197　新眼科診療機器 スマートアイカメラの臨床実用化	清水　映輔

【目的】失明および視機能障害は、患者の視覚の質や日常生活動作だけでなく、大きな障害調整生命年や経済的損失をもたらす。失明の原因の 51%は白内障であり、手術で治癒が可能な白内障は、医療機器不足と医師不足により、2020 年現在においても解決されない世界的問題である。この問題は国連が定義する「持続可能な開発目標」の 3 番目にユニバーサル・ヘルス・カバレッジの内容と合致し、早急な課題解決が求められており、全世界で 720 兆円の損失を生んでいると推定される。この問題を解決するために、我々は、眼科診療を場所はどこでも誰でも行うことを可能としたスマートフォンアタッチメント型医療機器 smart eye camera（SEC）を開発した。本研究においては、SEC の白内障診断に対する有用性を既存の細隙灯顕微鏡と言う眼科診療機器と比較し、SEC が既存の細隙灯顕微鏡の代替となる可能性を検討した。

【方法】本研究は、前向きに 2019 年 7 月から 9 月の間に、64 人 128 眼の白内障症例を対象に行われた。既存の細隙灯顕微鏡と、SEC で試験者の水晶体を撮影し、白内障の WHO 分類を用いて、それぞれ眼科専門医が重症度評価を行った。また、既存の細隙灯顕微鏡は評価者と別の眼科専門医が撮影を行い、SEC は視能訓練士が撮影を行った。白内障重症度分類の相関や、聞き手の評価結果の一致率などの解析が行われた。

【結果】眼科専門医によって診断された、白内障重症度は細隙灯顕微鏡および SEC との間に有意な高い正の相関を認めた（r＝0.871［95%CI：0.821 to 0.907、P＜0.001］）。SEC による既存の細隙灯顕微鏡に対する診断精度は有意に高いことが認められた（weighted κ＝0.807［95%CI：0.798 to 0.816、P＜0.001］）。これらの結果により、SEC は既存の細隙灯顕微鏡と比較し、白内障の診断及び重症度評価において、高い診断精度が認められ、場所を選ばず白内障診断が行えるとともに、今後遠隔診療や人工知能を用いた、新しい白内障診断方法の開発につながる可能性が示唆された。なお、当該研究は、以下の通り報告した。

Yazu H, Shimizu E, Okuyama S, et al. Evaluation of Nuclear Cataract with Smartphone-Attachable Slit-Lamp Device. Diagnostics (Basel). 2020;10(8):E576. Published 2020 Aug 9. doi:10.3390/diagnostics10080576

SEC と既存機器の図



197. 新眼科診療機器 スマートアイカメラの臨床実用化

清水　映輔

慶應義塾大学 医学部 眼科学教室

Key words：Artificial intelligence，telemedicine，Smart Eye Camera，Cataract，Diagnostic AI

緒　言

A slit-lamp microscope is an essential medical instrument in the field of ophthalmology [1]. This device irradiates the anterior segment of the eyes with a slit-light, and the reflection thereof is observed with its biomicroscope function [2]. However, most conventional slit-lamp microscopes are not portable, and patients have to visit the ophthalmologist for these examinations. Therefore, some patients (e.g. bedridden patients, children, the elderly, and infected patients) have less opportunity to undergo ophthalmology examinations. Although there are some portable slit-lamp microscopes, these devices are not recordable. External camera is needed to record the anterior eye images, but it requires to alter the instrument larger and heavier. Moreover, due to the large size and heavy weight of the conventional microscope to be used with one hand, it is difficult to use the microscope outside of the eye clinic which complicates validation between conventional non-portable and portable slit-lamp microscopes. Blindness is increasing globally. It is estimated that 36 million people are now blind, and this number will increase to 115 million in the next 30 years [3]. The main cause of global blindness is cataract. They account for 55% of blindness in adults older than 50 years globally [4]. Cataract is the most common age-related ophthalmological disease, and it is diagnosed using a reflection of the thin slit-light from the slit-lamp microscope [5]. Blindness caused by cataract is preventable by surgery [6]; nevertheless, lack of medical resources especially in undeveloped countries often hamper appropriate intervention [4，6，7]. An appropriate medical invention to detect cataract could be the solution for this problem. To address this issue, we have previously invented a portable and recordable slit-lamp device, the “Smart Eye Camera” (SEC), which convert the smartphone light source to the light needed for the ophthalmology diagnosis. In addition, SEC has a recording function using smartphone camera and was proven to be safe and feasible in an animal model [8]. We added slit-light converter to make a slit-beam thin enough to diagnose the cataract in direct focal illumination method [9]. Here, we verified the performance of SEC by the clinical trial, in which we evaluated and compared the efficacy and diagnostic performance for cataract diagnosis with those of a conventional slit-lamp microscope.

方　法

1. Study Design

This prospective study was performed according to the steps shown in Figure 1. We screened all patients who visited the Department of Ophthalmology, Tsurumi University School of Dental Medicine from July to September 2019. The patients who matched our inclusion criteria were recruited for the study. The inclusion criteria were (1) Japanese adult males and females (older than 20 years) who had been diagnosed as nuclear cataract (NUC), (2) cases with good mydriasis (>6 mm) to allow better evaluation of the crystalline lens, and (3) no obvious ocular surface infections and/or inflammations. Patients who had at least one of the following

were excluded: (1) Both pseudophakic or aphakic eyes, (2) Other types of cataract (i.e. cortical cataract [COR], anterior subcapsular cataract [ASC], and posterior subcapsular cataract [PSC]), (3) Severe corneal disease that adversely affected cataract grading (e.g. bullous keratopathy, band keratopathy, and corneal opacity), (4) Lack of data or patients who did not provide written informed consent. In total, 124 eyes in 62 cases were enrolled. The NUC grading of these eyes was evaluated with the portable and recordable Smart Eye Camera (SEC; OUI, Inc., Tokyo, Japan) and with a conventional slit-lamp microscope (SL130, Carl Zeiss AG, Oberkochen, Germany).

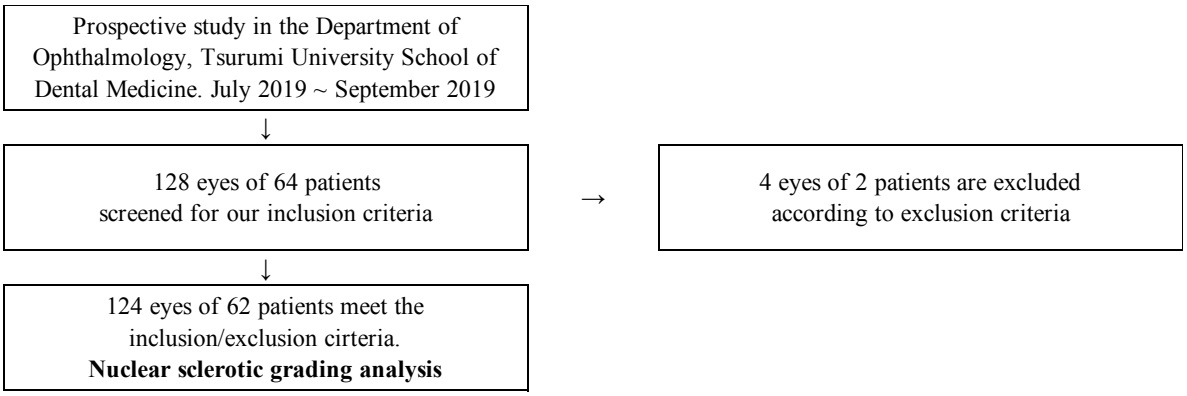


Figure 1. Study flowchart

This prospective study adhered to the tenets of the Declaration of Helsinki. All procedures were performed in compliance with the protocol approved by the Institutional Ethics Review Board of Tsurumi University Dental Hospital (Kanagawa Prefecture, Japan; IRB No. 1634). Patient data were anonymized before access or analysis.

2. Conventional non-portable slit-lamp microscope and SEC examination

We used the SL130 as the conventional, non-portable slit-lamp microscope. This instrument is widely used for screening and diagnosis of several ocular diseases. For a comparison, the portable SEC slit-lamp device was selected. SEC is a smartphone attachment that fits above the light source and camera lens of a smartphone (Figure 2). It is a Japanese pharmaceuticals and medical devices agency-certified medical device that is able to convert the light source of the smartphone to a thin slit-light, allowing the light to enter the non-dilated pupil and reach the crystalline lens (Japanese Medical Device approval number: 13B2X10198030101). The slit-light of the SEC is unmovable as it uses the light source of the smartphone itself. Moreover, the slit-light angle is fixed by 40 degree which commonly used by the direct focal illumination method9. To convert the light source of the smartphone to the 0.2 to 1.0 mm-width slit-light, a cylinder lens made from acrylic resin was attached in front of the light source. Above the camera lens of the smartphone, there is a removable convex macro lens to adjust the focus to the anterior segment of the eye. The frame was produced using a 3D printer (Multi Jet Fusion 3D Model 4210; Hewlett-Packard Company, Palo Alto, CA, USA) using polyamide 12. For the current study, an iPhone 7 (Apple Inc., Cupertino, CA, USA) was used as the camera and the light source. The resolution of the video was set at 1080 p and 30 frames per second, which equates to 2.1 megapixels (2,073,600 pixels) per file.

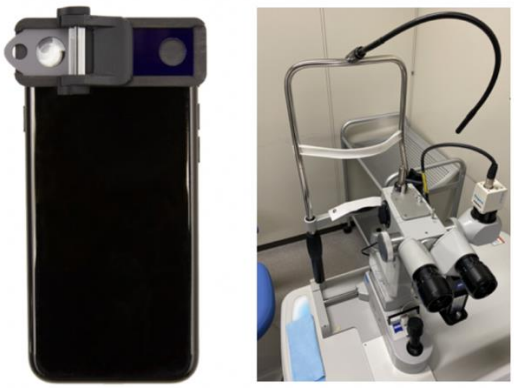


Figure 2. Appearance of (a) the SEC and (b) the conventional slit-lamp microscope

3. Cataract evaluation by the conventional slit-lamp microscope and the SEC

After dilating the pupil, the recruited cases were examined using both conventional slit-lamp microscope and SEC. To minimize selection bias in terms of the order of the instrument used, we randomized all cases using a table of random digits. First, three ophthalmologists (H.F., H.Y., and S.O.) used the conventional slit-lamp microscope to examine the grade of the cataract. Second, a single orthoptist (T.K.) used the SEC to record a video of the cataract according to an instruction by an ophthalmologist (H.Y.). These examinations were all performed under a darkroom as well as an ordinally environment in the ophthalmology department. Third, the images were documented in the medical records after filming. Finally, on another day, cataract grading was performed by a single ophthalmologist (H.F.) blinded to the patients' information. The grading of the cataract by both the conventional slit-lamp microscope examination and the SEC examination was based on the NUC grading system by the WHO Cataract Grading Group [10]. Although the Lens Opacities Classification system III is the most commonly used criteria, it mainly involves evaluation based on a specialist's subjective assessment. Moreover, the subjective grading may change according to the specialists' environment. When the diagnosis was different among the ophthalmologists, final diagnose of the NUC grading were decided by the majority consensus.

4. Data Analysis

Routine examinations, including a refraction test, visual acuity, intraocular pressure measurement using a non-contact tonometer, and fundus examination, were conducted for all cases, in addition to the clinical ocular evaluation using the SEC and conventional slit-lamp microscope. Visual acuity was measured using a standard Snellen chart, and the BCVA with spectacle correction was recorded. The results were measured in decimal acuity and converted to the logarithm of the minimal angle of resolution (logMAR) units using a visual acuity conversion chart.

5. Statistical Analysis

All data were analyzed using SPSS software (IBM SPSS statistics ver 25; IBM Corp, New York, NY, USA) and Prism software (ver. 6.04 for Mac; GraphPad Software Inc, San Diego, CA, USA). It was not appropriate to pre-define a sample size, as this is a comparison study between a conventional instrument and a new device. Therefore, we selected all of the patients who matched our inclusion criteria within a certain period of time. Mann–Whitney's U test was performed to compare the NUC grade differences between conventional slit-lamp microscope and the SEC. To assess the reproducibility of the cataract grading by the two devices (conventional slit-lamp microscope and SEC), weighted kappa statistics were

selected31. Moreover, Spearman's correlation coefficient was used to assess the correlation of the cataract grading evaluated using the 2 devices. Data were presented as adjusted means ± 95% confidence intervals (CI), ± standard deviation (SD), or ranges. P-value < 0.05 was considered to indicate statistical significance.

結　果

1. Demographics of the subjects

In the current study, 128 eyes of 64 individuals (30 males and 34 females) were enrolled. Four eyes were excluded because the complete data was missing. The mean age of participants was 73.95 ± 9.28 years. In the current study, 110 of 124 eyes were phakic, 14 of 124 eyes were pseudophakic, and no aphakic eye was observed. The mean severity of the NUC grading of the cataract was 1.84 ± 0.82 based on the evaluation by conventional slit-lamp microscope and 1.92 ± 0.82 by the SEC (P = 0.47, Table 1). There were no cases with NUC grade 0, which was not significant NUC formation, and grade 9, which was very advanced cataract that failed to provide adequate posterior illumination for grading cortical and/or PSC cataracts. The mean duration of the measurement by the SEC was 30.38 ± 6.27 seconds per 2 eyes, and the mean size of the filmed video was 85.96 ± 18.61 MB per 2 eyes (Table 1). Representative photos taken with the SEC are shown in Figure 3.

Table 1. Demographic of the subjects

		P value
Cases	64	
Male/Female	30/34	
Age	73.95 ± 9.28	
Eyes	128	
Phakia	110	
Pseudophakia	14	
Lack of data	4	
Nuclear Sclerotic grading		
Conventional/SEC	1.84 ± 0.82/1.92 ± 0.82	0.47*
SEC		
Examination time, seconds	30.38 ± 6.27	
File size, MB	85.96 ± 18.61	

Data shown as mean ± SD. SEC: Smart Eye Camera. MB: Megabyte.
*Mann-Whitney's U test.

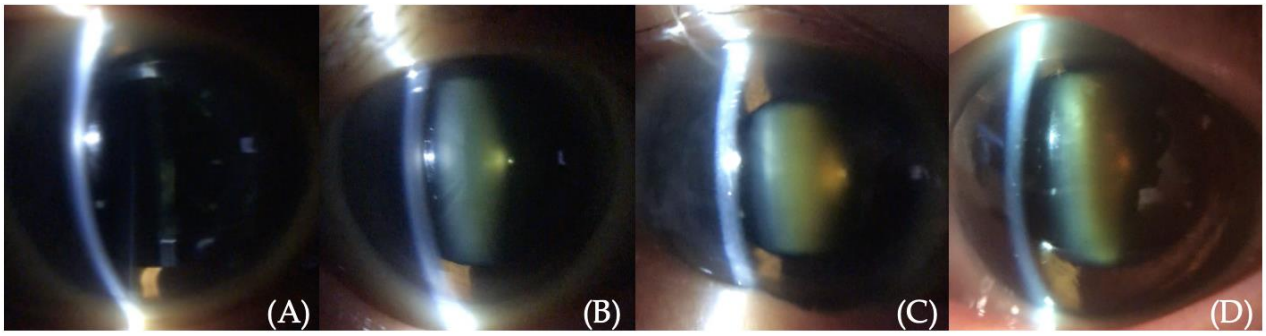


Figure 3. Representative cases imaged with the Smart Eye Camera.
Eyes with (**A**) the lens replaced by an intraocular lens (IOL), (**B**) NUC grade 1, (**C**) NUC grade 2, and (**D**) NUC grade 3 are shown.

2. Correlation of cataract grading evaluation by the two devices

To compare the performance of cataract grading by the conventional slit-lamp microscope and the SEC, the correlation of the NUC grading was evaluated. The NUC value from the conventional slit-lamp microscope and the SEC showed a significantly strong correlation in the right eye (r = 0.926 [95%CI: 0.881 to 0.955; P<0.001]; Table 2), left eye (r = 0.836 [95%CI: 0.743 to 0.898; P<0.001]; Table 2), and both eyes (r = 0.871 [95%CI: 0.821 to 0.907; P<0.001]; Table 2).

Table 2. Correlation of the cataract grading evaluated by the two devices

Eye	n	R	P Value*	95% CI	
R	**62**	**0.926**	**< 0.001**	0.881	0.955
L	**62**	**0.836**	**< 0.001**	0.743	0.898
Total	**124**	**0.871**	**< 0.001**	0.821	0.907

*Spearman's correlation coefficient

3. Reproducibility of the cataract grading evaluated by the two devices

To assess the reproducibility of the cataract grading by the conventional slit-lamp microscope and by the SEC, weighted kappa statistics of the NUC grading were evaluated. A high kappa value was observed between the cataract grading by the conventional slit-lamp microscope and that by the SEC (Kappa = 0.807 [95%CI: 0.798 to 0.816; P<0.001]; Table 3).

Table 3. Reproducibility of the cataract grading evaluated by the two devices

		Smart Eye Camera		
	Grade	1	2	3
Conventional microscope	1	4	0	0
	2	5	78	2
	3	0	5	16
P Value		**< 0.001**		
Weighted kappa		0.807		
95%CI		0.798-0.816		

考　察

In the current study, we evaluated the cataract diagnosis by the new portable and recordable slit-lamp device, the “SEC.” The diagnostic accuracy and the performance of this device were compared with those of the conventional slit-lamp microscope. When we compared the NUC grading between the conventional slit-lamp microscope and the SEC, we found no significant differences of the gradings between the two devices (Table 1). Moreover, there was a significantly strong correlation between the NUC grading of the conventional slit-lamp and SEC evaluations (Table 2). Furthermore, using weighted kappa statistics to assess cataract grading demonstrated a high kappa value, which suggested that the images obtained by both devices were highly reproducible (Table 3). These results demonstrated that the performance of the SEC is equivalent to that of the conventional slit-lamp microscope in evaluating cataract. On the other hand, we did not estimate statistical power due to lack of past references. To address this disadvantage, we designed our study to screen every patient who visited a single hospital during a certain period prospectively. Our functional analysis suggested that the slit-light converted by the SEC allows evaluation of the severity of the NUC grading in cataract eyes, equal to that done using the conventional slit-lamp microscope.

Currently, few devices that can record anterior segment images by slit-light are available, although similar technologies have previously been reported. Some studies have reported the usefulness of slit-lamp microscope accessories that can attach to a smartphone camera. Chen et al. demonstrated good reproducibility of cataract grading using the same diagnosis criteria as those used in our study. Moreover, Dubbs et al. reported a good rust ring image on the cornea taken using a smartphone. These devices are attachable to the conventional non-portable slit-lamp microscopes, but not to smartphones. Mohammadpour et al. demonstrated the effectiveness of images obtained with a smartphone combined with a macro lens, using a concept similar to that of the SEC. However, the light source of the smartphone could release only diffuse white light, which was only capable of illuminating the surface of the eye. Chiong et al. invented a smartphone-based anterior segment-examining device that could irradiate the eyes with thick slit-light. However, in ophthalmology departments, specialists require narrow slit-light that is thinner than the pupil width of 2–8 mm to ensure that the slit-light reaches the crystalline lens. To the best of our knowledge, no previous paper has reported that cataract grading was possible with a smartphone slit-lamp device. This may be due to the difficulty in converting the smartphone light source to a thin slit-light. The SEC has a function to overcome this problem by applying the slit structure above the light source and the cylinder lens to concentrate the light on the object. Therefore, we believe that SEC has an advantage over the conventional devices.

In this study, we demonstrated the usefulness of the SEC in cataract grading. The SEC may have the following potential advantages in healthcare: (1) It could be applied to other ophthalmological diseases, particularly in the anterior segment of the eye. We previously reported that this device could evaluate tear film breakup time and corneal epithelial disorder in a dry eye disease mouse model [8]. The size of the mouse eye is about 3-mm wide and is much smaller than that in humans. Therefore, the SEC has the potential to be useful for the screening of other anterior segment eye diseases. (2) It could be used outside of the eye clinic. In the current study, an orthoptist rather than an ophthalmologist filmed the patient's eye using the SEC. The average recording time was approximately 30 seconds for 2 eyes, which illustrates that the SEC is user-friendly for healthcare workers. Although the non-specialists can use this portable slit-lamp device, the ophthalmologists may need to evaluate the recorded images to make a cataract diagnosis. SEC is a smartphone attachment that allows video recording [8], and thus, it may be useful in

telemedicine. Several studies have demonstrated that ophthalmological diagnoses are amenable to remote medicine, as the diagnosis is made based on images of the eye. To the best of our knowledge, there is no other portable and recording device that can take a distinct eye photo with a thin slit-light. Therefore, the SEC may allow screening for and remote diagnosis of cataract outside of an eye clinic.

Our study only included NUC and did not include COR, ASC, and PSC. Other cataract variations could associate with reductions of visual acuity. However, NUC is the most common type especially in the elderly ages. Therefore, we selected NUC for our primary evaluation. Moreover, our study included cases over 53 years of age and NUC grade 1 to 3 which were similar population to previous report. Our findings justify conduct of similar trials on a larger number of subjects with other types of cataract which will definitely provide invaluable information.

The results of this study suggested that not only the conventional, non-portable slit-lamp microscope, but also the portable and recordable slit-lamp can diagnose and record cataract images appropriately. An ophthalmologist successfully evaluated the videos taken by a non-ophthalmologist using the device. It may hold great potential for the diagnosis of other ophthalmological diseases in the anterior segment of the eyes, application outside of the eye clinic, and application in telemedicine. The challenge for the future is to verify whether or not the same results can be obtained when the product is actually used in the different fields including overseas.

共同研究者・謝辞

Hiroyuki Yazu [1,2,3,*], Eisuke Shimizu [2,3], Sho Okuyama [1,2], Takuya Katahira [1], Naohiko Aketa [2], Ryota Yokoiwa [3], Yasunori Sato [4], Yoko Ogawa [2] and Hiroshi Fujishima [1,2]

[1] Department of Ophthalmology, Tsurumi University School of Dental Medicine, Kanagawa 230-0063, Japan; g.h.yazu@gmail.com (H.Y.); go_my_way1987@yahoo.co.jp (S.O.); katahira-t@tsurumi-u.ac.jp (T.K.); fujishima117@gmail.com (H.F.)

[2] Department of Ophthalmology, Keio University School of Medicine, Tokyo 160-0016, Japan; ophthalmolog1st.acek39@gmail.com (E.S.); nao.nao.pao.pao@gmail.com (N.A.); yoko.z7@keio.jp (Y.O.)

[3] OUI Inc., Tokyo 160-0022, Japan; ryota.yokoiwa@gmail.com

[4] Department of Preventive Medicine and Public Health, Biostatistics at Clinical and Translational Research Center, Keio University School of Medicine. Tokyo 160-0016, Japan; yasunori.sato@keio.jp

文　献

1) Friedenwald JS. Clinical studies in slit-lamp ophthalmoscopy. Arch Ophthalmol. 1929;1(5):575–582. doi:10.1001/archopht.1929.00810010596005

2) Tate GW, Safir A. The slit lamp: History, principles, and practice. In: Clinical Opthalmology, Duane TD (Ed), Harper & Row, New York 1981. Vol 1.

3) Bourne RRA, Flaxman SR, Braithwaite T, Cicinelli MV, Das A, Jonas JB, Keeffe J, Kempen JH, Leasher J, Limburg H, Naidoo K, Pesudovs K, Resnikoff S, Silvester A, Stevens GA, Tahhan N, Wong TY, Taylor HR; Vision Loss Expert Group. Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: a systematic review and meta-analysis. Lancet Glob Health. 2017 Sep;5(9):e888-e897. 2. doi:10.1016/S2214-109X(17)30293-0

4) Flaxman SR, Bourne RRA, Resnikoff S, Ackland P, Braithwaite T, Cicinelli MV, Das A, Jonas JB, Keeffe J, Kempen JH, Leasher J, Limburg H, Naidoo K, Pesudovs K, Silvester A, Stevens GA, Tahhan N, Wong TY, Taylor HR; Vision Loss Expert Group of the Global Burden of Disease Study. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. Lancet Glob Health. 2017 Dec;5(12):e1221-e1234. doi: 10.1016/S2214-109X(17)30393-5.
5) Brown NA, Bron AJ, Ayliffe W, Sparrow J, Hill AR. The objective assessment of cataract. Eye (Lond). 1987;1 (Pt 2):234-46. doi: 10.1038/eye.1987.43
6) Lee CM, Afshari NA. The global state of cataract blindness. Curr Opin Ophthalmol. 2017 Jan;28(1):98-103. doi: 10.1097/ICU.0000000000000340
7) Ramke J, Evans JR, Gilbert CE. Reducing inequity of cataract blindness and vision impairment is a global priority, but where is the evidence? Br J Ophthalmol. 2018 Sep;102(9):1179-1181. doi: 10.1136/bjophthalmol-2018-311985.
8) Shimizu E, Ogawa Y, Yazu H, Aketa N, Yang F, Yamane M, Sato Y, Kawakami Y, Tsubota K. "Smart Eye Camera": An innovative technique to evaluate tear film breakup time in a murine dry eye disease model. PLoS One. 2019 May 9;14(5):e0215130. doi: 10.1371/journal.pone.0215130
9) Nema HV, and Nema N. Diagnostic Procedures in Ophthalmology. Alpha Science International, 2003. ISBN 13: 9781842651377
10) Thylefors B, Chylack LT Jr, Konyama K, Sasaki K, Sperduto R, Taylor HR, West S; WHO Cataract Grading Group. A simplified cataract grading system. Ophthalmic Epidemiol. 2002 Apr;9(2):83-95. doi: 10.1076/opep.9.2.83.1523