Real-world effectiveness of screening programs for age-related macular degeneration: amended Japanese specific health checkups and augmented screening programs with OCT or AI

Running title: Practical effectiveness of AMD screening

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Abstract

Purpose: To investigate the effectiveness of screening and subsequent intervention for age-related macular degeneration (AMD) in Japan.

Study Design: Best-case-scenario analysis using a Markov model

Methods: The clinical effectiveness and cost-effectiveness of screening for AMD were assessed by calculating the reduction proportion of blindness and incremental cost-effectiveness ratio (ICER). The Markov model simulation began at the age of 40 years and ended at the age of 90. The first-eye and second-eye combined model assumed annual state-transition probabilities in the development and treatment of AMD. Data on prevalence, morbidity, transition probability, utility value, and treatment costs were obtained from previously published reports. Sensitivity analysis (SA) was performed to assess the influence of the parameters.

Results: In the base-case analysis, screening for AMD every five years, beginning at age 40 until age 74, reflecting the current Japanese legal “Specific Health Checkups” showed a decrease of 40.7% in the total number of blind patients. The screening program reduced the number of blind people more than did the additional AREDS/AREDS2 formula supplement intake. However, the ICER of screening versus no screening was 9,846,411 JPY/QALY with supplemental costs and 6,364,545 JPY/QALY without supplemental costs, which were beyond

what people were willing to pay in Japan. SA revealed that neither OCT nor AI improved ICER, and screening could be both clinically effective and cost-effective if started early and conducted frequently.

Conclusions: Ophthalmologic screening for AMD is highly effective in reducing blindness but is not cost-effective, as demonstrated by a Markov model based on real-world evidence from Japan.

251/250 words

Keywords

Age-related macular degeneration, Clinical effectiveness, Cost-effectiveness analysis, Markov model, Screening.

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries [1-5]. In Japan, AMD ranks fourth among the causes of visual impairment, and about 700,000 patients suffer from the disease [6]. Although no treatment for this condition has been available until recently, it is now commonly treated with anti-vascular-endothelial-growth-factor (anti-VEGF) intravitreal injection therapy [7, 8]. Nevertheless, the early detection of AMD is still important because it leads to a better visual prognosis through the long medical control period [9]. The considerable burden of disease associated with AMD, as well as the public health benefits of prevention, are also highlighted [10].

We reported the clinical effectiveness and cost-effectiveness of screening for AMD in adults for critical early detection, indicating the need for future reassessment as well as the limitations at the time[11]. Subsequently, long-term data have been accumulated, mainly of aflibercept, and many reports on the cost-effectiveness of treatment have been reported [9, 12-16]. Although the cost-effectiveness of treatment was not consistent, the treatment has been almost agreed to be cost-effective, especially after aflibercept was considered to be the dominant treatment option [17, 18].

In contrast, there are few reports regarding comprehensive AMD management, including health check-ups [19, 20]. Furthermore, there have been noticeable screening-related

changes, such as the increasing benefits of optical coherence tomography (OCT)[21, 22] ,improved accuracy of artificial intelligence (AI) for fundus images and OCT [21-24] , the guidance effect on smoking cessation [25], and the refinement of the strategy for nutritional supplement intake confirmed using AREDS/AREDS2 [10].

This article addresses the re-evaluation of the clinical effectiveness (reduction in the number of blind patients) and cost-effectiveness (from a value-for-money perspective) of screening and subsequent treatment of AMD in Japan using a Markov model that reflects the latest data, especially long-term and real-world evidence. The following improvements, which were not addressed in the previous study, were tackled with particular intensity using these latest and longer-term data: to reduce the proportion of uncertain parameters; to evaluate concerns regarding the long-term degradation of AMD treatment effects; to improve the differing utility values when the two eyes are in different stages; and to compare the effects of screenings and supplements. We also evaluated the impact of new technologies such as OCT and AI for fundus image classification.

Subjects and Methods

Markov model

In this study, a model was created and analyzed using TreeAge Pro 2017 (TreeAge Software,

Inc., Williamstown, MA, USA) to estimate screening outcomes as described in a previous report[11]. Briefly, the model consisted of a decision tree to group adults into those receiving ophthalmologic screening (the screened group) and those not receiving screening (the non-screened group), and a Markov model of disease progression to compare two strategies: a screening strategy and a non-screening strategy. We again employed the first-eye and second-eye combined model [15], time horizon of 50 years, and direct cost model. On the other hand, we refined the model in several aspects: the model involved early AMD patients at 40 years of age as the start of the model reflecting the Japanese cohort data [26]; the natural prognostic variables updated from MARINA sham data [27] to systematic review data in 2017 [28]; the transition probabilities from early AMD to late AMD in the fellow eye was also updated from data of 2000 [29]to data of 2014 [30]; patients who did not take the AREDS/AREDS2 formula supplement were considered to be only followed-up patients not dropout patients; aflibercept was adopted instead of ranibizumab as the primary treatment; a “stable state” with only follow-up during anti-VEGF treatment was added to the Markov states. Details of these changes will also be described in the following section.

Model parameters

Table 1 shows the parameters used in our model, including utilities, costs, and state transition probabilities. Table 2 indicates the parameters of anti-VEGF therapies, such as treatment

frequencies and state transition probabilities. For these parameters, clinical research data on the Japanese population was obtained to the extent possible; if no applicable Japanese data were available, overseas data were used.

Cohort (population)

The model simulated a hypothetical Japanese cohort of 500,000 people aged 40 years, and the simulation ran until they reached 90 years of age or died. At the beginning of the simulation, early AMD patients with one-eye involvement are presumed to exist as 3.85% of the natural cohort without any medical control, based on the prevalence in the Japanese population [26]. We used data estimated in a systematic review [28] for the natural prognostic variables.

State transition

The first- and second-eye combined models were again employed. The steps of disease progression in each eye were categorized by the following seven Markov states (Fig. 1): normal, early AMD, moderate late AMD, severe late AMD, blindness, stable, and death. Based on best-corrected visual acuity (VA), the following three states were defined: moderate late AMD (VA: 0.5–0.9), severe late AMD (VA: 0.1–0.4), and blindness (VA: < 0.1). A stable state was newly added in the current study, reflecting real-world clinical patterns. Since most AMD patients are reported to be affected in only one eye [31], early AMD develops independently in each eye, and the progression of AMD also occurs independently in each eye. It was assumed that the

cohort would develop early AMD as a prodromal stage and then moderate late AMD and later stages. In each cycle, evaluated annually, each patient's disease condition was rated as aggravated, maintained, or improved using transition probabilities, according to the reported real-world data in Japan [32]. The probability of AMD occurring in the second eye was determined using the reported accumulated incidence rates [30].

Mortality rate

The age-specific background mortality based on the 2017 Japan abridged life tables [33] was adopted as the mortality rate.

Treatments

Once AMD was detected in a patient, he/she was assumed to be set under medical control with the appropriate treatments principally in accordance with the Japanese clinical guidelines [34]; AREDS/AREDS2 formula nutritional supplement intake or follow-up in early AMD and intravitreal injection of anti-VEGF both in moderate and severe late AMD. The proportion of patients receiving supplements and the effect of supplements were set based on a previous Japanese report [35] and an RCT conducted in the United States [36], respectively.

In both moderate and severe late AMD, patients were supposed to receive aflibercept as an anti-VEGF injection, and the number of injections and effects were based on Japanese prospective reports [14] (Table 2). For those who did not drop out of a series of treatments, the

number of injections per year was set at seven for the first year, three for the second year, and later. However, since Nishikawa et al. reported that approximately 20% of patients did not require additional injections from the 2nd year to the 4th year [14], the model assumed that 20% of patients would transfer to the "stable state." In the stable state, no additional injection with aflibercept was assumed, but the aggravation probability was assumed to be the same as during the treatment period.

Since aflibercept is the current main treatment option for AMD in Japan and also considered the dominant treatment option in cost-effectiveness analyses of AMD treatment [17, 18], we included aflibercept treatment in the base-case analysis. Ranibizumab and photodynamic therapy with verteporfin (PDT), which are currently minor treatment options, were evaluated in a scenario analysis of treatment described below.

Among the adverse events and complications associated with the intravitreal injection of anti-VEGF agents, infectious endophthalmitis is reported to be the most significant and frequent [37]. The development of endophthalmitis was assumed to be a complication of the aflibercept injection and to occur within 1 year of the injection. The incidence rate was estimated according to a report on ranibizumab due to the absence of evidence on aflibercept [38]. When blind, patients were assumed to receive no treatment but to be observed.

Medical consultation without screening

For members of the non-screened group, AMD was detected during a coincidental consultation or spontaneous consultation due to subjective severity. In detail, our model assumed that patients visited ophthalmologic clinics with presbyopia via coincidental consultation. The prevalence of presbyopia in Japan is reported to be 43.8% [39] for those aged 40 years or older, and our estimate of the annual rate of increase in the prevalence of presbyopia was 3%. We assumed that 20% of those with presbyopia, within one year from the onset, would visit ophthalmologic clinics and be diagnosed with AMD. Regarding the spontaneous consultation due to subjective severity, when patients who were not under medical care became blind, all of them were supposed to be seen by the ophthalmologist with spontaneous consultation due to subjective severity.

Medical consultation after screening

In the screening group, we assumed that AMD was detected in a periodical screening program in addition to coincidental consultation or spontaneous consultation due to subjective severity. In the base-case analysis, the schedule of the periodical screening program was set to start at age 40 and continued every five years until age 74 (age at the last screening was 70 years), reflecting the current “Specific Health Checkups” legally conducted by the Japanese national government. During the checkups, ophthalmic screening with fundus photography is limited to people with abnormalities in blood pressure and blood tests for glucose and lipids. In this study,

to estimate the health-related economic effects of ophthalmic screening aimed at detecting AMD in all subjects in the context of "Specific Health Checkups," we used the same age for ophthalmologic screening. The screening participation percentage was set at 50% with reference to that of the "Specific Health Checkups" [40].

Ophthalmologic screening program

It was assumed that ophthalmologists used fundus photographs to make diagnoses for screening as a reference scenario.

Other outcomes

The number of AMD patients, the number of blind patients, and the duration of blindness (years) per person were estimated using the Markov model simulation. All of the values above are cumulative values at the end of the simulation, including the patients who were supposed to die during the simulation. The number of blind people was calculated by multiplying the percentage of blind people in the survivors per cycle by the Japanese population estimates as of 2017 [41].

Clinical Effectiveness Analysis

We calculated the reduction in the proportion of blind people among AMD patients by comparing both screening strategies (the screened group vs. the non-screened group).

Utility value

The utility value for each AMD patient, or the patient's preference-based QOL, was set at 1 for a healthy member of the population and at 0.97 for a patient with early AMD in both eyes. Utility data were obtained using a time trade-off (TTO) method for measuring visual-acuity–specific utility in patients with AMD by the categories of decimal visual acuity in the previous reports: 0.7–1.0 for moderate, mean of 0.2–0.3 and 0.4–0.6 for severe, and 0.01–0.15 for blindness [42]. However, when the conditions differed between the two eyes, the average of the utility values for the two eyes was adopted, considering the poor health-related QOL reported to be caused by the worse-seeing eye [43].

Costs

Our model was analyzed from the Japanese healthcare perspective. Thus, direct medical care costs, including the cost of screening and nutritional supplements, were considered. The time and transportation costs for the screened participants were not considered. Specialists estimated the costs of screening, the detailed examination required for the definite diagnosis of AMD, and treatments, based on the reimbursement rates defined in fee schedules for Japanese social health insurance. All costs were in Japanese yen (JPY) and were converted into US dollars (USD) (2020) using the Bank of Japan foreign exchange rates (1 US$ = ¥ 106) [44].

Cost-utility analysis

Cumulative costs of screenings, treatments, and quality-adjusted life years (QALYs) were

223 calculated per person for the entire simulation period, using an annual discount rate of 2%,
224 according to the guidelines for Japanese cost-effectiveness research [45].

225 We calculated an incremental cost-effectiveness ratio (ICER) to enable comparisons
226 between the cost and the utility value for each screening strategy. ICER was calculated using
227 the following formula: *ICER= incremental cost / incremental QALY Gained*

228 The threshold of cost-effectiveness was set at 5,000,000 JPY/QALY, or 47,286
229 USD/QALY, which is the willingness to pay (WTP) in Japan [46].

230 **Sensitivity analysis**

231 One-way sensitivity analysis (one-way SA) were performed to assess the influence of each of
232 the 40 parameters on the base-case results, yielding a cost-effectiveness acceptability curve. For
233 the sensitivity analysis, the range of values for each parameter was set for the 95% confidence
234 interval (CI) or ±50% from the reported baseline value.

235 **Scenario analysis of screening with OCT or AI**

236 In addition to the base-case analysis, we analyzed the effectiveness of OCT and the
237 effectiveness of interpretation by AI for fundus photographs or OCT in the screening program.
238 The sensitivity and specificity of OCT interpreted by ophthalmologists are 0.970 and 0.897,
239 respectively [22], while those for fundus photographs interpreted by AI are 0.718 and 0.871
240 [23]; The sensitivity and specificity for OCT interpreted by AI were 0.982 and 0.912,

respectively [22]. The cost-effectiveness was also calculated, assuming a cost of 2,000 JPY to add OCT and no additional cost for AI deployment.

Scenario analysis of treatment

Supplements are not covered by insurance, but the cost of supplements was considered in the base case analysis. In the scenario analysis, two cases were analyzed: no consideration of supplementation costs and no supplementation, and all patients detected as being in the prodromal state were only followed up. Given that ranibizumab is currently used only for a minor proportion of AMD treatments in real-world clinical practice, we also analyzed the mixed pattern of aflibercept and ranibizumab in a 3:1 ratio in the scenario analysis, according to real-world evidence in Japan [47]. The number of cases and the efficacy of ranibizumab treatment were based on the results of the LUMINOUS [48] and HORIZON [49] studies after the first and second years of treatment, respectively. Photodynamic therapy with verteporfin (PDT), although minor, is still a treatment option for AMD in Japan. We also analyzed the mixed pattern of combination therapy, adding PDT to the initial aflibercept treatment in the scenario analysis.

Scenario analysis of smoking cessation after AMD detection

Some reports have indicated suppression of AMD through smoking cessation [25] ; hence, the guidance effect on smoking cessation during “the specific health check-ups” was evaluated in the sensitivity analysis. The percentage of smokers in the target population was set at 22.9% [47] , the

259 incidence of early and late AMDs in smokers compared to nonsmokers were set at 1-fold and 1.5-
260 folds, respectively [50] , and the mortality rate in smokers compared to nonsmokers was set at 1.7-
261 folds[51]. Since smoking cessation guidance was reported to have a significant impact and a
262 cessation proportion of 32.6% was noted in the appropriately treated group at the smoking cessation
263 outpatient clinic [52], we assumed that a reduction of smoking among AMD patients would occur
264 at a rate between 0% and 30% after the early or late AMD detection. The cost for smoking cessation
265 guidance per person in this report was considered 40,010 JPY [52].

266 **Ophthalmologic screening schedule and cycle**

267 To determine the optimal screening program, the age at which screening was started, the age at
268 which screening was completed, and the interval between screenings were each varied within
269 their respective ranges shown in Table 1 to yield the incremental cost-effectiveness ratio and
270 the reduction of the prevalence of blindness.

271 **Model validation**

272 To validate our model, we compared the reported numerical values (for the prevalence of AMD
273 and the unilaterality of AMD in persons 40 years or older) with simulated values for the non-
274 screened group.

275 **Ethics Statement**

276 All investigations in the current study adhered to the tenets of the Declaration of Helsinki.

277 Institutional Review Board approval and the requirement for individual informed consent was
278 legally waived in the Ethical Guidelines for Medical and Health Research Involving Human
279 Subjects by the Ministry of Education, Culture, Sports, Science, and Technology and the
280 Ministry of Health, Labor, and Welfare because only published data were used, no new patients
281 were enrolled, and no patient data were utilized in the research.
282

283 # Results

284 **Clinical effectiveness analysis**

285 Table 3 shows the results of clinical effectiveness in the base case. Screening interventions
286 reduced the proportion of blind patients by 40.7%. The preventive effect of blindness was
287 56.9% after controlling for age; the proportion of blind people for those aged 40 years and
288 above was 0.0014% in the screening group and 0.0033% in the non-screening group. The mean
289 cumulative duration of blindness was 7.3 years per blind person in the screening group and 9.9
290 years per person in the non-screening group, indicating that screening can also reduce the
291 duration of blindness. At the end of the simulation, 64,305 patients (46.3%) in the screening
292 group and 19,198 patients (13.8%) in the non-screening group, respectively, were detected to
293 have AMD, among the 138,822 cumulative patients with AMD.

294 **Cost-effectiveness analysis**

The results of the base case analysis are shown in Table 3. The incremental cost of the screening group was 63,303 JPY, and the incremental utility of the screening group was 0.0064 QALY. Consequently, the ICER was calculated as 9,846,411 JPY/QALY.

Sensitivity analysis

The results for the top 10 most influential parameters among all 40 parameters in the one-way SA are shown in Fig. 2. The most influential parameter in the model was the utility value of the blind state, and the 2nd most influential parameter was the utility value of moderate late AMD, where utility values were found to have a significant impact on the model.

Scenario analysis of screening with OCT or AI

The screening program with fundus photography interpreted by AI and with OCT interpreted by AI, as well as with OCT by an ophthalmologist, prevented 34.6%, 40.7%, and 42.0% of the cases of blindness, respectively. Compared to the non-screening group, the ICERs were 10,524,003 JPY/QALY, 10,437,363 JPY/QALY, and 10,491,265 JPY/QALY for screening with fundus photography interpreted by AI, screening with OCT interpreted by AI, and screening with OCT interpreted by an ophthalmologist, respectively (Supplementary Table 1).

Scenario analysis of treatment

Fig. 3 shows the trends in the rate of occurrence of blindness by age in the screening and non-screening groups with and without supplementation. The age-adjusted blindness prevention

proportion was 57.9%, indicating that blindness can be prevented by the screening process even without supplemental treatment. Comparing the screening and non-screening groups, excluding supplement costs, the ICER significantly decreased to 6,364,545 JPY/QALY from the ICER in the base case analysis. Comparing the screening and non-screening groups, assuming just follow-up for the early AMD without supplementation, the ICER was 7,831,069 JPY/QALY. The calculated ICERs were 10,374,159 JPY/QALY and 10,002,945 JPY/QALY in sensitivity analyses of the mixed patterns of aflibercept and ranibizumab in a 3:1 ratio and adding PDT pattern as an initial treatment, respectively.

Scenario analysis of smoking cessation after AMD detection

Simulation in smoking cessation proportion using the guidance after AMD detection did not impact the clinical effectiveness, such as blindness prevention proportion, inhibition of late AMD development, and delay in the late AMD development (Supplementary Table. 2). In contrast, the ICERs were found to decrease with a decrease in smoking proportion. In particular, when the smoking proportion decreased to 30%, a possibility of ICER falling under the WTP is implied.

Ophthalmologic screening schedule and cycle

The ICER and cumulative blindness prevention were calculated for 163 patterns of screening programs, varying the age at the start of screening, age at the end of screening, and interval between screenings within the ranges shown in Table 1. All 163 calculated screening programs

had positive incremental costs and positive incremental utility values compared to the non-screening group. The ICER ranged from 5,368,641 JPY/QALY to 18,051,627 JPY/QALY, while the cumulative blindness prevention percentage ranged from -1.2% to 81.5%. None of the screening programs had an ICER of less than 5,000,000 JPY/QALY (Supplementary Table. 3).

The correlation between the ICER and the screening interval or the number of screenings was weak. The earlier the screening program started or ended the lower the ICER (Supplementary Fig. 1). On the other hand, the blindness prevention proportion was strongly correlated with the cumulative number of screenings (Supplementary Fig. 2), and was not affected by other factors such as age at the start of screening, screening interval, and age at the end of screening.

Model validation

The prevalence of AMD in the simulated cohort was 1.04%, and the model's unilaterality of AMD was 76.9%, which was controlled by the population aged over 40 years.

Discussion

The screening program prevented blindness caused by AMD and the cumulative incidence rate of AMD. The screening program evaluated in this study reduced the number of cumulative blind patients with AMD by 41%. Three times more detection and subsequent medical management

of AMD would have directly contributed to the prevention of blindness. The screening program also shortened the duration of blindness. The deployment of the screening program is expected to continue and boost the preventive effect of halving social blindness by anti-VEGF, as already shown in 2012 [53].

While the clinical effectiveness of the ophthalmologic screening program for AMD was again confirmed, its insufficient cost-effectiveness was again confirmed. The ICER in the base case was calculated as 9,846,411 JPY/QALY, which is higher than the WTP, although it significantly reduced from 27,486,352 JPY/QALY [11]. The ICERs were greater than the WTP threshold for any of the one-way SA with 40 parameters. These results indicate that ophthalmologic screening for AMD is not cost-effective. Combined with the significant improvement over the previous results, it is expected to be worth assessing the cost-effectiveness of the ophthalmologic screening for AMD in the near future.

The insufficient cost-effectiveness might be affected by the re-adoption of the first-eye and second-eye combined model, as discussed previously. We also adopted the strategy of lowering the utility when the binocular states were different to prevent the results from being extreme, referring to a previous report. Previous studies, focusing on the cost-effectiveness of treatments, have frequently used the second-eye model [9, 12-18]. The second-eye model may be a possible option for cost-effectiveness research specialized in treatment; however, the first-

367 eye and second-eye combined model would be a better strategy for cost-effectiveness research
368 of long-term models with screening.

369 In order to verify the model's external validity, we compared the simulated values for
370 the non-screened group (prevalence of AMD in those aged ≥40 years and incidence of unilateral
371 AMD) to reported data from Japanese cohorts. The prevalence of AMD in those aged ≥40 years
372 in the simulated cohort was 1.04 %, which was within the range of 0.09-1.40 %, including those
373 aged ≥35 years and those aged ≥50 years [54, 31, 55, 32]. The model's unilateral AMD
374 incidence of 76.9% was comparable to the 83.5% reported in the Nagahama study [31]. The
375 model was validated and shown to adequately represent the real-world epidemiologic status.

376 Indirect costs and non-medical costs were not included in the current study according
377 to the guidelines for Japanese cost-effectiveness research [45]. Supplement intake is included
378 in evaluations in the base-case analysis, although their marginal positioning characteristics may
379 cause some discussions. Supplements are widely used in actual clinical practice as
380 recommended in the guidelines [34], but they are not covered by public health insurance. Given
381 that it is not necessary to include the cost of supplements in the cost-effectiveness research from
382 the Japanese public health care perspective, we added a cost-effectiveness analysis excluding
383 the cost of supplements. The ICER without the cost of supplements was significantly lower
384 than the ICER for the base case analysis. The screening program prevented blindness more than

the additional intake of supplements did.

Considering that AREDS/AREDS2 formula supplements are not a burden on the society, the option of finding early AMD proactively with screening to increase clinical effectiveness and cost-effectiveness is becoming more realistic. On the other hand, it may be difficult to ensure continuous life-long usage of nutritional supplements due to the high burden on the patients themselves and their motivation to continue [35]. Assuming only follow-up for early AMD without supplement treatment, the effect of screening on blindness was higher even without supplemental treatment, although cost-effective issues remain. Regardless of supplement discussion, screening could be recommended.

The ICER and the prevention of blindness for a scenario analysis of a 3:1 ratio of aflibercept and ranibizumab, reflecting current clinical practice [47], was 10,374,159 JPY/QALY and 28.0%, respectively. Although ranibizumab is expected to improve the visual acuity to about the same degree as aflibercept, higher deterioration rates of ranibizumab resulted in more blindness than aflibercept [17] even when detected earlier in the screening program. The equivalent ICER to the base case analysis may be due to the assumption that only the follow-up cost was counted in the blind state. The scenario analysis including PDT in the treatment also did not differ significantly from the base-case analysis, or at least did not show a trend towards improving efficacy.

403 The necessity of the study on the economic impact of AI is discussed in a systematic
404 review [56]. We performed a cost-effectiveness analysis of AI, assuming no additional cost of
405 examination when the fundus photographs or OCT were interpreted by AI, and we reported that
406 the ICER for the screening group compared with that of the non-screening group was almost
407 equivalent to the base-case analysis. The cost of screening with AI is difficult to estimate; it
408 might be higher because of the cost of equipment and analytical software than the base-case
409 analysis; this might be lower because of the reduced cost of personal than the base-case analysis.
410 However, our results confirmed that the implementation of AI did not impair clinical
411 effectiveness. Cost effectiveness can be expected to improve depending on progress in the
412 implementation costs of AI.

413 In the OCT analysis, both clinical-effectiveness and cost-effectiveness were
414 comparable to those of the base-case analysis. Although OCT increases the accuracy of
415 screening [21, 22], the degree of improvement did not extend to a recommendation for
416 additional screening, as patients were more likely to be medically managed at the early AMD
417 stage in periodically repeated screening.

418 The 163 patterns of SA results with 40 varying parameters cover a wide range,
419 indicating that the choice of the program has a significant impact on blindness prevention and
420 cost-effectiveness. Younger age at the start and end of screening resulted in lower ICERs,

421 whereas blindness prevention proportion was highly correlated with the cumulative number of
422 screenings and was not affected by other factors. This indicates that screening can be both
423 clinically effective and cost-effective if it is started early and conducted frequently. Although
424 some of the simulated programs in SA were more cost-effective than the base case, it would be
425 practical and realistic to focus on adding a simultaneous ophthalmologic screening program to
426 “the specific health check-ups” as a base case [57].

427 In the current study, the cost effectiveness of screening for AMD was also beyond the
428 WTP; however, the ICER was significantly improved compared to that in the previous report
429 [11]. If the high efficacy of the new drugs is confirmed, costs are reduced, and the efficiency of
430 screening, including AI, is improved, it will be realistic to expect that cost effectiveness of the
431 screening of AMD alone will be lower than the WTP in future re-assessments. In particular, it
432 may be effective to consider customized implementations, such as increasing the weight of the
433 screening program for younger people in “the specific health check-ups”, since the cost
434 effectiveness of screening was better when it was started early and conducted frequently.
435 Furthermore, we would like to realize an integrated model by combining models for other major
436 diseases such as cataract, diabetic retinopathy, glaucoma, and degenerative myopia, which are
437 being investigated separately.

438 Continued smoking cessation was also considered as one of the important factors to

439 achieve cost-effectiveness in the AMD screening program. In this study, we combined several broad
440 assumptions but did not obtain robust results. However, it was hypothesized that the ICER would
441 be under the WTP, especially if a relatively higher retention rate than the current situation of 30%
442 smoking cessation could be achieved. In general, the effect of smoking cessation measures on health
443 care costs was reported to have a decreasing effect in the short term, but an increasing effect in the
444 long term [58] [59] . Although improvement in the effectiveness of smoking cessation following
445 smoking cessation guidance is expected, it is necessary to evaluate the cost-effectiveness of
446 AMD screening carefully, keeping these general principles in mind.

447 We implemented the current study with long-term real-world data, mainly of
448 aflibercept, from the perspective of comprehensive management for AMD. As a result, we have
449 improved many of the problematic issues of the previous study. Nevertheless, several
450 limitations should be noted. First, speculation on parameters lacking in evidence is needed, such
451 as utility when the state differs in two eyes, the proportion of patients dropping out of treatment,
452 the effectiveness and intake rates of supplements, and rates and costs of detailed examinations
453 or subsequent periodic examination. Regarding these parameters, relatively wider sensitive
454 analyses were used to compensate for the lack of evidence. We were, fortunately, able to
455 confirm that the base-case analysis was not far out of the focus because the impact of these
456 parameters on the results was limited. There still remains, however, a need to reevaluate the

results with more accurate parameters that will be reported in the future. Second, we could not include promising drugs such as brolucizumab in the model due to the lack of reported evidence since they are still in the early stages of real practice. Finally, we could not set the cost change when implementing AI and had to assume no change in cost. Expectations are increasing for the implementation of AI to both reduce costs and maintain high accuracy. However, due to the lack of sufficient evidence, it had to be assumed that there would be no cost reduction effect and that it was not cost-effective. Since these are all expected to improve further with the accumulation of evidence, re-assessment of the cost-effectiveness of ophthalmologic screening programs is needed in the future.

In conclusion, we evaluated the clinical effectiveness and cost-effectiveness of ophthalmologic screening for AMD in adults using a Markov model based on real-world data from Japan. The current study indicates that the screening program is highly effective in preventing blindness (clinically effective) but not cost-effective from a value-for-money perspective. The early start and frequent conduction of the screening program might lead to improvements in both perspectives.

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476 **Author contributions**

477 Data collection: HT, AY

478 Writing of the article: HT, AY, AK, MM

479 Critical revision of the article: YH, RK, RG, MY

480 Final approval of the article: HT, AY, YH, RK, AK, MM, RG, MY

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632

Tables

Table 1. Parameter values used in the Markov model with ranges used for univariate sensitivity analysis.

Model parameters group	Model parameters	Classification	Base-case value	Range for univariate sensitivity analysis	References
Probability of initial state					
	Aged 40 years	Normal	96.15%	-	[26]
		Unilateral early AMD	3.85%	±50%	[26]
	Age to terminate model		90 years	-	
	Age to start screening		40 years	40, 50, 60, 70 years	
	Age to end screening		74 years	60, 70, 80, 90 years	
	Interval between screenings		5 years	1–10 years	
Transition probabilities					
	Normal →early AMD	Age 40 years	0.181%	±50%	[26]
		Age 55 years	0.422%	±50%	[26]
	Early AMD → moderate AMD	Age 40 years	0.50%	±50%	
		Age 50 years	0.50%	±50%	[32]
	Early AMD → moderate AMD (second eye)		5.36%	±50%	[30]
	Moderate AMD → severe AMD		76.92%	±50%	[28]
	Severe AMD → blindness		18.52%	±50%	[28]
Epidemiology					
	Mortality rate		Census of 2017		[33]
Rates in screening					

	Participation rate for Screening				
		Screening	50.00%	30.00%–100.00%	[40]
		Detailed examination	60.00%	30.00%–100.00%	
		Occasional (irregular) screening	20.00%	10.00%–50.00%	
	Incidence rate of presbyopia		3.00%	±50%	[39]
	Prevalence of presbyopia	Early/ Late AMD	20.00%	-	
		Severe AMD	20.00% (in year 1 of stage change)	20.00% (between years 1 and 3 of stage change)	
	Consultation rate due to subjective severity	Severe AMD → blindness	100.00%	-	
	Detection rate in screening				
		Sensitivity	80%	60%–100%	
		Specificity	95%	80%–100%	
Utility		better eye/worse eye			
	Normal	Normal/normal	1.00	-	
		Normal/early	1.00	-	
		Normal/moderate	0.8265	-	
		Normal/severe	0.79675	-	
		Normal/blindness	0.767	-	
	Prodromal	Early/early	0.97	±30%	
		Early/moderate	0.8115	-	
		Early/severe	0.78175	-	
		Early/blindness	0.752	-	
	Moderate AMD	Moderate/moderate	0.653	±30%	[42]
		Moderate/severe	0.62325	-	
		Moderate/blindness	0.5935	-	
	Severe AMD	Sever/severe	0.5935	±30%	[42]
		Sever/blindness	0.56375	-	
	Blindness	Blindness/blindness	0.534	±30%	[42]

Cost				
	Screening	2,000 JPY	±50%	
	Detailed examination	14,160 JPY	±50%	*
	Observation: periodical examination	5,660 JPY	±50%	**
	Supplements (1 year)	54,432 JPY	±50%	
	Aflibercept (each time for one eye)	137,292 JPY	±50%	
	Endophthalmitis	1,052,750 JPY	±50%	
Discount rate		2.00%	0.00%–4.00%	[45]
Treatments (noninvasive)				
	For prodromal (supplements)			
	Intake rate	56.6%	25%–100%	[35]
	Rate of continuation of supplement intake each year	90%	50%–100%	
	Rate of suppression of AMD	25%	±50%	[36]
	Number of observations per year	4	2–6	
	For Blindness (only observation)			
	Number of observations per year	12	6–12	

636 AMD (age-related macular degeneration)

637 *The detailed examination cost was calculated by summing the following fee schedules in
638 Japanese social health insurance as of 2020: initial consultation (A000), slit lamp examination
639 (D257), fundus examination (D255), visual acuity tests (D263), refraction tests (D261),
640 measurement of corneal radius of curvature (D265), measurement of intraocular pressure

641 (D264), optical coherence tomography (D256-2), and fluorescein fundus angiography (D256
642 2).

643 **The observation cost was calculated by summing the following fee schedules in Japanese
644 social health insurance as of 2020: subsequent consultation (A001), slit lamp examination
645 (D257), fundus examination (D255), visual acuity tests (D263), and optical coherence
646 tomography (D256-2).

647

648 **Table 2. Parameter values regarding treatments used in the Markov model with ranges
649 used for univariate sensitivity analysis.**

Model parameters	Classification	Base-case value	Range for univariate sensitivity analysis	References
Number of observations per year		12	6–12	
Proportion of Aflibercept as initial treatment		100%		
Number of injections per year	1st year	7	3-12	
	After 2nd year	3	1–5	[14]
Positive state transition during treatment	Severe AMD →moderate AMD	21.9%	±50%	[14]
Negative state transition during treatment	Moderate AMD → severe AMD	1.40%	±50%	[14]
	Severe AMD → blindness	1.40%	±50%	[14]
State transition to stable state	1st year	0%	±50%	
	After 2nd year	20%	±50%	[14]
Sensor before treatment	Moderate/severe AMD	5%	±50%	
Sensor during treatment	Moderate/severe AMD	0%		
Incident rate of Endophthalmitis		0.03%	±50%	[38]

per injection

650 AMD (age-related macular degeneration)

651

652 **Table 3. Base-case cost-utility analysis in a simulated population**

	With screening	Without screening	Difference between 'with screening' and 'without screening'
Number of blindness in 500,000 simulated cohort	48	81	33
Proportion of prevented blindness	-	-	40.7%
Number of people detected to have late AMD	14,329	14,600	271
Number of people detected to have AMD	64,305	19,198	45,107
Detected in screening	51,063	-	51,063
Detected in coincidental consultation	7,237	10,704	3,467
Detected in spontaneous consultation due to subjective severity	6,005	8,494	2,489
Duration of blindness [years]	7.3	9.9	2.6
Cost per person [JPY]	118,063	54,761	63,303
QALY per person	28.3734	28.3670	0.0064
ICER [JPY/QALY]	-	-	9,846,411

653 AMD (age-related macular degeneration); QALY (quality-adjusted life year); ICER (incremental cost-effectiveness ratio)

654

655 **Figure Legends**

656 **Fig. 1. Basic concepts of state transition in Markov models for AMD**

657 In the current study, age-related macular degeneration (AMD) was assumed to develop from a
658 normal eye via early to late AMD. Late AMD is categorized into three stages: moderate AMD,
659 severe AMD, and blindness. All patients were assumed to die equally according to the mortality
660 rate of their age from any state. In the stable state, no additional injections with aflibercept were
661 assumed. In each cycle, evaluated annually, each patient's disease condition was rated as
662 aggravated, maintained, or improved using transition probabilities, according to the reported
663 real-world data in Japan.

664

665 **Fig. 2. Tornado diagram showing one-way sensitivity analysis targeting cost-effectiveness**
666 **of the ophthalmologic screening program for AMD as the outcome.**

667 The top 10 most influential parameters among all 40 parameters in the one-way sensitivity
668 analysis are shown. The most influential parameter in the model was the utility value of the
669 blindness state, and the 2nd most influential parameter was the utility value of moderate late
670 AMD, where utility values were found to have a significant impact on the model.

671

672 **Fig. 3. The transition in the proportion of blindness from age-related macular**

673 **degeneration, by age.**

674 The transition of in proportion blindness in the screening and non-screening groups with and
675 without supplementation treatment are described. Screening interventions reduced the
676 proportion of blindness by 40.7%. The reduction effect of blindness was 56.9% after controlling
677 for age.

Online Resource 1

Real-world effectiveness of screening programs for age-related macular degeneration: amended Japanese specific health checkups and augmented screening programs with OCT or AI

Supplementary Tables

Supplementary Table 1. Results of the scenario analysis for screening sensitivity and specificity with optical coherence tomography or artificial intelligence.

	Blindness prevention proportion [%]	ICER [JPY/QALY]
The base-case: fundus photographs interpreted by ophthalmologist	40.7	9,846,411
With OCT interpreted by ophthalmologist	43.2	10,483,508
Fundus photographs interpreted with AI	34.6	10,524,003
With OCT interpreted by AI	40.7	10,213,863

QALY (quality-adjusted life year), ICER (incremental cost-effectiveness ratio), OCT (optical coherence tomography), AI (artificial intelligence)

Supplementary Table 2. Results of scenario analysis in smoking cessation after AMD detection.

Proportion of smoking cessation in smokers after AMD detection	Blindness prevention proportion [%]	ICER [JPY/QALY]	Inhibition of late AMD development [%]	Delay in late AMD development [years]
The base-case:0%	40.7	9,846,411	1.9	0.19
10% of smokers	42.0	8,281,963	2.4	0.24

20% of smokers	41.6	6,012,733	2.8	0.23
30% of smokers	41.6	4,655,601	3.0	0.24

AMD (age-related macular degeneration); QALY (quality-adjusted life year); ICER (incremental cost-effectiveness ratio),

Supplementary Table 3. Results of scenario analysis in ophthalmologic screening schedule and cycle.

	Blindness prevention proportion [%]	ICER [JPY/QALY]	Age to start screening [y.o.]	Age to end screening [y.o.]	Interval between screening [years]
The base-case	40.7	9,846,411	40	74	5
The highest blindness prevention proportion	81.5	11,622,009	40	90	1
The lowest blindness prevention proportion	-1.2	5,653,116	40	50	7
The highest ICER	27.2	18,051,627	70	90	1
The lowest ICER	3.7	5,368,641	40	50	9

QALY (quality-adjusted life year); ICER (incremental cost-effectiveness ratio)