Fundus Screening Assessment Manual

Introduction

Visual impairment is not only an important health problem, but also a significant issue that may lead to increments in medical expenses and the number of people involved in medical care in Japan.[1,2] Eye diseases listed as major causes of blindness include glaucoma, diabetic retinopathy, and age-related macular degeneration in adult Japanese individuals. Early detection of these blinding eye diseases may be benefited to prevent blindness or serious visual impairment by initiating treatments at an appropriate timing. Fundus screening for this purpose is non-invasive and simple, and is performed with a fundus camera without mydriasis. In addition, fundus screening by screening by retinal images can provide screening for multiple eye diseases at aa time ensuring its cost effectiveness. Fundus images also provide an opportunity to serve as part of cardiovascular risk assessment. Screening for eye diseases, in particular age-related eye diseases causing blindness in an adult population meets the requirements for successful disease screening proposed by the World Health Organization in 1968 (Table 1).

In Japan, fundus examination has been used to evaluate microvascular damage as one of the target-organ damages associated with hypertension; therefore, it has been performed as part of cardiovascular screening. On the other hand, systemic fundus screening aiming to achieve early detection and prevention of eye diseases has been performed scarcely. The opportunity for systemic eye disease screening is limited to date. In 2008, fundus examination has been deleted from the essential items in the Specific Health Checkup program, the public and systemic health screening program provided by health insurer. Opportunistic health insurer screening such as the “Ningen Dock” program in Japan plays therefore an important role providing an opportunities for both cardiovascular assessment of microvascular target-organ damage in the retina as well as a screening for blinding eye diseases aiming to blindness prevention.

Here, the Japan Society of Ningen Dock and the Japan Ophthalmological Society revised the Fundus Screening Assessment Manual to update classifications of retinal vascular signs as part of cardiovascular screening with risk categories matched with specific recommendations; updated classification of eye diseases such as diabetic retinopathy, glaucoma, and age-related macular degeneration are provided following the latest evidence.

1) Retinal vascular signs in cardiovascular disease screening (Tables 2, 3, and 4[3])

Assessment criteria for hypertensive fundus findings include Scheie’s classification (Table 2) and the Keith-Wagener classification modified by Keio University (Table 3). Along with the improvement in the management of hypertension in the modern era, the number of patients with severe retinal findings has decreased. There have been scarce updates on the evidence for those who have mild findings in these classifications toto date, and there is a criticism that there has been no updated recommendation specific to each fundus signs to be used in a clinical practice, where the meaning of those milder signs are not definitive in the management of hypertension and cardiovascular risk factors

In recent years, there is an accumulated evidence regarding retinal vascular signs and hypertension or atherosclerotic diseases from large-scale epidemiological studies mainly in Western countries. Also, there are population-based cohort studies reporting that risk of incident cardiovascular disease such as stroke increases up to 2-fold in individuals with fundus findings of Keith-Wagener classification grade 1 to 2 (i.e., arteriolar narrowing, arterio-venous crossing, and increased reflex), more than 2-fold in individuals with findings corresponding to Keith-Wagener classification grade 3 (i.e., retinal hemorrhages and exudates known as hypertensive retinopathy), and that those with Keith-Wagener classification grade 4 (i.e., papilledema) have risk of increased cardiovascular death. Based on such updated evidence, Wong-Mitchell proposed a new simplified classification where severity of fundus findings is matched to risks of cardiovascular disease (Table 4).[4] Treatment Guidelines for Hypertension 2014 also lists hypertensive retinopathy corresponding to Keith-Wagener Classification grade 3 or more, which corresponds to "moderate" in Wong-Mitchell classification as an organ damage caused by hypertension and can be a "prognostic factor used in risk stratification for hypertension management plan,"[5]. Based on the recommendation in the guideline, for example, immediate consideration of hypotensive medication is recommended for even a case of high normal blood pressure (130-139/85-89 mmHg) in addition to instruction of lifestyle adjustment if "hypertensive retinopathy" is present. The Wong-Mitchell classification provides a simplified evidence-based classification to fully utilize fundus assessment in cardiovascular screening. Comparisons between classifications of hypertensive/arteriosclerotic retinal vascular findings are shown in Table 4.

2)Fundus screening in diabetes patients and individuals suspected to have diabetes (Table 5)

Diabetic retinopathy is a microangiopathy in patients with diabetes. Because early diabetic retinopathy presents little or no subjective symptoms, health screening can be an opportunity to detect diabetic retinopathy. For an individual who has already been diagnosed as having diabetes mellitus, however, it is recommended to have detailed fundus examination with pupil dilation by ophthalmologists on regular basis, and simplified fundus screening in a health screening program is not sensitive enough to capture the disease and potentially overlook diabetic retinopathy. Health screening providers should share this fact with all individuals with diabetes having simplified fundus screening in a health screening program. Evidence-Based Medical Care Guideline for Diabetes Mellitus 2013[6] states "patients should visit an ophthalmologist to be evaluated for presence of diabetic retinopathy" if they are definitely diagnosed as having diabetes mellitus, and "thereafter, it is desirable to have regular consultation at least once a year, and having consultations in shorter intervals is advisable for cases at risk." Here, consultation by ophthalmologists is recommended for patients who have already been diagnosed as having diabetes because fundus photographs without mydriasis commonly used in a health screening program have risk of overlooking diabetic retinopathy in the peripheral retina. Hence, once a patient is diagnosed as having diabetes, he/she should be recommended to have thorough fundoscopy with mydriasis immediately and regularly by an ophthalmologist instead of relying on the results of fundoscopy in the health screening. Because diabetic retinopathy may be present even in individuals with prediabetes or new-onset diabetes, fundoscopy in a health screening program could be valuable in such patients.

Classifications of diabetic retinopathy include Scott's classification, New Fukuda classification, and modified Davis classification. Scott's classification is no longer used in the clinical ophthalmology, because it does not match current understandings of pathology and progression pattern. New Fukuda classification is capable of providing detailed categorization. However, in a health screening program, most cases of diabetic retinopathy are at mild stage, and a simpler assessment would be sufficient. Modified Davis classification is simple and roughly classifies into 4 stages: no retinopathy, simple retinopathy, pre-proliferative retinopathy, and proliferative retinopathy. In recent years, International Severity Classification has been proposed as a classification linking severities and their corresponding evidence (Table 5).[7] This classifies the severity of diabetic retinopathy into non-proliferative retinopathy and proliferative retinopathy, and then non-proliferative retinopathy is further classified into mild, moderate, and severe. It is based on the Early Treatment Diabetic Retinopathy Study (ETDRS) classification that is often used in clinical studies, and this allows to match the evidence from a number of clinical studies into clinical practice. Comparisons of classifications for diabetic retinopathy and diabetic maculopathy are shown in Tables 5A and 5B.[8]

3) Fundus screening for early detection and prevention of ocular diseases

3-1) Glaucoma

Glaucoma is a common eye disease in Japanese older than 40 years with a prevalence as high as 5.0% and is the most frequent cause frequent of blindness in Japan.[9] Prevalence of glaucoma increases with age, and it is expected to continue to increase with accelerated population aging in Japan. In the Tajimi Study, only 10% of the subjects with identified as having glaucoma had been diagnosed at the time of screening. Hence, eye screening can be an important opportunity to screen patients with asymptomatic glaucoma.

In health screening, suspected glaucoma is assessed based on evaluation of optic disc on a fundus photograph in addition to intra-ocular pressure measurement. The optic disc cupping is evaluated by defining the ratio of the maximum vertical diameter of optic disc cupping to the maximum vertical diameter of the optical disc as vertical C/D ratio, and considering the ratio ≥0.7 as suspected glaucoma. The area between the outer edge of the optic disc and the outer edge of the optic disc cupping is referred to as rim. The ratio of the width of rim to the diameter of optic disc passing through the center of the disc is defined as R/D ratio. If the R/D ratio from the rim width in the top polar (11 to 1 o'clock direction) or the bottom polar (5 to 7 o'clock direction) is ≤0.1, it is considered to be suspected glaucoma (see Treatment Guideline for Glaucoma p. 813 Figure).[9]

In addition, if there are retinal nerve fiber layer defect, optic disc hemorrhages, or other glaucomatous change in the optic disc is observed, the case is assessed as being suspected glaucoma.

Suspected glaucoma (enlarged optic disc cupping, retinal nerve fiber layer defect, optic disc hemorrhages, or glaucomatous optic disc change) is all classified in the assessment category D2: *Thorough examination needed* (Table 6).

Intra-ocular pressure is the strongest association on the development of glaucoma and its progression where the higher the intra-ocular pressure, the faster the progress of glaucoma. Thus, if a patient has higher intra-ocular pressure at the screening, the case may have a rapid progress within a year even

without glaucomatous change in a fundus at that time. Hence, it should be noted that assessment of a fundus image is not sufficient to screen glaucoma in such cases.

3-2) Age-related macular degeneration

Age-related macular degeneration is an important cause of blindness in elderly people. There has been a report that oral anti-oxidant supplement in addition to smoking cessation is expected to reduce risk of developing the disease in persons with pre-clinical signs of age-related macular degeneration i.e., presence of large drusen in either eye or age-related macular degeneration has already developed in one eye. Therefore, screening for pre-clinical signs of age-related macular degeneration is desirable. The use of oral anti-oxidant supplement has been proposed by the Age-Related Eye Disease Study (AREDS). Even in a severe case, early detection leads to maintenance of visual acuity, as well as improvement of visual acuity by treatment (e. g., intravitreal injection of anti-vascular endothelial cell growth factor).[10]
According to AREDS, oral anti-oxidant supplement is expected to reduce risk of progression if age-related macular degeneration (wet type or dry type) has already been developed in one eye (corresponding to AREDS category 4) or having a preclinical signs of large drusen (sized ≥125 μm; approximately corresponding to the diameter of the retinal venule running through the optic disc rim) or a multiple smaller drusen are present (corresponding to AREDS category 3).
Assessment categories for suspected age-related macular degeneration are D2: Thorough examination needed for preclinical signs of age-related macular degeneration (drusen, abnormal retinal pigment epithelium) and D1: treatment needed for age-related macular degeneration (wet type or dry type) (Table 6).). (See Treatment Guidance for Age-Related Macular Degeneration).[10]

3-3) Other eye diseases

There are other eye diseases such as abnormal optic disc, suspected diabetic retinopathy (if diabetes is not confirmed), other retinopathy findings, retinal vascular disorder, abnormal macula appearance, chorio-retinal atrophy, myelinated nerve fiber, and others are assessed ad libitum as indicated in Table 6.
If the assessment of fundus images are difficult or impossible due to the presumed opacity of the optic media such as cataract, are assessed as D2: thorough examination needed. If other causes are likely, assessment category will be selected at the assessing physician’s decision.

4) Procedure for taking fundus photograph

4-1) Method

Photographs should be taken by accurately focusing on the adequate field with an appropriate brightness in a short period of time in a health screening program workflow. In a health screening, fundoscopy is performed in most cases using a non-mydriatic digital fundus camera without pupil dilation. Fundus photography has advantages to maintain reproducibility and objectiveness ensured through accuracy control and unified assessment criteria, storage of examination results allowing evaluation of time-dependent change or re-assessment in comparison with previous images, and short period of time required to complete the examination.

4-2) Image angle

Fundus photographs should be taken at the point where the center of the line connecting the optic disc and the fovea of the macula, including the upper and lower vascular arcades using a fundus camera with angle of view ≥45º. The nasal side of the optic disc is included by approximately the diameter of the optic nerve, allowing assessment of vascular findings in all four quadrants: upper/lower temporal/nasal quadrants with the optic disc centered. It is also desirable that the technician of fundus photography confirms whether the image taken indicates the site suitable to assessment clearly in an appropriate brightness on site and takes another photograph if the image is unclear.

4-3) Importance of screening fundus photographs for both eyes

Fundus photographs of both eyes should be screened for ophthalmologic diseases. If only one eye is screened, it may overlook a number of eye diseases. Recent non-mydriatic digital fundus cameras uses much lower flash light intensity, allowing photographing both eyes in a short interval by using a dark room or screen. The pupils open more easily if the individual closes the eyes gently after one eye is photographed, and then the other eye is photographed. If images taken by non-mydriatic fundus camera resulted an image with dark region around the macula it is because the pupil was not large enough. In such a case, the photograph is taken after waiting for sufficient time until the pupils open in a dark room or screen. Although some fundus cameras are equipped with small pupil mode allowing their range of photograph is narrowed. Standardized procedure should be predetermined for such individuals with small pupil in advance as a standard protocol for procedures in each institution.

5) Quality control of the grading

Quality control is important to ensure that there is no significant difference in assessment between image graders if more than one image grader is present and each image grader provides comparable assessment with other image graders. At the beginning of the assessment, it is helpful to confirm the assessment criteria by using training image set and to compare the results from the same fundus photograph between image graders to confirm the results are comparable. It is desirable that ophthalmologists or physicians who routinely conduct ophthalmologic practice make the assessment if possible.

6) Accuracy indices for grading reproducibility, and follow-up research

It is important for both patients and screening institutions to recognize that accurate performance of fundus screening is secured. It is desirable to establish a close cooperative relationship with medical institutions providing thorough examinations. Retinal vascular lesions detected in cardiovascular screening are useful to identify individuals with high risk of stroke or ischemic heart diseases and help those individuals to initiate a treatment of hypertension for the primary prevention of cardiovascular diseases. Therefore, cooperation between screening institutions and physicians for both internal medicine and ophthalmology is also important. In diabetic retinopathy screening, cooperative work with ophthalmologists should be needed when the disease is severe immediately after the screening,, in addition to cooperation with diabetologists. For a screening program for eye diseases, a partnership with

ophthalmologists is important.

It is also important to monitor the screening program with performance indices such as the prevalence of abnormal findings, the proportion of individuals who needed secondary examinations, and the proportion of actual attendance at the secondary examination be collected and by conducting a follow-up research to evaluate diagnostic accuracy such as the secondary examination, treatment status after secondary screening, and recommendation of the secondary examination for non-attender and individuals with past history of abnormal findings.

Table 1. Major causes of adult blindness from the view of disease screening requirement

	Glaucoma	Diabetic retinopathy	Age-related macular degeneration
Important disease	5% prevalence in the population older than 40 years of age. The number of patients increases in association with increasing elderly population. Without ocular hypotensive treatment, it has high risk of blindness, although it progresses slowly.	Diabetes prevalence is 10% in adults, and retinopathy is found in 35% of the diabetic population. Without treatment, diabetic retinopathy poses a great risk of adult blindness that not only damages the patient's daily motion, function, and quality of life but also increases social burdens such as workforce loss, family burden, and medical expenses.	1 to 2% prevalence in the population older than 50 years of age. The number of patients increases in association with increasing elderly population. Once it occurs, it progresses rapidly, posing a great risk of visual disorders.
Simple, accurate, and non-invasive test for diagnosis	Fundus photograph non-invasively provides definite diagnosis. Fundus cameras have already been popularized commonly and are relatively cheap. Digital imaging is also suitable for remote diagnosis.		
Post-diagnostic prevention, treatment, and rehabilitation established.	Although prevention of onset of glaucoma is difficult, ocular hypotensive treatment from early detection, prevention of evolution, and maintenance of visual acuity and visual field has been established.	Medical and surgical treatments have been established for prevention of onset and evolution of diabetic retinopathy and recovery of visual acuity. Treatments at appropriate timings can prevent blindness in almost all cases. Now improvement of visual acuity is expected.	Although prevention of onset of age-related macular degeneration is difficult, smoking cessation is recommended for smokers. Smoking cessation is also important in prevention of evolution. In cases of AREDS category ≥3 or 4, anti-oxidizing supplement is effective for prevention of evolution.
Early detection and post-diagnostic treatment by screening is cost-effective.	Simulation has demonstrated great medical effect of screening glaucoma. Δ Cost effectiveness requires setting of condition for evaluation.	Simulation has demonstrated great medical effect and cost effectiveness of screening diabetic retinopathy.	Simulation has demonstrated great medical effect of screening age-related macular degeneration. Δ Cost effectiveness requires setting of condition for evaluation, because of its high treatment expense.

Table 2. Scheie Classification

Scheie	Sclerotic change (S)			Hypertensive change (H)		
	Characteristics of sclerotic vessels	Specific health checkup code	Assessment	Hypertensive vascular change	Specific health checkup code	Assessment*
0		1	A		1	A
1	Arterial wall reflex is potentiated. Mild arteriovenous crossing is present.	2	B	Although mild diffuse narrowing is present in the retinal artery system, caliber variation is not definite. Severe narrowing may occasionally be present at the second arterial branch or lower.	2	B
2	Arterial wall reflex is severely potentiated with moderate arteriovenous crossing.	3	B	Mild diffuse narrowing of retinal artery is mild or severe with additional definite localized narrowing with caliber variation.	3	C
3	Copper wire artery, that is, the artery changed in its color and radiance to a copper wire-like appearance. Arteriovenous crossing is severe.	4	C	Narrowing artery and caliber variation become more prominent and seem like thread. Either or both of bleeding and white patches appear on the retinal surface.	4	D2
4	The arterial wall looks like silver wire (silver wire artery) or white wire in some cases.	5	C	Papilledema of various severities is present in addition to the 3rd degree findings.	5	D2

*Select taking age and arteriosclerosis risk factor into consideration.

Assessment categories A: Normal, B: Mild abnormality without problems, C: Following up needed, D: Medical care needed (D1: Treatment needed, D2: Thorough examination needed), and E: Under treatment.

Table 3. Keith-Wagener Classification

Fundus disease	Classification		Fundus findings	Specific health checkup code	Assessment *
Normal			S0H0 without findings	1	A
	Group I		Mild narrowing and sclerosis of arteriole (modified Scheie I)	2	B
Hypertensive	**Group II**	**a**	Obvious arteriosclerosis (modified Scheie II or higher) with narrowing severer than Group I	3	B or C
		b	Arteriosclerotic retinopathy or retinal vein occlusion in addition to the above	4	D2
	Group III		Vasospastic retinopathy is present in addition to marked sclerotic change. Retinal edema, cotton wool patches, and bleeding are present with marked arterial narrowing.	5	D2
	Group IV		Papilledema severer than measurable degree in addition to the findings in the above Group III	6	D2

*Select taking age and arteriosclerosis risk factor into consideration.

Assessment categories A: Normal, B: Mild abnormality without problems, C: Following up needed, D: Medical care needed (D1: Treatment needed, D2: Thorough examination needed), and E: Under treatment.

Table 4. Table of correspondence between hypertensive retinal vascular lesion classifications by Wong-Mitchell and Scheie Classification

Classification	Findings	Relationship to systemic diseases	Assessment*	Keith-Wagener classification	Scheie classification**
None	No findings	None	A	Group 0	H0S0
Mild	Diffuse narrowing of retinal arteriole, local narrowing/caliber variation of the retinal arteriole, arteriovenous crossing phenomenon, and enhanced reflection/opacity (copper wire artery)	Increasing risks of cerebral apoplexy, non-syndromic cerebral apoplexy, coronary disease, and cardiovascular death (odds ratio 1 to 2)	B or C	Group I/II	H0S1-4 H1S0-4 H2S0-4
Moderate	Retinopathy findings such as retinal bleeding (patchy, spotty, flammeus), capillary aneurysm, cotton wool patches, and hard exudate	High risks of cerebral apoplexy, non-syndromic cerebral apoplexy, lowered recognition, and cardiovascular death (odds ratio ≥2)***	D2	Group III	H3S0-4
Severe	Papilledema in addition to retinopathy findings	High cardiovascular death risk	D2	Group IV	H4S0-4

*Select taking age and arteriosclerosis risk factor into consideration.

**Retinal vascular findings may be present without hypertension. It was reported that even individuals with high normal blood pressure may have such retinal vascular lesions and that retinal vascular lesion have relationship independent from blood pressure to future onset of hypertension and cardiovascular disease. Select categories taking into consideration age and arteriosclerosis risk factors other than blood pressure.

*** They correspond to “hypertensive retinopathy” equivalent to “B. Visceral disorders/cardiovascular diseases” of “Prognostic factors used in risk stratification for hypertension management plan” in “Treatment Guidelines for Hypertension 2014.” These are in “3rd risk stratum,” that is to say, they indicate that cardiovascular disease risk is high and treatment for hypertension should immediately be considered in addition to lifestyle adjustment.

Assessment categories A: Normal, B: Mild abnormality without problems, C: Following up needed, D: Medical care needed (D1: Treatment needed, D2: Thorough examination needed), and E: Under treatment.

Table 5A. Table for correspondence of international severity criteria for diabetic retinopathy to Modified Davis classification, New Fukuda classification, and Scott classification

Severity classification	Fundus findings	Assessment	Modified Davis classification	New Fukuda classification	Scott classification
No definite retinopathy	Normal	A	No retinopathy	No retinopathy	No retinopathy
Mild non-proliferative diabetic retinopathy	Capillary aneurysm only	D2	Simple retinopathy	A1	Phase Ia/phase II
Moderate non-proliferative diabetic retinopathy	Although abnormal capillary aneurysm lesion is present, it is milder than severe non-proliferative retinopathy.	D2		A2	Phase IIIa/phase IIIb
Severe non-proliferative diabetic retinopathy	One or more of the following findings are present without proliferative retinopathy findings: 1. More than 20 intraretinal bleedings in all four fundus quadrants 2. Definite moniliform veins in 2 or more fundus quadrants 3. Definite intraretinal microvascular abnormalities in one or more fundus quadrants	D2	Pre-proliferative retinopathy	B1	Phase Ib
Proliferative diabetic retinopathy	Either of the following findings: 1. Neovascularity 2. Vitreous body bleeding/preretinal bleeding	D2	Proliferative retinopathy	A3-5 B2-5	Phase IV Phase Va/phase Vb

Note: Those who have already been diagnosed as having diabetes or those who are suspected to have diabetes should be recommended to have regular ophthalmologic examination by an ophthalmologist.

Assessment categories A: Normal, B: Mild abnormality without problems, C: Following up needed, D: Medical care needed (D1: Treatment needed, D2: Thorough examination needed), and E: Under treatment.

Table 5B. International Severity Classification for diabetic macular edema

Severity classification	Fundus findings	Assessment
No diabetic macular edema	Thickening of posterior pole of the fundus due to retinal edema, without hard exudate	A
Diabetic macular edema present	Thickening of posterior pole of the fundus due to retinal edema, with hard exudate	D2*
Mild diabetic macular edema	Retinal thickening and hard exudate are present but far from the macula	D2
Moderate diabetic macular edema	Retinal thickening and hard exudate are present not including the central macula	D2
Severe diabetic macular edema	Retinal thickening and hard exudate are present including the macula	D2

* Diabetic macular edema is difficult to detect and assess for its severity in a fundus photograph taken by fundus camera without mydriasis. Classify in mild, moderate, and severe only if possible.

Assessment categories A: Normal, B: Mild abnormality without problems, C: Following up needed, D: Medical care needed (D1: Treatment needed, D2: Thorough examination needed), and E: Under treatment.

Table 6. Ophthalmologic screening items

Suspected disease	Findings	Assessment
Suspected glaucoma	Enlarged optic disc cupping	D2
	Retinal nerve fiber layer defect	D2
	Optic disc bleeding	D2
	Suspected glaucomatous optic disc change	D2
Suspected age-related macular degeneration	Precursor lesion of age-related macular degeneration (drusen, and abnormal retinal pigment epithelium)	D2
	Age-related macular degeneration (wet type or dry type)	D2
Other suspected eye diseases		
Optic disc abnormality	Papilledema/congestive optic disc	D2
	Other optic disc abnormality	D2
Suspected diabetic retinopathy (if diabetes is not confirmed) and other retinopathy findings	Soft exudate	D2
	Hard exudate	D2
	Retinal bleeding (spotty/blot)	D2
	Spotty bleeding	D2
Retinal vascular disorder	Central retinal vein occlusion	D2
	Branch retinal vein occlusion	D2
	Central retinal artery occlusion	D2
Macular abnormality	Preretinal (epiretinal) membrane	D2
	Myopic maculopathy	D2
	Other macular abnormality	D2
Retinal/choroidal degeneration/atrophy	Retinal/choroidal degeneration/atrophy	D2
Myelinated nerve fiber	Myelinated nerve fiber	B
Others	Vitreous body opacity	D2
	Neoplasms	D2
	Pigmented spot in the retinal/choroidal membrane	D2
	Post-laser therapy	B/C
Difficult/impossible to Assess	Suspected cataract, etc.	D2
	Uninterpretable	Brank*

Assessment categories A: Normal, B: Mild abnormality without problems, C: Following up needed, D: Medical care needed (D1: Treatment needed, D2: Thorough examination needed), and E: Under treatment.
*Ophthalmologic examination is recommended depending on cases.

Japan Society of Ningen Dock

Image inspection decision manual making committee

Chairman: **Takashi Wada** (Professor, Health Science Center, Jikei University School of Medicine)

Members : **Akira Murakami** (M.D., Ph.D., Department of Ophthalmology)

Goji Tomita (Professor, Department of Ophthalmology, Toho University School of Medicine, Tokyo, Japan; Director, Department of Ophthalmology, Toho University Ohashi Medical Center, Tokyo, Japan)

Ryo Kawasaki (Graduate School of Medicine. Department of Public Health, Yamagata University Faculty of Medicine)

April, 2015