an asymptomatic disease which only raises suspicion when it becomes advanced. Studies have estimated the prevalence of undetected GL to be 50% in developed countries, and up to a striking 98.5% in developing countries (Dielemans et al., 1994) (Vijaya et al., 2005). On the other hand, approximately half of the patients diagnosed and treated with GL are found to be ocular hypertensives that may not be benefiting from treatment at all (Vaahtoranta-Lehtonen et al., 2007).

The notable number of undetected GL cases as well as over-treated patients has given rise to multiple evaluations of screening tools to trace unrecognized GL. Yet, the United States Preventive Services Task Force (USPSTF) has indicated a lack of convincing evidence to facilitate regular screening, whereas no screening tool has been shown cost-beneficial to date (Henderer, 2006). The current effort focuses on how to manage and follow the increasing number of patients with GL . Nevertheless, there is an increasing demand for organized screening programs that are cost-effective to prevent the load of future visual impairment in GL patients, similar to DR screening (Dielemans et al., 1994), (Vijaya et al., 2005), (Henderer, 2006).

In addition to the increasing burden of GL, the imminent shortage of health care professionals worldwide strengthens the need for the development of cost-beneficial screening methods (Naicker, Eastwood, Plange-Rhule and Tutt, 2011). Effective methods exist for DR, and in a similar evolution to DR screening, emphasis on office visits may shift to alternative methods with reading centers or even automated image analysis. While non-invasive OCT is rapidly progressing in means of optic disc and chamber angle assessment, and is considered a standard in angle-closure detection compared to gonioscopy (Nolan et al., 2007), with rising health care costs, demand and availability for the technology can split, leaving lower financed practices short of aid. Other simple, fast and low-cost forms of image analysis need to be incorporated to help in the management of GL or to pre-assess those attending for care. There is a notable increase in the cost effective portable high resolution smartphone-based retinal cameras, capable of taking, storing, and sharing images across platforms to assist in ophthalmic decision making

(Shah, Chhablani and Kaja, 2012). Though at present, image acquisition and interpretation is still having many limitations, it seems reasonable to develop methods and algorithms that can assess a mass of people at an affordable price to allocate further attention to those who are in need of medical care. In our pilot study, we analyzed the information gained from color photographs of the fundus and the chamber angle in regards to GL. Volumetric, geometric and segmentational data were gathered and compared with corresponding high definition OCT images to test for comparison and possible validity, while the cost-benefits of such processing are shown as well.

The global incidence of diabetes mellitus (DM) among adults (age 18 years and older) was 9% worldwide in 2014 (Danaei et al., 2011), while its prevalence still shows an increasing tendency due to obvious obesity epidemic and aging of the population (Danaei et al., 2011), (Global report on diabetes, 2021). In Hungary, a total of 865 069 patients (9.5% of the population) suffered from DM in the same age group in 2011 (Statistical Yearbook of Hungary, 2021), and some degree of DR could be observed among 19% of the patients with type 1 DM (T1DM) and 24% in those suffering from type 2 DM (T2DM) for 3 or 4 years. DR is the fourth most common cause of blindness in the overall population, but it is in second place among active adults in industrialized countries (Vision impairment and blindness, 2021), accounting for a significant drop in the working ability of the patients and the overall quality of life (QoF) (Langelaan et al., 2007), (Jones and Edwards, 2010). In a study comparing data from 35 populations, the global prevalence of STDR was estimated at 10.2% for all DM patients (Yau et al, 2010). Known risk factors for developing DR are age, gender, duration, and type of DM, elevated HbA_1c, high blood pressure, and retinopathy stage, while other correlating risk factors are being investigated. Unfortunately, 50% of the people with DM are unaware of the characteristics of their disease and the compliance in attending screening programmes is poor, with many only attending clinics when their condition is symptomatic. Since high blood sugar and fat destroy the wall of the arteries, it is not surprising that people with DM have 2 to 4 times higher cardiovascular mortality rate and 2 to 4 times higher risk of strokes than patients without DM. Renal failure is also a common complication with the estimated number of 30–40% of the patients with DM, while 60– 70% of the patients develop neuropathy. This is not only an individual problem, but a societal problem as well. According to a 2009 survey, the average annual health expenditure for patients with DM was $1205 per capita and for patients with complications this number was $2276 per capita. Half of this cost is made up of drugs, but only a quarter of the cost spent on drugs is for antidiabetics (Vokó, Nagyjanosi and Kalo, 2010). Similarly, the treating expenses doubled in Germany and America, where $174 billion was spent on the treatment of DM in 2007 (Vokó, Nagyjanosi and Kalo, 2010). The Hungarian data cover only the cost of the National Health Insurance Fund, while there are other economic aspects like time off from work or restricted work due to complications of the disease. DR is caused by retinal microvasculature damage DR screening is the best way to ensure early intervention with efficient laser photocoagulation and/or anti-vascular endothelial growth factor (anti-VEGF) treatment for preventing and treating visual loss (Ferris, 1991). According to the NHS standards for diabetic eye screening, four stages can be distinguished for the purposes of telemedicine screening, and these are: pre-retinopathy (R0), background retinopathy (R1), pre-proliferative retinopathy (R2), and active proliferative retinopathy (R3A) (2021) (Diabetic eye screening: retinal image grading criteria, 2021). Subclassifications also exists for stable proliferative retinopathy (R3S) in patients who have typically received pan-retinal laser photocoagulation (PRP) when classified as R3A, and then became "stable" at a later timepoint; provided previous images are available for reference and comparative study, these cases can be considered safe to keep in a surveillance clinic (Diabetic eye screening: surveillance pathways, 2020). According to this NHS severity scale, when retinal lesions visibly manifest as a result of DM, they can be considered to be either low, intermediate, or high risk for developing DR according to a screening program. Therefore, early intervention should be the focus, and rather preventive programs for early detection and ongoing monitoring, including the successful treatment of the disease should be set up.

Like GL, DR is usually asymptomatic before the appearance of any vision loss, but it is detectable by retinal imaging techniques objectively and by accurately taken best corrected VA measurements. Much of the research around the world has been focused on the use of telemedicine tools for fundus imaging and screening, the UK system standing up at the top in terms of reliability, precision, and standardized input and output. The results so far have been very promising, with each study being reported to date pointing out the high sensitivity for detecting several fundus lesions in the initial DR stages utilizing standard fundus cameras and dedicated grading software (Lund et al., 2015).

The Spectra DR electronic medical record (EMR) software is designed around the requirements of the UK National Health Service (NHS) national screening program for DR; which is highly complex and requires a high level of sophistication in the software to meet its requirements for analogue human grading. Spectra DR enables patient appointments to be created, data entry, image capture, and human grading, including the detection of other eye diseases such as GL. Patient results are generated together with the prognosis of their condition via a "plug-in" algorithm. The patients' willingness to participate in future screening tests will greatly increase with the inclusion of dedicated non-mydriatic and/or hand-held portable cameras, which are especially useful for wheelchair bound immobile individuals, who may be confined to care homes and unable to attend conventional DR screening clinics.

In 1980, Iceland began regular DR screening for T1DM patients, which resulted in the reduction of disease-related blindness from 2.4% to 0.5% (Stefánsson et al., 2000). In Iceland, the population is more homogenous in relation to their ethnic and socioeconomic differences, compared to the population in Hungary, which is reflected in a study for the development of a (now commonly used) risk calculator (Risk Medical Solutions, Iceland). These new screening and telemedicine tools can realistically expect to harvest similar results in other European countries, such as in Hungary within 5 to 10 years' (Somfai et al., 2007).

Our research has involved telemedicine tools and examination through free participation in a fundus camera screening program which took place in a South-Eastern county (Csongrád) in Hungary, and explores how DM patients subjectively experience the screening, and also obtains their feedback on their likely participation in further examinations in the future. Furthermore, demographic factors such as age, gender and economic activity are being examined for their effect upon participation in future screening programs. Introduction of automated systems such as EyeArt have been shown to reduce the human staffing costs and costs to patients (Tufail et al., 2016); in order to setup screening services in 2nd and 3rd world countries, one may need to create or integrate into existing EMR systems in order to have a good workflow. This will result in a reliable, safe, cost-effective delivery of screening services and allow for a smoother transition to automation.

While the process and management of DR screening is relatively well understood, the need for improved management of GL monitoring and possible screening seems obvious, with the increasing prevalence worldwide. A recent study correctly predicted a total of 79.6 million people will be affected by GL in 2020, which is indeed the case today. Out of these, bilateral blindness was estimated to occur in 11.2 million (Quigley, 2006). The following 20 years might bring rise in the number of GL patients up to 111.8 million (Tham et al., 2014). While the prevalence of GL has a societal burden, there is an associated economic burden, which affects both developing and developed countries with at least the United States spending approximately $6 billion in 2013; the latter accounted for productivity losses and individual patient care per year (Wittenborn et al., 2013). In the United Kingdom, medical costs were approximately over 40% of the direct costs (Traverso, 2005). In sub-Saharan African countries, the lowest income patients diagnosed with GL can spend almost 100% of their salary on treatment while middle-income earners spent at least 50% of their salary on the disease treatment (Adio Adedayo Omobolanle and Onua, 2012, Lazcano-Gomez et al., 2016).

This Thesis is concerned with the development of an effective screening program, initially for a human based assessment of DR, and how technology can possibly identify difficult-to-observe glaucomatous features from 2-dimensional (2D) images.

2. Aims of the study

- To determine if 3D volumetric measurement of image intensity in the angle is possible from gonioscopy images.

- To determine if 3D volumetric measurement of image intensity of the fundus and analysis of the cup profile is possible from 2D fundus images.

- To compare fundus images to analogous images obtained by OCT.

- Determine the self-perceived satisfaction with the classical pupil dilation versus fundus camera examination based in variables including; sex, age, HbA1c, presence of hypertension, occupation, education, marital status, and attendance of blood sugar screening

- To observe the distribution of DM types and DR grade in the studied population in Hungary in comparison to the UK-based grading system.

- To determine the reliability, satisfaction, and willingness to participate again in a classical or fundus camera examination for DR screening.

3. Methods

Photographic imaging analysis for glaucoma

Images from the GL and fundus assessment were used in this study, including freely available/online color fundus photographs, standard optic nerve OCT, and additional digital slit lamp images of the angle which were obtained by gonioscopy (for the image analysis, no patient contact was needed and personal data for the images included in the processing was not known).

A novel method is hereby aimed at showing similarities and possible data correlation in the findings, allowing for the diagnostic classification of GL.

Contrast enhancement

Standardization of the fundus images was achieved through known methods of image processing by Image J (NIH, USA). Volumetric representation was derived from image intensity after normalization of the histographic information in each image. As image intensity varied according to camera exposures, histogram equalization (HE) was needed to standardize the images. In addition, comparative to HE, adaptive histogram equalization Contrast Limited Adaptive Histogram Equalization (CLAHE) - a tool designed to prevent the over amplification of noise that adaptive HE can give rise to, was used in the study. Optimal comparison and dynamic range of the images acquired was achieved by splitting the color fundus images into Red, Green and Blue (RGB) channels.

3D volumetric measurement of image intensity and analysis of the profile of the cup

After application of CLAHE in the regions of interest (ROI), the images were converted into a 3D representation in Image J by adjusting volumetric measurements of the image intensity through a 3D rendering on the screen and an interactive 3D surface plot function. Splitting of the RGB was carried out consequently and the optimal channel selected for further analysis. Images taken from the fundus were imported into Image J for further analysis.

Retinal nerve fiber layer (RNFL) detection method

Images were split into RGB and then the differences between the channels were observed and a spectrum look up table was applied to allow image intensities to be compared to the gold standard images and data produced by the Retinal Nerve Fiber Layer (RNFL) analysis given by the spectral domain Topcon 3D-2000 OCT. RGB fundus imaging separates a fundus image into three wavelength components to help visualize the retinal pigment epithelium/choroid (red filter), neural retina (green filter), and nerve fiber layer (blue filter). This allows for better visualization of the retinal tissues (Shah et al., 2013).

Screening and fundus image analysis for diabetic retinopathy

For the DR project, a free screening test was performed on a random population including 178 eyes from 89 patients with confirmed DM diagnosis. A qualified professional in a darkened room acquired the images with a fundus camera, these images were then analyzed by a specialist doctor/ophthalmologist (A. F./M. C. M.) or ROG (G. R., P.R.). Where a patient exhibited a constricted pupil, cyclopentolate (5 mg/mL) eye drops were applied to achieve mydriasis, t thereafter another image was taken. Within 10 working days, the assessment of the fundus images took place using the Spectra DR software. The image database was safely archived inaccessible to third parties for 10 years in a central server; this was in order to allow for further use in comparative studies on DR in the future.

The images were acquired by an 18-megapixel Canon EOS 70D digital camera which was connected to a Canon CR2-AF color, non-mydriatic, 45° retinal camera. Two pictures were taken of the participants' each eye: one with the macula and another with the optic nerve in the center—this is in line with the UK screening requirements (Diabetic eye screening: pathway for images and where images cannot be taken, 2021). In case of presence of amblyopia or non-transparent media (e.g. visual axis obstructing conditions such as cataract and other corneal media opacities), patients were excluded from the study. During image evaluation, the graders (A. F./M. C. M./G. R.) classified the signs and the stages of DR and maculopathy in the standardized UK-based software Spectra DR and graded the images in alignment with the UK standard grading protocols (Diabetic eye screening: assuring the quality of grading, 2021). Each image was evaluated in two stages: first, the ROG (G. R./P. R.) evaluated them, then a supervisor/ophthalmic consultant confirmed the diagnosis (A. F./M. C. M.). At the end of this process, an expert opinion regarding the retinopathy grade was sent to the screening site determining the severity scale of retinopathy (R0/1/2/3A/S) and any existence of maculopathy (M0/1). Other abnormalities were not actively diagnosed in this study, although they were recorded in the data, as they could provide further information about past symptoms and observations which may be important, and require medical attention over a specified period of time.

The detailed classification of the DR was as follows:

M0: no maculopathy detected; repeated screening was recommended at 12 months' time.

M1: there was a sight-threatening maculopathy; within one month a medical examination is required.

R0: there was no clinical anomaly; repeated screening was recommended one year later.

R1: mild non-proliferative phase, microaneurysms, dot- or blot-like hemorrhages, or exudates could be seen; control examination was recommended one year later.

R2: moderate or severe non-proliferative phase, major bleeding(s), cotton-wool spots, venous looping, and intraretinal microvascular abnormalities (IRMAs) were visible; control examination was required within one month.

R3A: active proliferative phase, neovascularization of the optic disc (NVD) or elsewhere (NVE) or preretinal bleeding(s), vitreous bleeding, preretinal fibrosis, and tractional retinal detachment could be observed; immediate medical examination was required within two weeks.

R3S: stable proliferative retinopathy; a fundus image showing stable post-PRP laser together with no signs or reactivation or active referable retinopathy; this is only to be determined in the presence of "benchmark images" taken at the time of discharge specifically for comparison; the screening intervals may be at the discretion of the trained ROG.

Age-related macular degeneration (AMD), GL changes in the optic nerve, changes/fundus pathology and any other signs of eye disease were also recorded, but not reported hereby.

Self-Completed Questionnaire.

The general part of the questionnaire was based on the European Health Interview Survey 2009 (European Health Interview Survey 2009), and it collected data about DR associated exposure parameters and some other health connected parameters, type of DM, or presence of hypertension, as well as the type of eye diseases. Furthermore, data were collected about the frequency of measuring blood sugar levels and also about participation in screening programs, which are important for preventing retinopathy, including the frequency of attending Diabetology or Ophthalmology specialist clinics. Questions regarding willingness to participate again (yes/no/maybe), the perceived reliability of results (yes/no/maybe), and the comfortability (dissatisfied/satisfied/acceptable) of this test were recorded, as well as recording the overall perception of the screening examinations. Additionally the patients where asked whether they would participate in a similar examination next time were being asked/collected as well. Some categories underwent merging due to missing data, for example, the intensity of blood sugar measurement (monthly/less than a month, weekly/every few days, and daily/more than once a day). If the participants struggled to understand or read the questionnaire, they received professional help accordingly to assist in their completion.

Statistical Analysis

The analysis of the data was performed by descriptive statistical analysis on N number of participants, percent distribution, median. The interquartile range (IQR) are then shown. The Chi-square (χ^2) and Fisher exact tests were used to test differences of the distributions of categorical variables. The relationship between the two variables was considered to be statistically significant when $P < 0.05$. The graphs were made in GraphPad Prism 5.01 (GraphPad Software Inc., La Jolla, CA, USA). The statistical analysis of this data was then performed by using Stata (Intercooled Stata 8.0, Stata Corporation, College Station, TX, USA) and Excel software (Microsoft Corporation, USA).

Ethical Issues

The Regional and Institutional Human Medical Biological Research Ethics Committee of the Albert Szent-Gyorgyi Health Centre, University of Szeged, approved this study with protocol (number 197/2015). The research provided anonymity to the participants. The participants signed a written consent form in which they agreed to permit the use of data for research purposes before the beginning of their test.

4. Results

Photographic image analysis for glaucoma

Contrast enhancement

RGB color splitting allowed for a more averaged distribution of the intensity range across the ROI selected by the user (**Figure 1**). The color fundus and gonioscopy images were split into RGB channels to allow for expert observation and comparison of findings. The green channel was found to show the highest dynamic range for the anterior images, and was used to further select the ROI to be processed with the CLAHE filter.

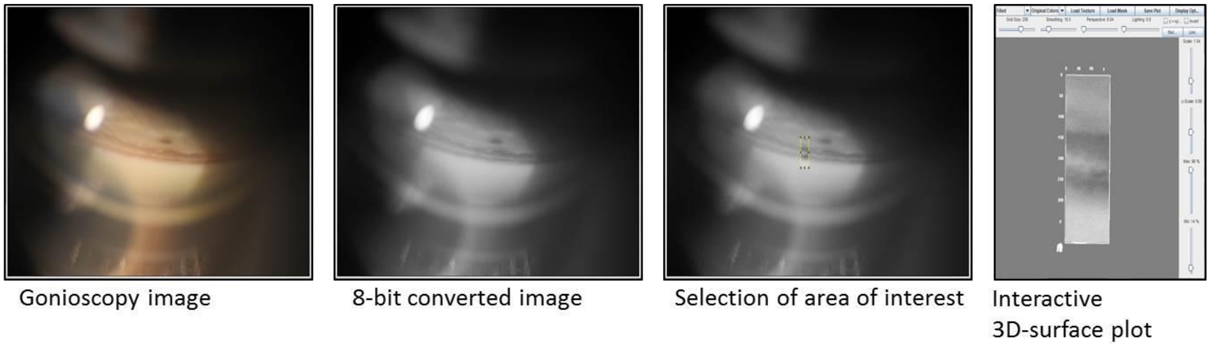


Figure 1. Gonioscopy channels in the images using ROI selection and consequent CLAHE filtering.

3D volumetric measurement of image intensity in the angle

The parameters in the screen were adjusted to the range as shown in **Figure 2** for the gonioscopy images, which happened before any adjustments, avoiding clipping of the intensity range, the angle was then calculated as shown. The detected angle was then compared to the angle shown from the anterior OCT scan.

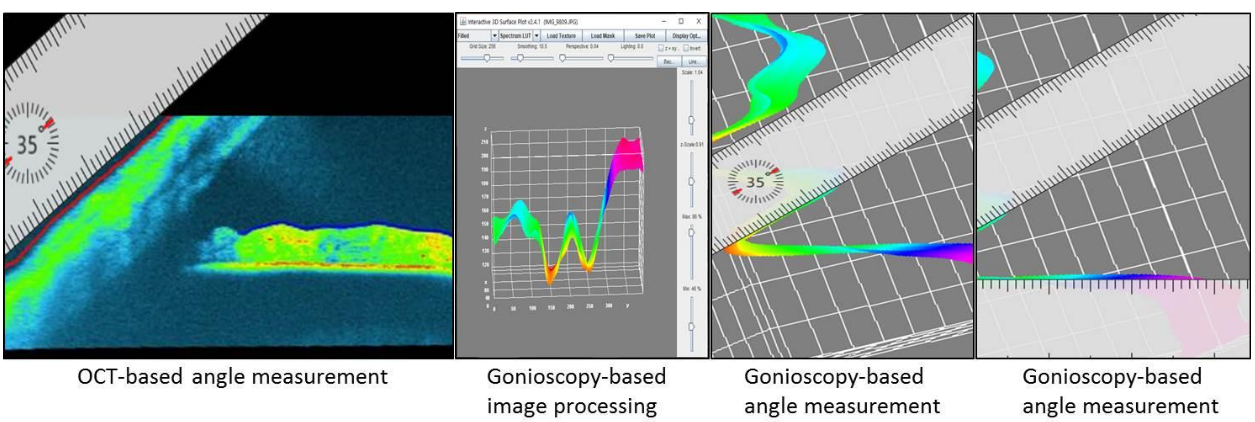


Figure 2. 3D measurement of the image intensity and angle from gonioscopy images in comparison to angle measurements obtained by Anterior OCT. A gonioscopy-based image processing includes intensity adjustment and clipping of the intensity range, followed by angle

measurement; for comparison, the corresponding angle obtained by anterior OCT measurement is shown.

3D volumetric measurement of image intensity of the fundus and analysis of the cup profile

The review of split RGB channels concluded that the green channel harvested better information (**Figure 1**). When applied to the fundus and the optic nerve images (**Figure 3**), the Red channels offered a less obstructed view of the cup region of the images compared to the Blue and Green channels. It was considered important for the dynamic range to support the analysis of the cup volume through the profile shown.

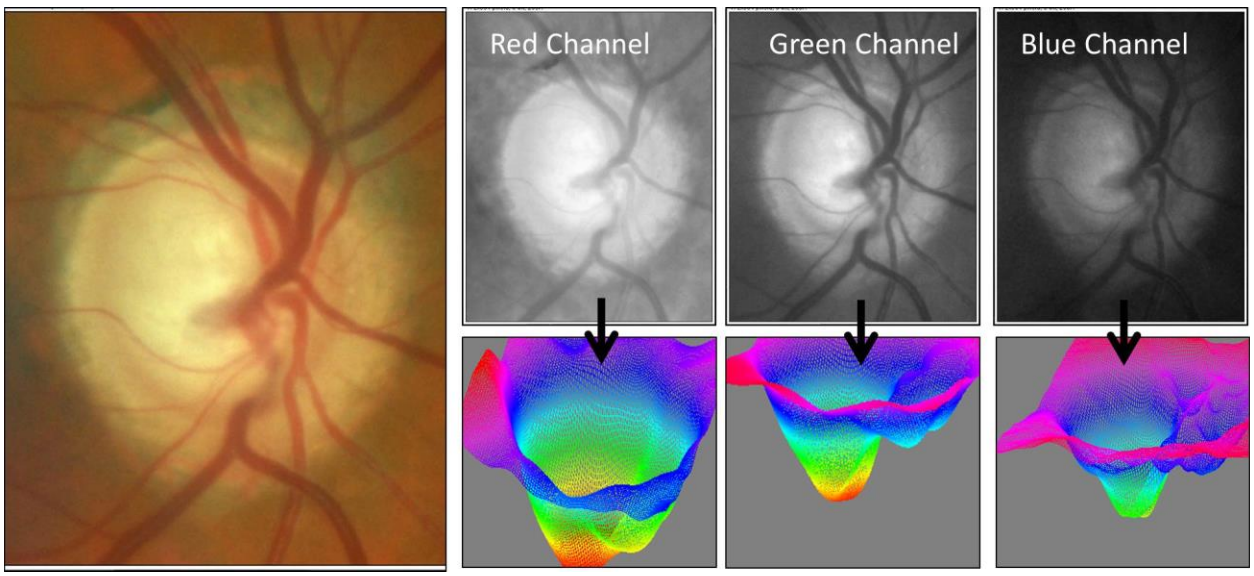


Figure 3. Splitting of the RGB channels in the fundus images of the optic nerve and 3D volumetric conversion.

Note that the images, both by profile and when rendered in 3D, show a close resemblance in appearance to the tomographical images shown in **Figure 4**.

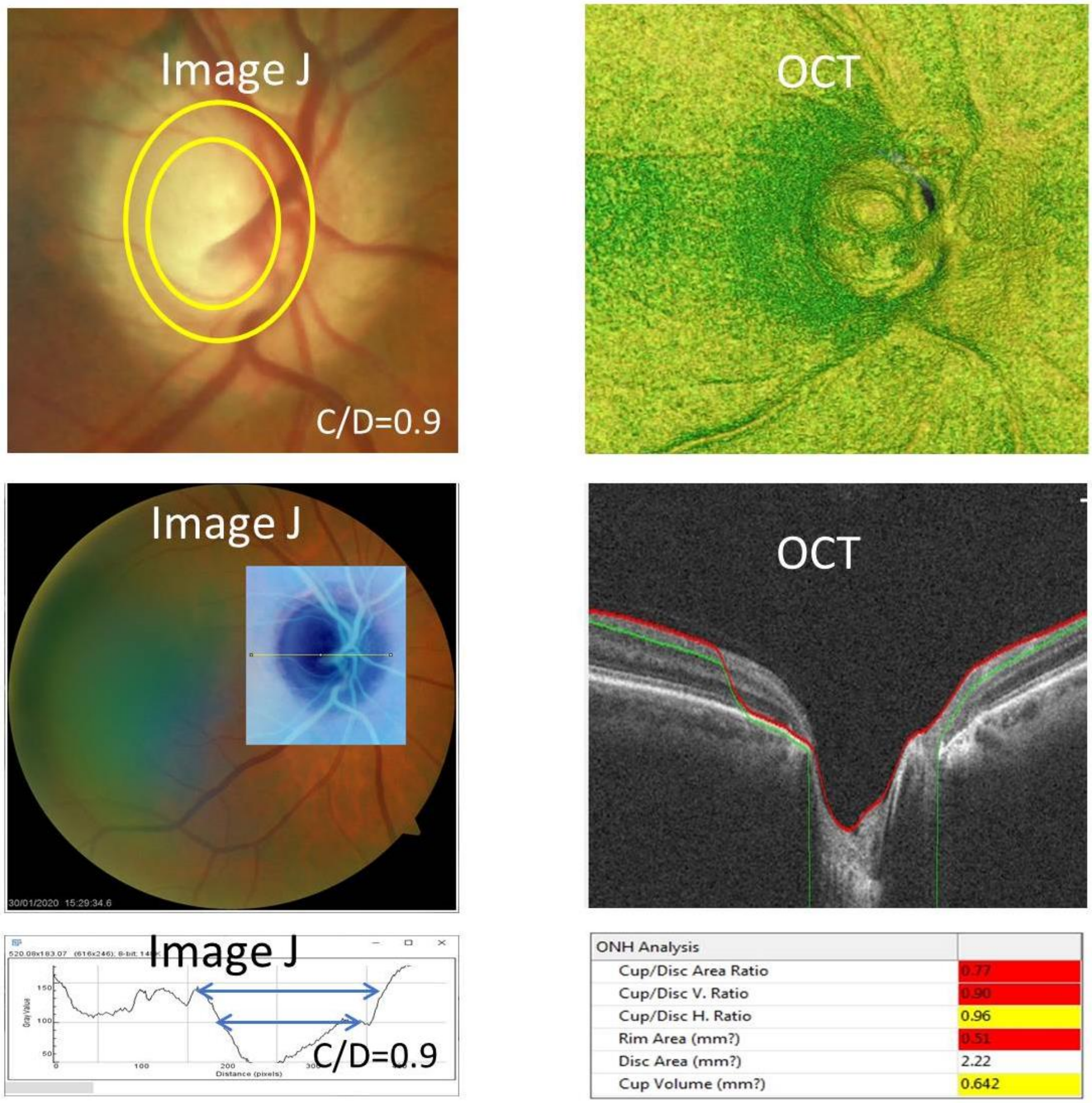


Figure 4. Resemblance of the Image J histogram and cup/disc (C/D) ratio based on the 3D fundus images compared to the analogous images obtained by OCT.

RNFL detection

Splitting of the RGB channels in the fundus/optic nerve images (**Figure 5**) and obtaining differential images between the color channels resulted in the blue channel showing similar intensity when analyzed by Image J as the Topcon 3D OCT channel shown in the same figure.

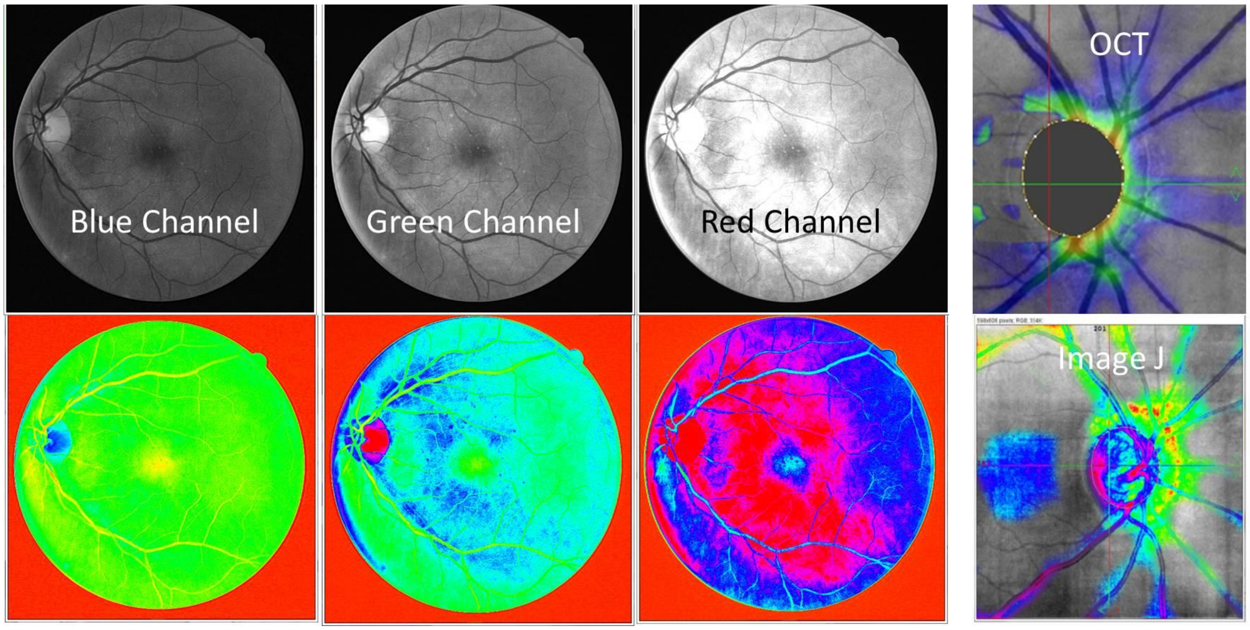


Figure 5. Splitting of the RGB channels in fundus images/optic nerve and resemblance of the Blue channel Image J to the OCT Thickness Map of the RNFL.

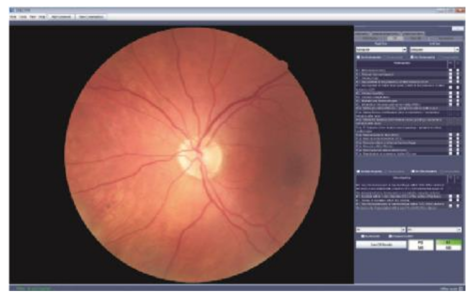
Screening and fundus image analysis for diabetic retinopathy

In this study, 178 eyes of 89 people were examined, of which 30 were men (33.7%) and 59 were women (66.3%). Table 1 shows the distribution of the types of DM and the stages of DR in the screened population, based upon and compared to the UK grading system and software (Spectra DR). Twenty percent of the participants had T1DM out of which 70.8% had T1DM diagnosed by a Diabetology department, the rest being yet undiagnosed or hidden disease patients. Mild non-proliferative DR (grade R1) was detected in 23.0% of the participants, while higher (moderate/R2 and proliferative/R3) grade DR was detected in 1.4% and 1.4% of the subjects, respectively; maculopathy/M1 was present in 5.4% of the studied group (representative images from these were captured from each grade and processed in the Spectra software as shown in **Figure 6**. Another retinal pathology was detected in 28.4% of the participants. Most likely, due to existence of well-established screening programs in the UK which actively search for early detection of the disease, there was an observable left-shift in the distribution of the early stages of DR in the UK population based upon the Spectra DR software in comparison to the representation of the Hungarian graded images.

Table 1: Distribution of the DM types and DR grade in the studied population in relation to the UK-based grading system implemented by the Spectra analysis.

	T1DM	T2DM	R0	R1	R2	R3	M1
Csongrád County, Hungary´	20.2%	79.8%	73.0%	23.0%	1.4%	1.4%	5.4%
East Anglia, UK	15.0%	85.0%	68.7%	27.5%	0.6%	0.3%	3.2%

(a) R0



(b) R1

(c) R2

(d) R3A

(e) M1

Figure 6. Spectra DR based grading of the DR retinopathy. Representative images of the different

grading stages are shown in the studied population.

Table 2: Reliability, satisfaction, and willingness to participate again in a classical or fundus camera examination for DR screening.

Variables	Pupil dilation $N = 89$ (%)	Fundus camera $N = 89$ (%)	P^*
Reliability of the examination			
Yes	75.5%	72.0%	
No	6.1%	12.0%	0.3
Maybe	18.4%	16.0%	
Willingness to participate again			
Yes	78.2%	67.3%	
No	9.1%	10.9%	0.01*
Maybe	12.7%	21.8%	
Satisfaction with the comfort of the screening			
Dissatisfied	37.0%	9.1%	
Satisfied	20.4%	83.6%	0.9
Acceptable	42.6%	7.3%	

According to the self-perceived satisfaction with the classical pupil dilation versus fundus camera examination, 20.4% versus 83.6% of the participants expressed satisfaction, respectively, while 37.0% versus 9.1% were unsatisfied, and 42.6% versus 7.3% could not decide. The classical pupil dilation versus fundus camera examination was found to be definitely reliable by 75.5% versus 72.0%, possibly reliable by 18.4% versus 16.0%, and unreliable by 6.1% versus 12.0%, respectively. The willingness to participate in classical pupil dilation versus fundus camera examination was found to be positive by 78.2% versus 67.3%, while 9.1% versus 10.9% responded that they would not participate in future tests, and 12.7% versus 21.8% responded as maybe participating in the future. There was no significant difference in the satisfaction data from the examination (*P* = 0.9) and reliability (*P* = 0.3), although it was also noted that the willingness to participate had significantly differed between the classical versus the fundus camera examination (*P* = 0.01) (**Table 2**).

5. Discussion

Image analysis technique

It is important to standardize the image intensity across a dynamic range and across the image ROIs, which in our study was performed by normalization of the histographic information across angle images obtained from gonioscopy. The CLAHE filter can be applied initially to RGB split images to look for the best possible profile in the intensity images. The strength of the Green channel is very important, showing more dynamic range and resolving more information than the other color profiles do.

Image J splitting of fundus images into Red, Green and Blue color channels allows a simple way to obtain monochromatic renderings from any full color acquisitions; a disadvantage of doing so is that some loss in resolution can occur as a result of viewing just a single channel. Nevertheless, as exposure often needs to be increased to compensate for light loss when a physical filter is introduced into the light path of the fundus camera, the splitting channels' technique allows for a lower, more comfortable flash for the patient when taking the image.

Green light focuses very well in the intraretinal depth, while red light is particularly well suited for visualizing the retinal pigment epithelium and the choroid; blue light assists visualization in the superficial nerve fiber layer - this phenomenon has been explored in many previous studies ((NR and TW, 1978, Peli et al., 2009, Frisen, 1980, Roloff, 1984). Digital retinal photography is unique in comparison to film-based techniques, as it allows for the immediate adjustment of exposure settings and offers an easy contrast enhancement. The disadvantage to digital imaging is the linear response and narrow exposure latitude of currently available digital sensors, although it can be argued that this is going to improve; in the strive for economy and miniaturization of telemedicine products, sensors have become smaller, while the quality has suffered as a consequence. Some fundus manufacturers follow the original convention of simply bolting on a conventional SLR camera to the fundus unit. The problem of limited dynamic range has been acknowledged by a number of digital single lens reflex (DSLR) manufacturers, some cameras having an automatic exposure bracketing mode that is used in conjunction with high dynamic range imaging software. In particular (Super CCD - Wikipedia, 2021) lar, some sensors like the Fujifilm super CCD, EXR, and now the X trans sensors (Fujifilm X-Trans sensor - Wikipedia, 2021) with Backside illuminated (BSI) that uses a novel arrangement of the imaging elements to increase the amount of light captured and thereby improve low-light performance (Back-illuminated sensor - Wikipedia, 2021), have recently been on the rise, while other manufacturers have used in-camera software to prevent highlight overexposure such as the D-Lighting feature from Nikon (Photography Lighting | Active D-Lighting Great for Cameras from Nikon | Nikon, 2021).

Unlike the traditional Single Lens Reflect camera, screeners take images on a fundus camera where the exposure settings have been typically predetermined by software for standardization. The only variable the screener has to consider is the limited dynamic range of some digital sensors which can be partly exacerbated by a small pupil setting and/or the flash level of the fundus camera. It is true to say, some camera manufacturers such as Canon have modified their SLR sensor on the CR2 range of fundus to increase sensitivity to the IR range, this is to help with initial IR visualization in “live mode” alignment prior to image capture. Screener adjustment to flash settings is especially important to consider when imaging the optic nerve, because of the stark contrast between the nerve and the surrounding retina. Images can also suffer from degradation caused by media opacity, and after anatomical positioning (image adequacy); indeed, assessability has to be considered before reading such images (Russell, McLoughlin and Nourrit, 2012).

It is important to have proper exposure as well: over or under exposure can be detrimental to digital image quality, while the exposure control requires a delicate balance between flash output, sensor gain and gamma settings. The International Standards Organization (ISO) has a standardized scale for measuring the sensitivity of the film to light. These standards have traditionally been used with film based cameras (Clarkvision: Digital Camera Review and Sensor Performance Summary, 2021). However, contrary to the popular belief, ISO in film speed is not connected to exposure in digital photography, therefore, native signal-to-noise ratio is all important in digital imaging. ISO is applied gain after the image has been taken (ISO and Digital Cameras, ISO Myths www.Clarkvision.com, 2021). The English National Diabetic Eye Screening Programme (ENDESP) has provided information on recommending camera setting previously, and these are to ensure the correct resolution file size and white balance setting are used on such based fundus cameras (Diabetic eye screening: approved cameras and settings, 2021).

The 3D volumetric measurement of image intensity and analysis of the profile of the cup in our study was made possible by applying CLAHE in the ROI, as well as by conversion of the images into 3D representative images in Image J and adjusting the volumetric measurements of the image intensity through a 3D rendering on the screen and an interactive 3D surface plot function. Splitting of the RGB allowed for selection of optimal channel for further analysis. Illustrating multiple filters' outputs in a photo assay, one can provide the examiner with multiple monochromatic interpretations of the ROI, assisting in the cases of epiretinal membranes and macular pigmentary changes detected at 490nm, 540nm and 615nm wavelengths.

Using modern color retinal fundus cameras, retinal ganglion axons can also be directly observed. The fine nerve fibers reflect when imaged (Airaksinen et al., 1984) and allow implementation of a scoring system; furthermore, texture analysis for severe RNFL defects can be performed from such images (Kanagasingam, Eikelboom, Barry and loss., 1989). The microtexture analysis of the RNFL in grey level digitized photographs has been described before (Tuulonen et al., 2000); depending on the aperture of the pupil, the flash intensity settings and presence of, if any, polarization or cross polarizing filters in the optical pathway, appropriate images for assessment of RNFL can be obtained. One would also need to ensure some degree of normalization to average out the color range, hence our use of CLAHE contrast enhancement filter. In this Thesis, we made an attempt to 'color' the nerve fiber layer with a look up table to show spectral analysis and compare it to the OCT structural texture analysis. Under such conditions, the dynamic and tonal range is important to be able to see the finest differences within the visible color gamut. The justification for using the blue channel comes naturally from the optical properties of the blue filter, which corresponds to the absorption spectrum of rhodopsin which is around 500 nm.

Possible applications of the image analysis in ophthalmology

Multiple examinations are used in conjunction for diagnosis of GL. The lack of ground-thruthed reference standard is a definitive limit to both specificity and sensitivity. Furthermore, there is no evidence that any combination of tests is superior in terms of patient outcome or cost-effectiveness (European Glaucoma Society Terminology and Guidelines for Glaucoma, 4th Edition - Part 1Supported by the EGS Foundation, 2017). GL is most frequently diagnosed via opportunistic case findings. Of all parameters that are taken into consideration, many practitioners are still relying heavily on IOP measurements, while disc assessment alone with or without visual field damage is underrepresented (Quigley, Friedman and Hahn, 2007). Findings suggest that variation amongst observers is large, and the rate of improper diagnosis is high, with more than half of GL patients being missed on former ophthalmic visits (Grødum, Heijl and Bengtsson, 2002). With GL being an optic neuropathy with functional loss occurring at later stages (LA et al., 2000), it would seem reasonable to give emphasis to structural changes first, if one were to detect those at risk of a debilitating future visual disturbance, and allocate further appointments to specialist care accordingly. Because quality of life can be severely impaired if the disease is advanced bilaterally (Goldberg et al., 2009), selected cases require further attention. Current experience in GL screening is not promising. The range of sensitivity and specificity for tests is large, while the study design, execution and examined populations differ greatly. Though some tests may outperform others, no combination suitable for implementation to the general population has been established (AM et al., 2012), Accurately identifying a population at risk poses challenges. Performing a community-based mass screening in an office setting has high financial, temporal and professional requirements, thus not suitable for health systems already lacking funding. Narrowing of the target population is highly desired. Pre-publicizing the risk factors for GL does not seem to increase the number of patients successfully screened, for in self-recruited screening, overall health anxiety may surpass the actual rate of risk factors present (Holló, Kóthy, Géczy and Vargha, 2009). Several studies suggest that there is possible relationship between diabetes and POAG, the condition occurring almost twice as often in diabetics than in non-diabetics (Klein, Klein and Jensen, 1994; Mitchell, 1997). It would seem plausible to use the large amount of fundus photos acquired during diabetic screening to devise and test an algorithm that can aid in the detection of optic disc pathologies, notably GL. The higher-than-normal prevalence of POAG can be anticipated, while the additional costs for screening GL in such a way would be minimal. Furthermore, as individuals screened for any reason might have a false sense of security that they underwent a comprehensive eye test (Salim et al., 2009), screening for more than one condition could improve the hit ratio, and lower the number of missed follow-up visits.

When making the diagnosis of GL, physicians fail to properly complete gonioscopy about 50 percent of the time (Quigley, 2006). It should be recognized that the prevalence of true PACG is easily underestimated. Since all cases of GL should be considered closed until confirmed otherwise (Day et al., 2012), gonioscopy is an essential and compulsory tool for decision making. PACG although less frequent than POAG, leads to blindness more often, therefore, screening for narrow or closed angles would be worthwhile. Currently, only a few reports exist discussing the topic, mainly in well-defined Asian subgroups (He et al., 2006). A popular method for detecting narrow angles - the van Herick method for assessing the peripheral limbal depth, has been found to have a sensitivity and specificity of 61.9% and 89.3%, respectively (Thomas, George, Braganza and Muliyil, 1996). Even with emerging OCT technology (Nolan et al., 2007), 360^{o} visualization of the drainage structures is best achieved by gonioscopy, which is still a gold standard in angle grading. The total internal reflection from the chamber angle cannot, to our knowledge, be surpassed, and as a result the necessity of a contact gonioscopy lens appears to be a major hindrance in designing a fast, infection-proof, non-contact and reliable method suitable for screening. We are aware, however, that the image analysis of angle anatomy is useful for future screening applications. By using contrast enhancement and volumetric measurement, using the same techniques described above in the temporal corneal periphery from photographs of the anterior segment, it would allow to simulate the examination without the need of an additional light source for the slit beam.

To initially look at the practicality of setting up a screening programme for a combination of GL and DR, we targeted a southeastern county (Csongrád) in Hungary. We were keen to investigate patients' experience with the use of telemedicinal tools, and the ability to collect the parameters needed to calculate DR risk (age, gender, type and duration of DM, HbA1c, hypertension, and fundus image grading). Due to the availability of tools for DR, there is a strong justification for using healthcare tools aimed at screening DR, allowing for the prevention and avoidance of late complications such as STR. There can be an argument for looking for Glaucomatous features in these patients in the same screening encounter, or even expanding the screening to incorporate the general public https://pubmed.ncbi.nlm.nih.gov/25264989/.

Screening and fundus image analysis for diabetic retinopathy

The population of Csongrád County is very plausible for initiating a DR, and possibly, future GL screening study, since it has a known higher prevalence of DM and GL compared to other counties in Hungary (Statistical Yearbook of Hungary, 2021). In addition, our study followed the progressive trend of sight threatening disorders in the working age population worldwide, and examined the willingness to participate in screening tests, the attitude towards attendance of the test, the demographics and socioeconomic factors like education, financial, and marital status that influence patients' decisions. Regarding the risk factors, the socioeconomic status (SES) has been already shown to have a very significant impact on the attendance in screening examinations, while occupation has been related to non-attendance in retinal screenings

(Zackrisson, Andersson, Manjer and Janzon, 2003). It was noted that the screening frequency for blood glucose was significantly lower in our study in full-time workers, however the willingness to participate in fundus screening examination was actually higher in that subpopulation.

High blood pressure itself or as a co-disease gives poorer prognosis for patients with DM, this is due to the predisposition for premature vascular sclerosis; 76.4% of the patients in this study suffered from high blood pressure. The occurrence of DR in the studied sample population was 25.5%, which is higher than any previous results in Hungary (Telemedical diabetic´ retinopathy screening. Hungarian pilot study, 2010), although somewhat expected in Csongrád County. As with GL many of these features can be determined by a retinal screening programme (Diabetic Eye Screening Results | East Anglia Diabetic Eye Screening Programme | EADESP, 2021).

Just over a quarter of the participants performed blood glucose level checks several times a day, despite the Diabetology guidelines recommending this. Strikingly, 60% of the study participants performed blood glucose testing every few days, if not more rarely. Typically upon diagnosis, a Diabetologist or General Practitioner informs the patient of the possible complications from DM, recommending an annual eye screening test. Our results coincide with the International Diabetes Federation's (IDF's) observation that 50% of the people with DM are not aware of the characteristics of their disease (IDF Diabetes Atlas 9th edition 2019, 2021). In Hungary, the number of known patients with DM makes nearly 10% of the total population. It would take 100 ophthalmologists (from the total of 968 practicing) working full-time, if they want to carry out only the annual screenings by using traditional tools on such a sized population. Hopefully, using the telemedicine system this may change (Somfai et al., 2007).

The adoption of a new screening program always faces local challenges, but previous studies in other similar countries show promising results. DR could be detected at early stages by digital imaging even in rural areas (Zimmer-Galler, 2015). Diabetes causing vision loss in the working age population is successfully confined in countries like England, where regular screening is implemented.

In our study, only a third of the participants had not visited an ophthalmologist, while 12.4% of them have been diagnosed with DM within a year; only 56.2% of the participants complied with the one-year recommendation. In the UK, patients' compliance in attending traditional screening was 45% and 50% in fundus camera screening in the first year (Tu et al., 2004). Compliance significantly raised to 80% in the fifth year, after using mobile fundus cameras screening units to reach more patients (Harding et al., 1995). Patient attendance is a highly influential factor of cost-effectiveness because of the fixed costs associated with a screening program (digital imaging cameras, computer systems, etc.) (Tu et al., 2004). Patient dissatisfaction can adversely affect the attendance rate of the screening. The response to the subjective experiences perceived during fundus examination did produce satisfactory results: more than three-quarters of the participants were satisfied with the fundus camera examination and one out of five with the traditional method. In both cases, three-quarters of the participants considered the results of the study to be reliable, a significant difference being found between the two screening procedures. There were fewer logistical problems than expected (e.g., subjects not able to drive after pupil dilation because of blurring of the vision), but this may have been due to the older age average of the sampled population. It is interesting to note, however, that during the procedure of pupil dilation, those who had lower education found administering eye drops being irritating or uncomfortable, this comprised of one quarter of the subjects. Some contradiction in the assessment of reliability and satisfaction in the study exists, as significantly more people were actively willing to participate in a traditional retinal screening method than in the fundus camera test (78.2% versus 67.3%). A possible weakness of the study is the size of the sample. 83.6% of the participants were dissatisfied with the examination, which raises the suspicion they could have chosen "Other" for their response to having no other comments, and this could have been done out of necessity.

The "Other" category was chosen by 4.1% who wished to express inconvenience experienced during the test with pupil dilation, and although this was a low figure, there was typically no mention of any reasons for their decision to make this selection.

It appears that the economic activity and education seem to affect the individual's willingness to participate in the screening test. The fundus camera test was preferred mostly by the full-time employees, with whom it was presumably important to see well after the test in order to be able to continue their work during the same day. The few subjects evaluating the fundus camera test as satisfactory were those who were the most uncomfortable in the traditional test; this correlated with the higher levels of education. These data are somewhat contradictory, as mydriatic drops are always required in traditional testing. People with higher education were 100% satisfied with the fundus camera test, and only found the driving restriction and the bad sight after the examination as negative aspects of the screening itself.

The telemedicine part of the study concerns patient anonymity, archiving and data safety, which are now guided by an EU law contained in the Charter of Fundamental Rights of the European Union, Article 8 (2000/C 364/01) (Article 8 - Protection of personal data, 2021), as well as the need to safely store and make backup files for high resolution fundus images acquired from the patients and their archiving. The present study observed these rules followed entirely. The issue of having accessibility to DR screening programs and a centralized image reading center remains to be evidenced in future Hungarian telemedicine studies. Globally, the current golden standard for achieving the task properly remains being the UK.

6. Summary

Screening strategies for glaucoma (GL) with early diagnostic and prognostic value may decrease the societal cost in all regions of the world as can be clearly seen with such screening programs for diabetic retinopathy (DR). With the rising availability of less costly retina digital cameras compared to optical coherence tomography (OCT) technology, such a cost-minimizing image assessment system may lead to decreased costs and reduced individual burden associated to GL such as fear of blindness, psychological health and physical functioning due to vision loss. Such assessment can reduce the number of referrals for double (GL/DR) screening, which takes patient time, and may lead to disease progression, as well as provide a form of standardization for the rising concern about optometrists using gonioscopy in the primary care setting for GL detection; it will also increase screening sensitivity / specificity to a level of accurate positive prediction. The care of patients with diabetes is a multidisciplinary task of diabetologists, dietologists, ophthalmologists, optometrists, primary care physicians, and public health specialists – all being responsible for giving vital lifestyle directions to patients, encouraging them towards essential screening tests.

While OCT technology is rapidly developing in the area of optic disc and chamber angle assessment, rising health care costs and lack of availability of the technology, opens demand for alternative forms of image analysis in GL.

The present state in DR screening, unfortunately, seems to involve lack of realistic assessment of the risk from complications by the patients; therefore a neglect to participate in the recommended screening tests. The patients need a fast, easy, and accurate fundus camera examination as an alternative to traditional, time-consuming, and “unsatisfactory” fundus tests.

In conclusion, we present an alternative low-cost method to detect and manage GL and DR prospectively. We apply a GL assessment method using volumetric, geometric and segmentational data obtained through digital image analysis, which correspond well to those obtained by high definition OCT imaging. These strategies will lead to DR becoming no longer the leading cause of blindness in the working age population, and there is no reason to question the unison between DR and GL screening systems. Further research should look at full automation of both DR and GL assessments to optimize the future early detection of preventable blindness worldwide.

7. References

2010. *Telemedical diabetic´ retinopathy screening. Hungarian pilot study*. [online] Available at: <https://pubmed.ncbi.nlm.nih.gov/25712110/> [Accessed 3 June 2021].

Adio Adedayo Omobolanle and Onua, 2012. Economic burden of glaucoma in Rivers State, Nigeria. *Clinical Ophthalmology*, p.2023.

Airaksinen, P., Drance, S., Douglas, G., Mawson, D. and Nieminen, H., 1984. Diffuse and Localized Nerve Fiber Loss in Glaucoma. *American Journal of Ophthalmology*, 98(5), pp.566-571.

AM, E., MV, B., EH, M., J, P., B, H., D, V., D, W., C, S. and KA, R., 2012. *Screening for Glaucoma: Comparative Effectiveness [Internet]*. [online] PubMed. Available at: <https://pubmed.ncbi.nlm.nih.gov/22649799/> [Accessed 3 June 2021].

American Academy of Ophthalmology. 2021. *Glaucoma Diagnosis*. [online] Available at: <https://www.aao.org/eye-health/diseases/glaucoma-diagnosis> [Accessed 3 June 2021].

Apps.who.int. 2021. *Global report on diabetes*. [online] Available at: <https://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf;jsessionid=21737ECD00B0D5CB8DB9D017A35A4A3F?sequence=1> [Accessed 3 June 2021].

British Journal of Ophthalmology, 2017. European Glaucoma Society Terminology and Guidelines for Glaucoma, 4th Edition - Part 1Supported by the EGS Foundation. 101(4), pp.1-72.

Cdc.gov. 2021. *Vision Loss and Age | CDC*. [online] Available at: <https://www.cdc.gov/visionhealth/risk/age.htm> [Accessed 3 June 2021].

Chalakkal, R., Abdulla, W. and Hong, S., 2020. *Fundus retinal image analyses for screening and diagnosing diabetic retinopathy, macular edema, and glaucoma disorders, In Computer-Assisted Diagnosis, Diabetes and Fundus OCT*. [S.l.]: ELSEVIER, pp.59-111.

Clarkvision.com. 2021. *Clarkvision: Digital Camera Review and Sensor Performance Summary*. [online] Available at: <https://clarkvision.com/imagedetail/digital.sensor.performance.summary/> [Accessed 3 June 2021].

Clarkvision.com. 2021. *ISO and Digital Cameras, ISO Myths www.Clarkvision.com*. [online] Available at: <https://clarkvision.com/articles/iso/> [Accessed 3 June 2021].

Courses.cs.washington.edu. 2021. *Chapter 12 Perceiving 3D from 2D Images*. [online] Available at: <https://courses.cs.washington.edu/courses/cse576/book/ch12.pdf> [Accessed 3 March 2000].

Danaei, G., Finucane, M., Lu, Y., Singh, G., Cowan, M., Paciorek, C., Lin, J., Farzadfar, F., Khang, Y., Stevens, G., Rao, M., Ali, M., Riley, L., Robinson, C. and Ezzati, M., 2011. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. *The Lancet*, 378(9785), pp.31-40.

Day, A., Baio, G., Gazzard, G., Bunce, C., Azuara-Blanco, A., Munoz, B., Friedman, D. and Foster, P., 2012. The prevalence of primary angle closure glaucoma in European derived populations: a systematic review. *British Journal of Ophthalmology*, 96(9), pp.1162-1167.

Diabetesatlas.org. 2021. *IDF Diabetes Atlas 9th edition 2019*. [online] Available at: <https://www.diabetesatlas.org/en/> [Accessed 3 June 2021].

Dielemans, I., Vingerling, J., Wolfs, R., Hofman, A., Grobbee, D. and de Jong, P., 1994. The Prevalence of Primary Open-angle Glaucoma in a Population-based Study in The Netherlands. *Ophthalmology*, 101(11), pp.1851-1855.

Digital Diagnostics. 2021. *Digital Diagnostics | AI The Right Way*. [online] Available at: <https://dxs.ai> [Accessed 3 June 2021].

Dl.acm.org. 2021. *Texture Analysis of Retinal Images to Determine Nerve Fibre Loss | Proceedings of the 14th International Conference on Pattern Recognition-Volume 2 - Volume 2*. [online] Available at: <https://dl.acm.org/doi/10.1109/ICPR.1998.712039> [Accessed 3 June 2021].

Eadesp.co.uk. 2021. *Diabetic Eye Screening Results | East Anglia Diabetic Eye Screening Programme | EADESP*. [online] Available at: <http://www.eadesp.co.uk/screening-results/> [Accessed 3 June 2021].

En.wikipedia.org. 2021. *Back-illuminated sensor - Wikipedia*. [online] Available at: <https://en.wikipedia.org/wiki/Back-illuminated_sensor> [Accessed 3 June 2021].

En.wikipedia.org. 2021. *Fujifilm X-Trans sensor - Wikipedia*. [online] Available at: <https://en.wikipedia.org/wiki/Fujifilm_X-Trans_sensor> [Accessed 3 June 2021].

En.wikipedia.org. 2021. *Super CCD - Wikipedia*. [online] Available at: <https://en.wikipedia.org/wiki/Super_CCD> [Accessed 3 June 2021].

European Union Agency for Fundamental Rights. 2021. *Article 8 - Protection of personal data*. [online] Available at: <https://fra.europa.eu/en/eu-charter/article/8-protection-personal-data#:~:text=Article%208%20%2D%20Protection%20of%20personal%20data,-1.&text=Everyone%20has%20the%20right%20to,data%20concerning%20him%20or%20her.&text=Everyone%20has%20the%20right%20of,right%20to%20have%20it%20rectified.> [Accessed 3 June 2021].

Eyenuk, Inc. ~ Artificial Intelligence Eye Screening. 2021. *Home - Eyenuk, Inc. ~ Artificial Intelligence Eye Screening*. [online] Available at: <https://www.eyenuk.com/en/> [Accessed 3 June 2021].

Ferris, F., 1991. Photocoagulation for diabetic retinopathy. Early Treatment Diabetic Retinopathy Study Research Group. *JAMA: The Journal of the American Medical Association*, 266(9), pp.1263-1265.

Frisen, L., 1980. Photography of the retinal nerve fibre layer: an optimised procedure. *British Journal of Ophthalmology*, 64(9), pp.641-650.

Goldberg, I., Clement, C., Chiang, T., Walt, J., Lee, L., Graham, S. and Healey, P., 2009. Assessing Quality of Life in Patients With Glaucoma Using the Glaucoma Quality of Life-15 (GQL-15) Questionnaire. *Journal of Glaucoma*, 18(1), pp.6-12.

GOV.UK. 2020. *Diabetic eye screening: surveillance pathways*. [online] Available at: <https://www.gov.uk/government/publications/diabetic-eye-screening-surveillance-pathways/diabetic-eye-screening-surveillance-pathways> [Accessed 3 June 2021].

GOV.UK. 2021. *Diabetic eye screening: approved cameras and settings*. [online] Available at: <https://www.gov.uk/government/publications/diabetic-eye-screening-approved-cameras-and-settings> [Accessed 3 June 2021].

GOV.UK. 2021. *Diabetic eye screening: assuring the quality of grading*. [online] Available at: <https://www.gov.uk/government/publications/diabetic-eye-screening-assuring-the-quality-of-grading> [Accessed 3 June 2021].

GOV.UK. 2021. *Diabetic eye screening: pathway for images and where images cannot be taken*. [online] Available at: <https://www.gov.uk/government/publications/diabetic-eye-screening-pathway-for-images-and-where-images-cannot-be-taken> [Accessed 3 June 2021].

GOV.UK. 2021. *Diabetic eye screening: retinal image grading criteria*. [online] Available at: <https://www.gov.uk/government/publications/diabetic-eye-screening-retinal-image-grading-criteria> [Accessed 3 June 2021].

Grødum, K., Heijl, A. and Bengtsson, B., 2002. A comparison of glaucoma patients identified through mass screening and in routine clinical practice. *Acta Ophthalmologica Scandinavica*, 80(6), pp.627-631.

Harding, S., Broadbent, D., Neoh, C., White, M. and Vora, J., 1995. Sensitivity and specificity of photography and direct ophthalmoscopy in screening for sight threatening eye disease: the Liverpool diabetic eye study. *BMJ*, 311(7013), pp.1131-1135.

He, M., Foster, P., Ge, J., Huang, W., Zheng, Y., Friedman, D., Lee, P. and Khaw, P., 2006. Prevalence and Clinical Characteristics of Glaucoma in Adult Chinese: A Population-Based Study in Liwan District, Guangzhou. *Investigative Opthalmology & Visual Science*, 47(7), p.2782.

Henderer, J., 2006. Screening for Primary Open-Angle Glaucoma in the Primary Care Setting: An Update for the US Preventive Services Task Force. *Yearbook of Ophthalmology*, 2006, pp.69-70.

Holló, G., Kóthy, P., Géczy, A. and Vargha, P., 2009. Health anxiety in a non-population-based, pre-publicised glaucoma screening exercise. *Eye*, 24(4), pp.699-705.

Ittarat, M., Itthipanichpong, R., Manassakorn, A., Tantisevi, V., Chansangpetch, S. and Rojanapongpun, P., 2017. Capability of Ophthalmology Residents to Detect Glaucoma Using High-Dynamic-Range Concept versus Color Optic Disc Photography. *Journal of Ophthalmology*, 2017, pp.1-7.

Jones, S. and Edwards, R., 2010. Diabetic retinopathy screening: a systematic review of the economic evidence. *Diabetic Medicine*, 27(3), pp.249-256.

Kanagasingam, Y., Eikelboom, R., Barry, C. and loss., T., 1989. *dblp: Texture analysis of retinal images to determine nerve fibre loss.*. [online] Dblp.org. Available at: <https://dblp.org/rec/conf/icpr/YogesanEB98.html> [Accessed 3 June 2021].

Klein, B., Klein, R. and Jensen, S., 1994. Open-angle Glaucoma and Older-onset Diabetes. *Ophthalmology*, 101(7), pp.1173-1177.

Klein, B., Klein, R. and Jensen, S., 1994. Open-angle Glaucoma and Older-onset Diabetes. *Ophthalmology*, 101(7), pp.1173-1177.

Ksh.gov.hu. 2009. *European Health Interview Survey 2009*. [online] Available at: <http://www.ksh.gov.hu/elef/archiv/2009/pdf/elef_kerdoiv_alap.pdf> [Accessed 3 June 2021].

Ksh.hu. 2021. *Statistical Yearbook of Hungary*. [online] Available at: <https://www.ksh.hu/docs/hun/xftp/idoszaki/evkonyv/evkonyv_2011.pdf> [Accessed 3 June 2021].

LA, K., HA, Q., ME, P., DF, K. and RS, M., 2000. *Number of ganglion cells in glaucoma eyes compared with threshold visual field tests in the same persons*. [online] PubMed. Available at: <https://pubmed.ncbi.nlm.nih.gov/10711689/> [Accessed 3 June 2021].

Langelaan, M., de Boer, M., van Nispen, R., Wouters, B., Moll, A. and van Rens, G., 2007. Impact of Visual Impairment on Quality of Life: A Comparison With Quality of Life in the General Population and With Other Chronic Conditions. *Ophthalmic Epidemiology*, 14(3), pp.119-126.

Lazcano-Gomez, G., Ramos-Cadena, M., Torres-Tamayo, M., Hernandez de Oteyza, A., Turati-Acosta, M. and Jimenez-Román, J., 2016. Cost of glaucoma treatment in a developing country over a 5-year period. *Medicine*, 95(47), p.e5341.

Lund, S., Aspelund, T., Kirby, P., Russell, G., Einarsson, S., Palsson, O. and Stefánsson, E., 2015. Individualised risk assessment for diabetic retinopathy and optimisation of screening intervals: a scientific approach to reducing healthcare costs. *British Journal of Ophthalmology*, 100(5), pp.683-687.

Mitchell, P., 1997. *Open-angle glaucoma and diabetes: the Blue Mountains eye study, Australia*. [online] Available at: <https://pubmed.ncbi.nlm.nih.gov/9111268/> [Accessed 3 June 2021].

Naicker, S., Eastwood, J., Plange-Rhule, J. and Tutt, R., 2011. Shortage of healthcare workers in sub-Saharan Africa: a nephrological perspective. *Clinical Nephrology*,.

Nikonusa.com. 2021. *Photography Lighting | Active D-Lighting Great for Cameras from Nikon | Nikon*. [online] Available at: <https://www.nikonusa.com/en/learn-and-explore/a/products-and-innovation/active-d-lighting.html> [Accessed 3 June 2021].

Nolan, W., See, J., Chew, P., Friedman, D., Smith, S., Radhakrishnan, S., Zheng, C., Foster, P. and Aung, T., 2007. Detection of Primary Angle Closure Using Anterior Segment Optical Coherence Tomography in Asian Eyes. *Ophthalmology*, 114(1), pp.33-39.

NR, M. and TW, G., 1978. *Monochromatic (red-free) photography and ophthalmoscopy of the peripapillary retinal nerve fiber layer*. [online] PubMed. Available at: <https://pubmed.ncbi.nlm.nih.gov/700962/> [Accessed 3 June 2021].

Peli, E., III, T., McInnes, T., Hamlin, J. and Schwartz, B., 2009. Nerve fiber layer photography. *Acta Ophthalmologica*, 65(1), pp.71-80.

Quigley, H., 2006. The number of people with glaucoma worldwide in 2010 and 2020. *British Journal of Ophthalmology*, 90(3), pp.262-267.

Quigley, H., 2006. The number of people with glaucoma worldwide in 2010 and 2020. *British Journal of Ophthalmology*, 90(3), pp.262-267.

Quigley, H., Friedman, D. and Hahn, S., 2007. Evaluation of Practice Patterns for the Care of Open-angle Glaucoma Compared with Claims Data. *Ophthalmology*, 114(9), pp.1599-1606.

Roloff, L., 1984. High-Resolution Photography of the Retinal Nerve Fiber Layer. *American Journal of Ophthalmology*, 97(2), p.252.

Rudnicka, A., Mt-Isa, S., Owen, C., Cook, D. and Ashby, D., 2006. Variations in Primary Open-Angle Glaucoma Prevalence by Age, Gender, and Race: A Bayesian Meta-Analysis. *Investigative Opthalmology & Visual Science*, 47(10), p.4254.

Russell, G., McLoughlin, N. and Nourrit, V., 2012. *Enhancement of color retinal images in poor imaging conditions*. [online] Ieeexplore.ieee.org. Available at: <https://ieeexplore.ieee.org/document/6295584> [Accessed 3 June 2021].

Salim, S., Netland, P., Fung, K., Smith, M. and Aldridge, A., 2009. Assessment of the Student Sight Savers Program Methods for Glaucoma Screening. *Ophthalmic Epidemiology*, 16(4), pp.238-242.

Shah, A., Szirth, B., Sheng, I., Xia, T. and Khouri, A., 2013. Optic Disc Drusen in a Child. *Optometry and Vision Science*, 90(10), pp.e269-e273.

Shah, V., Chhablani, J. and Kaja, S., 2012. Smartphones in ophthalmology. *Indian Journal of Ophthalmology*, 60(2), p.127.

Somfai, G., Ferencz, M., Varga, T., Somogyi, A. and Nemeth, J., 2007. Diabetic retinopathy at the beginning of the 21th´ century: prevention, diagnostics and therapy. *Magyar Belorvosi Archivum,*, 60, pp.123-127.

Stefánsson, E., Bek, T., Porta, M., Larsen, N., Kristinsson, J. and Agardh, E., 2000. Screening and prevention of diabetic blindness. *Acta Ophthalmologica Scandinavica*, 78(4), pp.374-385.

Tham, Y., Li, X., Wong, T., Quigley, H., Aung, T. and Cheng, C., 2014. Global Prevalence of Glaucoma and Projections of Glaucoma Burden through 2040. *Ophthalmology*, 121(11), pp.2081-2090.

Thomas, R., George, T., Braganza, A. and Muliyil, J., 1996. The flashlight test and van Herick's test are poor predictors for occludable angles. *Australian and New Zealand Journal of Ophthalmology*, 24(3), pp.251-256.

Traverso, C., 2005. Direct costs of glaucoma and severity of the disease: a multinational long term study of resource utilisation in Europe. *British Journal of Ophthalmology*, 89(10), pp.1245-1249.

Tu, K., Palimar, P., Sen, S., Mathew, P. and Khaleeli, A., 2004. Comparison of optometry vs digital photography screening for diabetic retinopathy in a single district. *Eye*, 18(1), pp.3-8.

Tu, K., Palimar, P., Sen, S., Mathew, P. and Khaleeli, A., 2004. Comparison of optometry vs digital photography screening for diabetic retinopathy in a single district. *Eye*, 18(1), pp.3-8.

Tufail, A., Kapetanakis, V., Salas-Vega, S., Egan, C., Rudisill, C., Owen, C., Lee, A., Louw, V., Anderson, J., Liew, G., Bolter, L., Bailey, C., Sadda, S., Taylor, P. and Rudnicka, A., 2016. An observational study to assess if automated diabetic retinopathy image assessment software can replace one or more steps of manual imaging grading and to determine their cost-effectiveness. *Health Technology Assessment*, 20(92), pp.1-72.

Tuulonen, A., Alanko, H., Hyytinen, P., Veijola, J., Seppänen, T. and Airaksinen, J., 2000. Digital Imaging and Microtexture Analysis of the Nerve Fiber Layer. *Journal of Glaucoma*, 9(1), pp.5-9.

Vaahtoranta-Lehtonen, H., Tuulonen, A., Aronen, P., Sintonen, H., Suoranta, L., Kovanen, N., Linna, M., Läärä, E. and Malmivaara, A., 2007. Cost effectiveness and cost utility of an organized screening programme for glaucoma. *Acta Ophthalmologica Scandinavica*, 85(5), pp.508-518.

Vijaya, L., George, R., Paul, P., Baskaran, M., Arvind, H., Raju, P., Ramesh, S., Kumaramanickavel, G. and McCarty, C., 2005. Prevalence of Open-Angle Glaucoma in a Rural South Indian Population. *Investigative Opthalmology & Visual Science*, 46(12), p.4461.

Vokó, Z., Nagyjanosi, L. and Kalo, Z., 2010. PDB24 DIRECT HEALTH CARE COSTS OF DIABETES MELLITUS IN HUNGARY. *Value in Health*, 13(7), p.A288.

Weinreb, R. and Kaufman, P., 2011. Glaucoma Research Community and FDA Look to the Future, II: NEI/FDA Glaucoma Clinical Trial Design and Endpoints Symposium: Measures of Structural Change and Visual Function. *Investigative Opthalmology & Visual Science*, 52(11), p.7842.

Who.int. 2021. *GHO*. [online] Available at: <https://www.who.int/data/gho> [Accessed 31 May 2021].

Who.int. 2021. *Vision impairment and blindness*. [online] Available at: <https://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment> [Accessed 3 June 2021].

Wittenborn, J., Zhang, X., Feagan, C., Crouse, W., Shrestha, S., Kemper, A., Hoerger, T. and Saaddine, J., 2013. The Economic Burden of Vision Loss and Eye Disorders among the United States Population Younger than 40 Years. *Ophthalmology*, 120(9), pp.1728-1735.

www.amdbook.org. 2021. *Pathogenic Mechanisms | www.amdbook.org*. [online] Available at: <https://amdbook.org/content/pathogenic-mechanisms> [Accessed 3 June 2021].

Yau, J., 2010. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*, 35(3), pp.556–564.

Zackrisson, S., Andersson, I., Manjer, J. and Janzon, L., 2003. Non-attendance in breast cancer screening is associated with unfavourable socio-economic circumstances and advanced carcinoma. *International Journal of Cancer*, 108(5), pp.754-760.

Zimmer-Galler, I., 2015. Diabetic retinopathy screening and the use of telemedicine. *Current Opinion in Ophthalmology*, 26(3), pp.167-172.

8. List of publications of the author

Publications related to this Thesis:

Russell, G., Hertzberg, SNW., Anisimova, N., Gavrilova, N., Petrovski, BÉ., Petrovski, G. (2020) Digital Image Analysis of the Angle and Optic Nerve: A Simple, Fast, and Low-Cost Method for Glaucoma Assessment. J Ophthalmology, 2020: 3595610 (**full first authorship**)

Eszes, D., Szabó, D., **Russell, G.**, Kirby, P., Paulik, E., Nagymajtényi, L., Facskó, A., Moe, MC., Petrovski, B. (2016) Diabetic Retinopathy Screening Using Telemedicine Tools: Pilot Study in Hungary. Journal of Diabetes Research, 2016, pp.1-9. (**co-authorship**)

Other publications:

Eszes, DJ., Szabó, DJ., **Russell, G.**, Lengyel, C., Várkonyi, T., Paulik, E., Nagymajtényi, L., Facskó, A., Petrovski, G., Petrovski, BÉ. (2021) Diabetic Retinopathy Screening in Patients with Diabetes Using a Handheld Fundus Camera: The Experience from the South-Eastern Region in Hungary. J Diabetes Research, 2021:6646645.

Josifovska, N., Lumi, X., Szatmari-Tóth, M., Kristóf, E., **Russell, G.**, Nagymihály, R., Anisimova, N., Malyugin, B., Kolko, M., Ivastinović, D., Petrovski, G. (2019) Clinical and molecular markers in retinal detachment-From hyperreflective points to stem cells and inflammation. PLoS One, 2019, 11;14(6):e0217548.

Holm, S., **Russell, G.**, Nourrit, V. and McLoughlin, N. (2017). DR HAGIS—a fundus image database for the automatic extraction of retinal surface vessels from diabetic patients. Journal of Medical Imaging, 4(1), p.014503.

Lund, S., Aspelund, T., Kirby, P., **Russell, G.**, Einarsson, S., Palsson, O. and Stefánsson, E. (2015). Individualised risk assessment for diabetic retinopathy and optimisation of screening intervals: a scientific approach to reducing healthcare costs. British Journal of Ophthalmology, 100(5), pp.683-687.

Aldington, S., Stratton, Im, Gazis, T., Sivaprasad, S., **Russell G.**, and Scanlon, Ph. "Validation of a risk stratification algorithm for progression to referable diabetic retinopathy." European journal of ophthalmology 25 (2015): E13–E13.

9. Acknowledgements

I would like to acknowledge my supervisors ***Professor Goran Petrovski and Dr. Beáta Éva Petrovski*** for their indefinite support, patience and inspiration throughout the time.
I am also grateful for the vision and encouragement, as well as the analytical skills they provided me, in addition to the opportunity to learn clinical pearls from a science normally dedicated to physicians.

I also want to thank ***Professor Andrea Facskó***, the former Head of the Department of Ophthalmology (University of Szeged), who during the period of my PhD studies provided a warm welcome to the department, giving me the opportunity to study with the best of her clinical and research staff.

I am thankful to my previous head - Mr Phil Kirby (Health Intelligence, UK), as well as my current head - Dr Kushal Solanki (Eyenuk, Inc., USA) who between them have given me the time and support needed to complete this work. Additionally, I would like to thank all the Eyenuk management team including Dr Chaithanya Ramachandra who has offered me encouragement and support over the recent years.

Last, but not least, I am grateful to all of my family, especially my late Father who suggested that I work as a medical illustrator/photographer 20 years ago at Chelsea Westminster Hospital London, and later motivated me to attempt a PhD.