Innovative Technology to Support Cost-Effective Diabetic Retinopathy Screening Programs

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Introduction

The Challenge

Diabetic Retinopathy (DR) is a sight threatening complication of Diabetes and the main cause of vision loss in working age population. Diabetes is a medical condition with epidemic proportions, growing every year, today affecting more than 382 Million people.

The recommend best practices for diabetics, in order to prevent worsening DR, are performing yearly eye examinations. Screening Programs are also a cost-effective way to address this public health issue. With the increase of the number of diabetics, performing and evaluating these yearly exams is causing a growing burden for health systems.

Retmarker

Retmarker analyses retinal fundus photographs (a non-invasive exam) and safely identifies diabetics that do not need medical attention. This reduces the burden on DR Screening Programs by up to 75%.

Retmarker is already used in DR Screening Programs and the accumulated expertise, procedures and technology can support setting up from scratch new DR Screening Programs.
The Epidemic of Diabetes

Diabetes affects 5% of the world’s population and its prevalence doubles every generation. The International Diabetes Federation (IDF) estimates that in 2013 approximately 382 million people in the world had diabetes.

IDF publishes the IDF Diabetes atlas¹ (currently on the sixth edition), and the key messages underline that 80% of people with diabetes live in low- and middle-income countries, and that the greatest number of people with diabetes are between 40 and 59 years of age, i.e., it affects working age population.

Every 18 seconds someone is diagnosed with Diabetes². Even more worryingly, according to the IDF, by 2035 the number of diabetics in the world is expected to rise to 592 million.

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¹ http://www.idf.org/diabetesatlas
² http://fastercures.org/reports/view/14

Figure 1. The epidemic of Diabetes
Diabetes is also growing at a faster pace in low- and middle-income countries.

Figure 2. Projected increase on the number of Diabetics
Vision Threatening Complication: Diabetic Retinopathy

Diabetes Mellitus, a systemic disease, brings with it an increased risk of long-term complications. The major complication relates to damage to blood vessels. Diabetes affects the capillaries and blood vessel formation in the retina of the eye, i.e., causes Diabetic Retinopathy. Diabetic Retinopathy is the most frequent and most serious complication of Diabetes that afflicts vision, affecting up to 80 percent of all patients who have had diabetes for 10 years or more³.

Available forecasts for the United States suggest that the number of people with DR and vision-threatening DR complications will almost triple during the next 45 years. The number of people with DR is expected to increase from 5.5 million in 2005 to 16.0 million in 2050, and the number with vision-threatening DR complications is expected to increase from 1.2 million in 2005 to 3.4 million in 2050.⁴

Diabetic Retinopathy often causes vision loss and blindness during working age years, resulting in more disability and person-years of vision lost than any other eye disease⁵. Diabetic Retinopathy (DR) is composed of a characteristic group of lesions observed in the retina of individuals having diabetes.

Medical intervention can decrease some of the risk to vision caused by DR, i.e., the control of glycaemia decreases the risk of incidence and progression of retinopathy, but DR may still in many cases progress to visual loss in well-controlled patients.

In patients with Diabetes Mellitus, the retinal disease that results from these complications initially is nonproliferative (also referred to as “background”) retinopathy. On clinical examination, retinal abnormalities can be observed, including microaneurysms and/or hemorrhages, i.e., red-dots in the fundus, and exudates. The initial stages of DR are characterized by the presence of red-dots (microaneurysms and/or hemorrhages) and indirect signs of vascular damage.

The retina has a large functional reserve and changes in visual function can only be detected after relatively extensive structural changes. Therefore, structural changes are detected earlier than changes in visual function and we need to use structural changes as markers of disease activity and progression.⁶

The classification of DR is based on which part of the retina is affected and the degree of pathology seen on examination of the eye. It is not necessarily correlated to the degree of vision, which may be almost normal until the very late stages of the disease when little can be done to save it.⁷

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³ Kertes PJ, Johnson TM, “Evidence Based Eye Care”
⁶ Ribeiro ML et al. “Surrogate Outcomes for Progression in the Initial Stages of Diabetic Retinopathy” http://www.ingentaconnect.com/content/ben/iemamc/2013/00000013/00000001/art00003
As DR progresses it may develop two major sight-threatening complications, depending on different predominant mechanisms of disease progression: macular edema and proliferative retinopathy.

The involvement of retina in diabetes may, therefore, be divided into:

- Clinical retinopathy (background or nonproliferative DR)
- Complications of DR:
  - diabetic macular edema
  - proliferative retinopathy

**Timely treatment and follow-up care are critical for diabetics with Diabetic Retinopathy.** Laser treatment and vitrectomy reduce the risk of blindness in patients with severe diabetic retinopathy by 90% 8. Nearly 50% of diabetic retinopathy patients who received anti-VEGF treatment experienced substantial visual improvement after a year of injections, and effectively halt progression of the disease.

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Clinically Significant Macular Edema (CSME)

CSME is the largest cause of visual acuity reduction in diabetes. It may affect central vision from the early stages of retinopathy and is extremely frequent, particularly in older type 2 diabetic patients. Its role in the process of vision loss in diabetic patients and its occurrence in the evolution of the retinopathy is being increasingly recognized.

Macular Edema is frequently the first alteration occurring in the retina that causes visual loss.

Extracellular edema is directly associated with a situation of open blood-retinal barrier, i.e., results from a breakdown of the inner blood-retinal barrier, one of the earliest alterations occurring in the diabetic retina. The increase in tissue volume is due to an increase in the retinal extracellular space and the breakdown of the blood-retinal barrier.

The ETDRS (Early Treatment Diabetic Retinopathy Study), made an effort to establish some guidelines to define “Clinically Significant Macular Edema” in order to establish an outcome when designing clinical trials to test the efficacy of treatment for diabetic macular edema (Figure 3). They paid special attention to the involvement of the center of the macula taking into the consideration the associated visual loss, with its clinical significance.

Figure 3. Example of lesions representative of Clinically Significant Macular Edema.

The ETDRS classification of Clinically Significant Macular Edema is as follows:

- Thickening of the retina (as seen either by slit lamp biomicroscopy or by stereo fundus photography) at or within 500 microns of the center of the macula.
- Hard exudates at or within 500 microns of the center of the macula, associated into the thickening of the adjacent retina (but not residual exudates remaining after disappearance of retinal thickening);
- A zone, or zones, of retinal thickening one disc area or larger size, any part of which is within one disc diameter of the center of the macula.
Proliferative Diabetic Retinopathy (PDR)

One of the specific characteristics of PDR is the formation of new vessels. The exact cause of new vessel formation is not known. It is however always secondary to the presence of large areas of capillary nonperfusion. It is, therefore, not specific to DR, as it occurs also in a number of other retinal vascular diseases characterized by marked ischemia, such as sickle cell disease and retinal vein occlusion.

New vessels arise from the optic disk or from the retina (Figure 4 and 5). While the vitreous is attached to the retina the new vessels are symptomless. However the presence of the new vessels leads to retraction of the vitreous. It is this pulling effect that leads to the progressive complications associated with retinal neovascularization, such as vitreous hemorrhage and progressive visual distortion.

Figure 4. Proliferative DR. Fluorescein angiography showing extensive vascular closure and neovascularization at the optic disk.

As the vitreous shrinks, possibly due to the abnormal leakage associated with the abnormal new vessels, it gradually pulls the neovascular fronds, causing preretinal and intravitreal bleeding, a frequent cause of acute vision loss in diabetes. Proliferative retinopathy responds well to photocoagulation (laser treatment), but it is essential that it be treated early and adequately, at time when it is symptomless, before tractional complications have developed.

Figure 5. Proliferative DR. Neovascularization in the optic disk.
Screening – Cost-effective prevention

Screening for a pathology refers to the process where the whole population is examined, and individuals with the pathology are identified. **Screening is particularly relevant when individuals with the pathology are not aware of their condition. This is the case for Diabetic Retinopathy (DR), a pathology that progresses without symptoms, until very advanced stages.**

The purpose of Screening is to enable timely treatment. In the case of DR, timely treatment is particularly relevant, since it is possible to treat patients so that progression of pathology is halted, but after vision loss occurs it may not be reversible.

A study evaluating quality of life using utility values, found that diabetic retinopathy patients who were legally blind from diabetes were willing to trade 41% of their remaining years in return for perfect vision⁹.

**Why DR Screening?**

Computer-simulation models have been designed to predict the medical and economic effects of applying accepted methods for controlling diabetic retinopathy among patients with diabetes. A cost-utility analysis using a computer model of detection and treatment of diabetic retinopathy in patients with type 1 and type 2 diabetes demonstrated that ophthalmic care reduced the prevalence of blindness by 52% and that the direct costs of care were less than the losses in productivity and the costs of facilities provided for disability¹⁰.

It is widely accepted that screening for diabetic retinopathy represents both good clinical practice and cost-effective healthcare. The natural history of the disease is known, and early detection and treatment of retinopathy has been shown to be effective in preventing visual impairment. With appropriate medical and ophthalmological intervention, including good glycemic and blood pressure control, it has been estimated that blindness may be prevented in at least one eye in 60-70% of cases with CSME and 90% of cases of PDR. The disability caused by blindness and partial sight, as well as the social costs in terms of loss of earning capacity and the required social support are considerable. Lack of screening may also result in costly compensation claims.

Principal recommendations for a Screening Committee are:

- **Annual screening** for all diabetic patients
- **Digital imaging** is the preferred modality.
- **Quality assurance** should be included in any program.
- The screening program should be **accessible to all patients with diabetes**. The exact details of a program are determined by local factors.

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¹⁰ American Academy of Ophthalmology “Preferred Practice Pattern”
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Retmarker

Implementation of DR Screening Programs causes a great human burden on the health system, requiring resources to photograph patients, but even more importantly to carefully analyze the photographs and decide which patients need referral for medical appointments. **Considering that the vast majority of patients attending DR Screening (more than 90%) do not need referral, the cost of handling healthy patients is enormous.**

Technology can be very helpful in supporting Screening Programs. To handle this need, Retmarker technology has been successfully deployed in running Screening Programs, identifying patient images where no lesions can be found. **This automated technology decreases the human burden for grading, and allows for more urgent patients to be given priority.**

Retmarker makes use of image processing algorithms that were trained and developed to detect vascular lesions caused by diabetic retinopathy. The most frequent lesions occurring in the initial stages of DR are microaneurysms (MAs), which are red-dot shaped lesions, typically 20 µm to 200 µm in size, occurring in the retina and visible in retinal fundus photography.

**Human grading is particularly costly since most of the patients do not need referral for treatment.** It is also an inherently subjective task, since a human grader performance is influenced by various factors such as weariness or fatigue. Since the number of cases needing referral is low, these factors are further aggravated. **Introducing Retmarker technology in a Screening Program is also a means to bring objectivity, and repeatability, to the task of identifying patients that need medical attention.**

Retmarker is a class Ila medical device certified by TUV Rheinland through the EC Directive 93/42/ECC Annex II, Article 3. Retmarker technology enables the automatic calculation of the MA Turnover (MA Formation Rate), a biomarker of progression to CSME, the most frequent sight-threatening complication of Diabetes Mellitus. This technology allows for estimating the individual risk of progression for each patient.

**Retmarker Biomarker**

Retmarker underlying technology has enabled the automated calculation of the MA Turnover (i.e. the MA Formation Rate) Biomarker. Using proprietary retinal photograph registration algorithms, successive images from the same patient are compared in order to calculate the number of microaneurysms that develop. This number is an indicator of disease activity. When focusing on clinical research, consistently tracking microaneurysms in color fundus photographs provides valuable information for clinical trials. MA Turnover is a fully automated measurement that is not feasible to achieve manually.

**This Biomarker concept has been validated in both retrospective and prospective studies** performed by AIBILI, a prestigious European Clinical Research Institute and the coordination center...
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for the EVICR.net\textsuperscript{11}. These studies have been published in leading peer-reviewed publications, namely *Ophthalmologica*\textsuperscript{12} and *Diabetes Care*\textsuperscript{13}.

Further independent validation was obtained at the Ludwig-Maximilians Institute (LMU) in Munich, which retrospectively analyzed patient images from the large CALDIRET clinical trial, and obtained corroborating results. This analysis has also been peer-reviewed and published at *Retina*\textsuperscript{14}. Retmarker has also started a formal qualification process with the European Medicine Agency (EMA) to validate the usage of the MA Turnover biomarker for clinical trial enrichment.

**Retmarker Screening**

The same Retmarker technology used in the Biomarker has been adapted to be used in a screening context\textsuperscript{15}. The concept is that, in patients that do not need referral, there will be no lesions detected, and thus priority is given to the patients with lesions detected.

**What can Retmarker Offer?**

Retmarker technology has been deployed in DR Screening Programs in Portugal since 2011, and has been improving the technology continuously to better tackle the challenges occurring in the “real world” deployment, such as image quality issues or data integrity.

![Retmarker technology workflow](image)

Figure 6. Retmarker technology workflow

\textsuperscript{11} EVICR.net (European Vision Institute Clinical Research Network) is the largest European network of clinical research in Ophthalmology, [http://www.evicr.net/](http://www.evicr.net/)

\textsuperscript{12} Nunes S et al. “Microaneurysm turnover is a biomarker for diabetic retinopathy progression to clinically significant macular edema: findings for type 2 diabetics with nonproliferative retinopathy” [http://www.ncbi.nlm.nih.gov/pubmed/19372723](http://www.ncbi.nlm.nih.gov/pubmed/19372723)


The entire methodology used in a Portuguese Screening Program is described in detail in a new publication\textsuperscript{16} that covers all aspects relevant for the set up of a Screening Program, namely:

- which target population to consider,
- which grading scale to use,
- performance obtained, including quality control measures (software and graders),
- among several others.

Published results show already that a reduction of 50\% of human burden was already achieved and they can increase significantly as we are about to see.

\textit{Increased Burden Reduction}

The performance of the Screening Program is fundamental when thinking about scaling it. The previous results were obtained with 12 years old cameras that were in the meantime replaced.

Preliminary data with new, state-of-the-art, fundus cameras indicates a human burden reduction between 60\% and 70\%!

Such results are a clear confirmation on the impact of the decisions to be made when setting up a new program. Previous expertise on similar situations can translate into a direct impact on the return on investment made.

This Portuguese Screening Program is responsible for 200,000 screenings since its beginning, of which 45,000 were already performed with Retmarker after its introduction in 2011.

\textsuperscript{16} Ribeiro L et al “Screening for Diabetic Retinopathy in the Central Region of Portugal. Added Value of Automated ‘Disease/No Disease’ Grading” \url{http://www.ncbi.nlm.nih.gov/pubmed/25427567}
Conclusion

Diabetes Mellitus is a pathology with epidemic proportions, and every year is affecting a wider population range, also fueled by sedentary lifestyle and wrong dietary habits. Diabetic Retinopathy is the sight-threatening complication of diabetes, which progresses without symptoms until irreversible vision loss occurs. Screening Programs are effective to provide timely treatment and avoid vision loss. The Retmarker certified technology enables highly efficient screening of DR.

What is the Value created?
The main value that Retmarker enables is the great Human burden reduction when compared to a DR screening performed by traditional means. Effectively, what this reduction means is that:

- Screening becomes more cost-effective;
- More population can be screened using the same resources.

Using the technology and accumulated experience has also been proved to reduce errors that accidently occur in manual handling of data. Retmarker solution comprises the handling of patient information from the fundus camera to an individual risk assessment report. Risk assessment makes use of the unique Biomarker that Retmarker technology calculates in an automated way.

The workflow is fully automated, making it simple and flexible to manage and run. It includes several measures of Quality Control, performed on a regular basis, so that the Screening Program can be audited and any irregular behavior identified and promptly corrected.
The following is a compilation of the scientific papers related to Retmarker, referred in our documents, here included for direct access.

<table>
<thead>
<tr>
<th>Paper Title</th>
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- Ribeiro ML et al. “Surrogate Outcomes for Progression in the Initial Stages of Diabetic Retinopathy”
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- Nunes S et al. “Microaneurysm turnover is a biomarker for diabetic retinopathy progression to clinically significant macular edema: findings for type 2 diabetics with nonproliferative retinopathy”

- Ribeiro ML et al. “Microaneurysm turnover at the macula predicts risk of development of clinically significant macular edema in persons with mild nonproliferative diabetic retinopathy”

- Haritoglou et al. “Microaneurysm formation rate as a predictive marker for progression to clinically significant macular edema in nonproliferative diabetic retinopathy.”

- Oliveira CM et al. “Improved Automated Screening of Diabetic Retinopathy”

- Ribeiro L et al “Screening for Diabetic Retinopathy in the Central Region of Portugal. Added Value of Automated ‘Disease/No Disease’ Grading”

- Suggests that a portable retinal camera is a more cost-effective means of screening for diabetic retinopathy than a retina specialist.


- The development and application of solutions that use information technology, such as teleretinal imaging, to enhance healthcare providers’ effectiveness and provide seamless integration across the healthcare system is critical to improving quality and delivering care at lower costs.


- The number of Americans 40 years or older with Diabetic Retinopathy and Vision-Threatening Diabetic Retinopathy will triple in 2050.


- Appropriately trained imagers can accurately identify sight threatening Diabetic Retinopathy.
