International Review on
Computers and Software (IRECOS)

Contents

(continued)

Praise Worthy Prize

International Review on Computers and Software (I.RE.CO.S.), Vol. 8, N. 8
ISSN 1828-6003 August 2013

A Method for Prognosis of Primary Open-Angle Glaucoma

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Abstract – *A method for prognosis of primary open-angle glaucoma (POAG) using the mathematical apparatus of Markov processes is developed in the article. The mathematical apparatus of Markov processes with discrete states and discrete time was used to describe the course of glaucoma. According to the clinical approbation of the proposed method, the prognosis was made unmistakably in 16 surveyed patients. Prognosis was confirmed in 82% of cases. The proposed method increases the prognosis of POAG development significantly. The introduction of this method for POAG prognosis in ophthalmology practice allows improving the quality level of medical service for patients.*

Keywords*: Duration, Markov Chain, Primary Open-Angle Glaucoma, Probability, Prognosis*

I. Introduction

Worldwide, glaucoma is the second-leading cause of blindness (70 million people) after cataracts [1]. This fact emphasizes social significance of the problem. The vision loss is caused by damage to the optic nerve.

There are two main types of glaucoma: primary open-angle glaucoma (POAG), and angle-closure glaucoma [2]. POAG is the most common type of glaucoma [3] (about 80%).

There are no symptoms at first, but gradually the person loses peripheral (side) vision. Over time, central vision may be lost, too. As much as 40% of vision can be lost without a person noticing it [4].

Risk factors for POAG include: advanced age, a family history of glaucoma, diabetes, glucocorticoid responsiveness, arterial hypotension, farsightedness or nearsightedness, past eye injury, elevated eye pressure [5]. Additional high-risk groups include those of African, Asian, and Hispanic descent.

Early diagnosis is vital in stopping the progression of the disease. Identification of glaucoma at the early stages of pathological process largely determines the effectiveness of its treatment. Also one of the priorities in the problem-solving of glaucoma is prognosis of the clinical course of disease for prevention and stabilization of pathological process.

Currently known methods for prognosing the course of glaucoma [6] - [9] do not fully meet the requirements of ophthalmic practice. Some of them are described below.

A method of detecting non-stabilized glaucoma is based on assessments of visual acuity, field of vision and cup of the optic disc [10]. Disadvantages of this method are as follows:

- long-term monitoring of patients (at least 5-6 months) and the state of their visual system for the purpose of evaluating dynamics of the process. It can lead to irreversible reduction of visual function;
- subjectivity and insufficient estimation accuracy of investigated parameters: the state of the field of vision – according to the statement of the patient, the optic disc – according to ophthalmologist's estimation.

Another example of existing methods is method for diagnosis of the course of glaucoma [11] based on comprehensive investigation of patient, including the measurement of intraocular pressure (IOP), systolic and diastolic blood pressure, biochemical blood study by erythrocytes deformability index, haematocrit and total cholesterol; microcirculation study of bulbar conjunctiva of the eye apple, determination of hemodynamic parameters with the help of Doppler – the linear blood flow velocity in the supratrochlear artery with the calculation of Purcell and Gosling indices. Based on these parameters, the stability of glaucoma is determined by the corresponding formula. Disadvantages of this method are as follows:

- the high cost of direct labour. It relates primarily to the number of diagnostic tests (at least 7) required for a particular patient;
- the duration of the measurements – for several hours;
- the invasiveness of obtaining material (blood) – for biochemical analysis;
- the preliminary preparation – blood test on an empty stomach;
- the inability to prognose the rate of glaucoma progression.

A method of predicting the progression of primary glaucoma after normalization of IOP [12] is to measure the biologically active points with "Imedis-Foll" apparatus. The disadvantage of this method is that the important changes of morphological (the state of the optic disc) and functional (the state of the vision field) criteria are not taken into account. It does not fully inform us about the stabilization of the disease and its treatment.

Manuscript received and revised July 2013, accepted August 2013

Thus, the search of new methods for prognosing the development of the disease is currently a relevant aim in ophthalmology. It will contribute to timely effective treatment of patients and prevention of disability.

II. Materials and Methods

The research involved 300 patients with POAG for developing a method for prognosis of POAG. All patients were divided into the following 4 groups:

- group 1: 87 patients with stage I of POAG (29%);
- group 2: 120 patients with stage II of POAG (40%);
- group 3: 69 patients with stage III of POAG (23%);
- group 4: 24 patients with stage IV of POAG (8%).

In all patients complex ophthalmologic examination was performed: visometry, kinetic perimetry, biomicroscopy, gonioscopy, ophthalmoscopy, Goldmann tonometry, Humphrey automated perimetry. Confocal scanning laser ophthalmoscopy with the help of Retina Tomography HRT-II (Heidelberg Retina Tomograph II, Heidelberg Engineering, Germany, software IR1-V1.7/4956) was done for recording structural changes of the optic nerve and retinal nerve fiber layer.

Also, for all patients a specific glaucoma treatment was prescribed depending on the stage of the disease and the IOP level.

We used three directions of glaucoma treatment: drug, laser and surgical. Drug therapy was conducted in: 72 patients of group 1; 71 patients of group 2; 16 patients of group 3; 5 patients of group 4.

It included local hypotensive therapy and neuroprotective therapy. Laser trabeculoplasty or selective laser trabeculoplasty, and argon laser trabeculoplasty were performed. Laser treatment was conducted in: 7 patients of group 1; 19 patients of group 2; 3 patients of group 3; 0 patients of group 4. Drug therapy after laser treatment was needed for: 3 patients of group 1; 6 patients of group 2; 0 patients of group 3; 0 patients of group 4. Surgical treatment involved conducting non penetrating deep sclerectomy and its variations. Surgical treatment was conducted in: 8 patients of group 1; 30 patients of group 2; 50 patients of group 3; 19 patients of group 4. Drug therapy after surgical treatment was needed for: 1 patients of group 1; 4 patients of group 2; 12 patients of group 3; 8 patients of group 4.

Results of laser and surgical treatment were evaluated on a daily basis for 3 days after the operation and in 10-20 days. Examinations were repeated at 3, 6, 12 and 14 months after the surgery. Observation period lasted 2.5 years. The mathematical apparatus of Markov processes with discrete states and discrete time was used to describe the course of glaucoma. It is a particular type of random processes [13]. The special place of Markov processes among other classes of random processes is due to the following facts: the mathematical apparatus is well developed for Markov processes and this allows to solve many practical tasks; the behavior of complex systems can be described using Markov processes.

20 patients with glaucoma (40 eyes) were examined for testing a method for prognosis of POAG.

Out of these there were: 14 eyes - stage I of glaucoma, 16 eyes - stage II of glaucoma, 6 eyes - stage III of glaucoma, 4 eyes - stage IV of glaucoma.

The studies were conducted at Kharkiv Municipal Clinical Hospital №14 of Professor L.L. Hirschman (Ukraine). Mathematical processing of the obtained results was performed with the software package MATLAB. The investigators certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research and the study protocol adhered to the tenets of the Declaration of Helsinki.

III. Results and Discussion

The proposed method for prognosis of primary open-angle glaucoma is performed in the following sequence.

Step 1. Information gathering required to prognose the progression of glaucoma, and graph construction of a Markov chain. The conditions of patients at the different stages of glaucoma can be represented as discrete states.

The time intervals between the occurrence of one or another patient's condition can be represented as discrete values. Thus, POAG can be viewed as a Markov chain, consisting of 18 discrete states (see Fig. 1) [14].

For simulation of POAG the time discretisation was selected equal to one week. The different states of patients are described as follows:

0, 5, 10, 15 – the state «stage I, II, III, IV of open-angle glaucoma, indications for drug therapy» (respectively 0 - stage I (early stage), 5 -stage II (moderate stage), 10 - stage III (advanced stage), 15 - stage IV (end-stage);

1, 6, 11 – the state «stage I, II, III of open-angle glaucoma after laser treatment not requiring drug therapy»;

2, 7, 12 – the state «stage I, II, III of open-angle glaucoma after laser treatment requiring drug therapy»;

3, 8, 13, 16 – the state «stage I, II, III, IV of open-angle glaucoma after surgical treatment not requiring drug therapy»;

4, 9, 14, 17 – the state «stage I, II, III, IV of open-angle glaucoma after surgical treatment requiring drug therapy»;

18 – the state "anophthalmos" (the absence of eye).

Step 2. Determination of the transition probability in the possible states.

For Markov chain on Fig. 1 the transition probability matrix is presented as:

$$M = \begin{Vmatrix} Q & R \\ O & E \end{Vmatrix} \quad (1)$$

where:

Q – the matrix, describing the behavior of process prior to exiting the set of irrecoverable states;

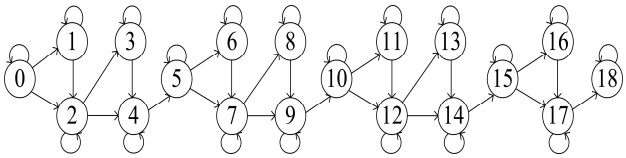

Fig. 1. Graph of the developed Markov chain

R – the matrix, describing transitions from the irrecoverable states to the absorbing states;
O – the null matrix;
E – the identity matrix.

Step 3. Determination of probability vector of the patient's standing in one or another state.

Thus, the initial probability vector for state 0 is presented as:

$$\beta = (1,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0) \qquad (2)$$

Step 4. Calculation of the fundamental matrix of transition probabilities [15]-[18]:

$$N = (E - Q)^{-1} \qquad (3)$$

Step 5. Determining the vector variances of residence time in each state.

The proposed Markov model is an absorbing Markov chain. The state 18 is an absorbing state. The main aim is the prognosis of the residence time of patient in all non-absorbing states.

In the Markov chain the Poisson process occurs. So, it is correct to speak not of absolute values of the time parameters, but of their statistical evaluations, such as the mean or variance. The time t_i is viewed as a random variable. It is the time duration while the patient remains in non-absorbing state *i* after this state was reached. The variance is calculated according to the formula:

$$D(t_i) = \frac{p_{ij}}{(1 - p_{ij})^2} \qquad (4)$$

where p_{ij} – the probability that the system will remain in the state i in the next step ($i = j$).

Step 6. Determination of the probabilities of patient's standing in one or another state and a list of therapeutic and diagnostic activities needed to stabilize the state:

$$B = N \cdot R$$
$$H = (N - E) \cdot N_{dg}^{-1} \qquad (5)$$

where N_{dg} – the diagonal matrix consisting of the matrix elements N. These elements are located on the main diagonal of the latter. Taking into account the initial distribution β, the calculated probability will be in the row with the number corresponding to the number state at the time of prognosis for matrix B and H.

Step 7. Formation of the diagnostic and therapeutic conclusions.

Transition probability matrix was obtained on the basis of the expert evaluation. It is presented in Fig. 2.

Probabilities of all states on the first 600 steps were calculated according to this matrix. For that, the identity matrix with a 19 × 19 dimension was used. It is a set of vectors of the initial states.

The matrix of the standing durations in one or another state within 600 weeks is shown in Fig. 3.

As a result, the probabilities of patient's standing in one or another state and a list of therapeutic and diagnostic activities needed to stabilize the state were obtained.

Obtained state probabilities for different initial states of the model allow generating the movement trajectories of random process. According to the clinical approbation of the proposed method, the prognosis was made unmistakably in 16 surveyed patients. Thus, the prognosis was confirmed in 82% of cases.

This method for prognosis of POAG is illustrated by the following clinical example.

$M=$

0,978	0,017	0,005	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0,979	0,015	0,006	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0,977	0,019	0,004	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0,974	0,026	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0,972	0,028	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0,97	0,02	0,01	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0,98	0,02	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0,969	0,029	0,002	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0,97	0,03	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0,968	0,032	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0,969	0,028	0,003	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0,975	0,025	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0,975	0,023	0,002	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0,9785	0,0215	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0,978	0,022	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0,98	0,017	0,003	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0,987	0,013	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0,99	0,01
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Fig. 2. Transition probability matrix on the basis of the expert evaluation

$D=$

B	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
0	55	46	13	15	62	32	57	5	19	18	13	36	60	42	33	19	13	10	52
1	0	69	4	24	54	35	54	7	21	20	15	36	58	42	33	22	15	14	77
2	0	0	55	10	48	38	50	9	23	21	18	36	56	42	33	25	18	16	102
3	0	0	0	38	37	40	46	11	25	23	21	36	53	42	34	27	21	19	127
4	0	0	0	0	35	42	42	13	27	24	23	36	52	42	34	29	24	21	156
5	0	0	0	0	0	39	41	14	29	25	26	35	50	42	35	31	26	24	183
6	0	0	0	0	0	0	70	7	29	27	27	35	49	42	35	32	27	25	195
7	0	0	0	0	0	0	0	32	31	27	29	35	45	42	36	35	30	29	229
8	0	0	0	0	0	0	0	0	33	28	30	35	44	41	37	36	32	31	253
9	0	0	0	0	0	0	0	0	0	29	32	34	42	42	37	38	34	33	279
10	0	0	0	0	0	0	0	0	0	0	31	35	40	42	37	40	36	35	304
11	0	0	0	0	0	0	0	0	0	0	0	38	40	42	38	41	38	36	327
12	0	0	0	0	0	0	0	0	0	0	0	0	39	42	39	43	40	40	357
13	0	0	0	0	0	0	0	0	0	0	0	0	0	46	39	46	42	43	384
14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	42	48	46	45	419
15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	48	49	46	454
16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	68	51	481
17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	68	532
18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	600

Fig. 3. The matrix of the standing durations in one or another state within 600 weeks

Patient no. 6, referred with a diagnosis of «open-angle glaucoma (stage I), the destruction of the vitreous in the right eye». Complaints about the «dark fly» in front of the right eye. From the anamnesis: None of the relatives suffer from glaucoma. During examination, the following was tested:

1) visometry: visual acuity OD 6/7.5 sph +0.5 D = 6/6; visual acuity OS 6/6;
2) kinetic perimetry by Forster. OD: field of vision 1 - 45º, field of vision 2 - 50º, field of vision 3 - 45º, field of vision 4 - 90º; OS: field of vision 1 - 50º, field of vision 2 - 55º, field of vision 3 - 45º, field of vision 4 - 90º, where field of vision 1 - field of vision along the upper nasal radius, field of vision 2 - along the horizontal nasal radius, field of vision 3 - along the inferior nasal radius, field of vision 4 - along the horizontal temporal radius. Defects in the central visual field were not detected;
3) Goldmann tonometry: IOP OD 26 mm Hg., OS 18 mm Hg.;
4) biomicroscopy OD: eye is calm, cornea is transparent, anterior chamber of medium depth, eye moisture is transparent, subatrophy of the iris, stroma of the iris is not changed. The lens is transparent. The destruction of the vitreous in the right eye is detected. Biomicroscopy OS: eye is calm, cornea is transparent, anterior chamber of medium depth, eye moisture is transparent, iris is not changed. The lens is transparent;
5) gonioscopy OU: anterior chamber angle is open, without pathological changes, trabecular pigmentation is weakly expressed;
6) ophthalmoscopy OD: optic disc is pale pink, with sharp boundaries. Cup of the optic disc is slightly extended, circular shape, medium depth. Cup/Optic Disc = 0.5-0.6. Arteries are moderately narrowed. Veins are slightly full-blooded. Ophthalmoscopy OS: optic disc is pale pink, sharp boundaries, cup of the circular shape and medium depth, temporal edge is flat. Cup/Optic Disc = 0.3. Arteries are moderately narrowed. Veins are slightly full-blooded;
7) Humphrey automated perimetry OD: MD +1.57 dB, PSD 2.77 dB P< 10%. Paracentral depressions up to -11 dB;
8) confocal scanning laser ophthalmoscopy (Heidelberg Retina Tomograph II, Heidelberg Engineering) OD: Disc Area = 2.297 mm2, Cup Area = 0.744 mm2, Cup / Disc Area Ratio = 0.324, Cup Volume = 0.157 mm3, Linear Cup / Disc Ratio = 0.569, Rim Area = 1.552 mm2, Rim Volume = 0.237 mm3, Cup Shape Measure = -0.139, Mean Cup Depth = 0.212 mm, Mean RNFL Thickness = 0.152 mm, RNFL Cross Sectional Area = 0.819 mm2, Reference Height = 0.274 mm.

Thus, a diagnosis of «open-angle glaucoma (stage I), the destruction of the vitreous body in the right eye» was confirmed with the help of complex diagnostic procedures. This diagnosis corresponds to the state 0 – «stage I of open-angle glaucoma, indications for drug therapy». To compensate IOP, 1-2 drops of Xalatan was prescribed into the right eye 1 time per day. For patient in the state 0 – «stage I of open-angle glaucoma, indications for drug therapy» the transition probabilities and durations of the patient's standing in the different states were calculated (Table I). According to this table the patient may be present in the state 0 – «stage I of open-angle glaucoma, indications for drug therapy» 55 weeks with probability 0.9780. Control examination after 3 (12 weeks), 6 (24 weeks), 9 (36 weeks), 12 months (48 weeks) did not reveal any significant clinical changes.

The patient is really in the state 0 – «stage I of open-angle glaucoma, indications for drug therapy» which fully coincides with the supplied prognosis (Table I). The patient's condition is stable.

It was recommended to continue Xalatan instillation into the right eye. The study was conducted after 14 months (56 weeks).

The following was examined:

1) visometry: visual acuity OD 6/9.5 sph +0.5 D = 6/7.5; visual acuity OS 6/6;

2) kinetic perimetry by Forster. OD: field of vision 1- 45º, field of vision 2 - 45º, field of vision 3 - 40º, field of vision 4 - 90º; OS: field of vision 1 - 50º, field of vision 2 - 55º, field of vision 3 - 45º, field of vision 4 - 90º, where field of vision 1 - field of vision along the upper nasal radius, field of vision 2 - along the horizontal nasal radius, field of vision 3 - along the inferior nasal radius, field of vision 4 - along the horizontal temporal radius. The blind spot is expanded in the central visual field.
3) Goldmann tonometry: IOP OD 23 mm Hg., OS 18 mm Hg.;
4) biomicroscopy OD: eye is calm, cornea is transparent, anterior chamber of medium depth, eye moisture is transparent, subatrophy of the iris, stroma of the iris is not changed. The lens is transparent. The destruction of the vitreous in the right eye is detected. Biomicroscopy OS: eye is calm, cornea is transparent, anterior chamber of medium depth, eye moisture is transparent, iris is not changed. The lens is transparent;
5) gonioscopy OU: anterior chamber angle is open, trabecular pigmentation is weakly expressed;
6) ophthalmoscopy OD: optic disc is pale pink, with sharp boundaries. Cup of the optic disc is extended, of circular shape. Cup/Optic Disc = 0.6. Arteries are moderately narrowed. Veins are slightly full-blooded. Ophthalmoscopy OS: optic disc is pale pink, of sharp boundaries, cup of the circular shape and medium depth, temporal edge is flat. Cup/Optic Disc = 0.3. Arteries are moderately narrowed. Veins are slightly full-blooded;
7) Humphrey automated perimetry OD: MD -3.53 dB P< 2%, PSD 2.62 dB P< 10%. Depression is observed in the upper arcual zone.
8) confocal scanning laser ophthalmoscopy (Heidelberg Retina Tomograph II, Heidelberg Engineering) OD: Disc Area = 2.297 mm2, Cup Area = 0.792 mm2, Cup / Disc Area Ratio = 0.345, Cup Volume = 0.164 mm3, Linear Cup / Disc Ratio = 0.587, Rim Area = 1.505 mm2, Rim Volume = 0.227 mm3, Cup Shape Measure = -0.124, Mean Cup Depth = 0.214 mm, Mean RNFL Thickness = 0.148 mm, RNFL Cross Sectional Area = 0.808 mm2, Reference Height = 0.261 mm.

Clinical disease progression was identified at this stage. That is confirmed by the clinical examination and HRT-tomography (constriction of the peripheral visual field, defects in the central visual field, overall decrease of sensitivity -3.53 dB, expansion of the optic cup relative to the size of the optic disc, decreasing neuroretinal rim area and volume, RNFL thickness decreasing) which fully coincides with the supplied prognosis (Table I).

As a result of this, laser trabeculoplasty on the right eye was conducted.

The patient has entered the state 1 – the state «stage I of open-angle glaucoma after laser treatment not requiring drug therapy».

TABLE I
DURATIONS AND PROBABILITIES OF THE PATIENT'S STANDING IN THE DIFFERENT STATES (FOR THE INITIAL STATE 0)

The state	The probability of the patient's standing in the state	The duration of the patient's standing in the state (week)
0	0.9780	55
1	0.2881	46
2	0.1934	13
3	0.1791	15
4	0.1725	62
5	0.1473	32
6	0.1316	57
7	0.1142	5
8	0.1123	19
9	0.1089	18
10	0.1074	13
11	0.1084	36
12	0.1151	60
13	0.1203	42
14	0.1220	33
15	0.1243	19
16	0.1282	13
17	0.1347	10
18	0.1429	52

For patient in the state 1 – «stage I of open-angle glaucoma after laser treatment not requiring drug therapy» the transition probabilities and durations of the patient's standing in the different states were calculated (Table II). According to this table the patient may be present in the state 1 – «stage I of open-angle glaucoma after laser treatment not requiring drug therapy» 69 weeks with probability 0.9584. Control examination after 3 (12 weeks), 6 months (24 weeks) did not reveal any significant functional and morphometric changes.

According to prognosis (Table II) the patient is really in the state 1 – «stage I of open-angle glaucoma after laser treatment not requiring drug therapy».

As a result, further observation of the patient's state is continued. Thus, the proposed method allows significant prognosis of POAG progression.

TABLE II
DURATIONS AND PROBABILITIES OF THE PATIENT'S STANDING IN THE DIFFERENT STATES (FOR THE INITIAL STATE 1)

The state	The probability of the patient's standing in the state	The duration of the patient's standing in the state (week)
1	0.9584	69
2	0.2264	4
3	0.2197	24
4	0.2014	54
5	0.1675	35
6	0.1448	54
7	0.1248	7
8	0.1216	21
9	0.1170	20
10	0.1150	15
11	0.1157	36
12	0.1222	58
13	0.1264	42
14	0.1277	33
15	0.1295	22
16	0.1339	15
17	0.1413	14
18	0.1533	77
1	0.9584	69

IV. Conclusion

Therefore, a method for prognosing POAG progression was developed. It is distinguished by the use of the theory of Markov processes to describe the development of glaucomatous process.

Thus, it increases the quality of therapeutic and diagnostic measures. The introduction of the proposed method for POAG development prognosis in ophthalmology practice will allow the improvement of the quality level of medical service for patients.

Acknowledgements

We would like to thank Dr Kateryna McDonald (University of Central Lancashire, UK) for her valuable help in preparing this manuscript. We are also grateful to Dr A.I. Byh (Head of Department of Biomedical Engineering), our study optometrist, and the patients who participated in this study.

The authors declare no conflict of interest.

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