Andrew G. Lee, MD; Anne Louise Coleman, MD, PhD*

The aging of the baby boomers has created a dramatic demographic shift toward an older population in the United States. The health care needs of this aging population will impact ophthalmology disproportionately. ¹ Although ophthalmologists are accustomed to caring for elderly patients, they may not be familiar with some of the issues associated with visual loss in the geriatric population. Traditional clinical measures of visual function (eg, Snellen acuity, perimetry) are not adequate to determine the functional impact of visual impairment or the satisfaction or dissatisfaction with therapy of older patients. ^{1–33} Most ophthalmologists recognize that with age, visual impairment and blinding disorders occur with increasing frequency. ^{34–56} However, they should also recognize that poor visual function affects other quality-of-life parameters, including disability, ^{11,32,57} falls and fractures, ^{58–75} activities of daily living (ADLs) and independence, ^{76–84} use of community support services, sense of well-being, ^{85–87} and mortality. ⁸⁸

This chapter reviews the available pertinent literature in geriatric ophthalmology, identifies gaps in the current knowledge base, and provides a needs assessment that is the basis for the recommended research agenda.

METHODS

Two searches were conducted on this topic, both on the National Library of Medicine's PubMed database. The time period covered was from 1980 through March 2, 2001. The first search strategy combined terms for ophthalmologic surgical procedures or low vision with terms for risk factors, age factors, postoperative complications, or outcomes. This search generated 2235 references, but only a sampling of the most current 300 were sent to the authors. The second search combined terms for vision disorders or eye diseases with terms for functional status or ADLs. This search resulted in 779 references, all of which were sent to the authors. The titles were reviewed for topicality, currency, and appropriateness. Relevant full articles were retrieved from the refined list. Papers that addressed the following issues were identified:

- age as a risk factor for ophthalmic diseases;
- age as a prognostic indicator for treatment outcome;
- age-related risk factors for poor outcomes, including comorbidity, functional status, cognitive impairment, emotional status, self-assessed heath, socioeconomic level, and social support;

^{*} Lee: Associate Professor of Ophthalmology, Neurology, and Neurosurgery, University of Iowa Hospitals and Clinics, Iowa City, IA; Coleman: Professor of Ophthalmology, Jules Stein Eye Institute, University of California, Los Angeles, CA.

Acknowledgment: This work was reviewed by the American Academy of Ophthalmology, Committee on Aging and the Inter-specialty Education Committee.

- the impact of vision on positive and negative outcomes, eg, hospitalization, length of stay, delirium, falls, and depression;
- specific diseases or surgical procedures or risks in elderly adults.

Case reports and letters were excluded unless they added significant information. Pre-1990 articles were included only if they added significant historical or other information.

In the discussion that follows, we give particular emphasis to randomized clinical trials, when available, and to meta-analyses of such trials. We also highlight the four ocular pathologies that have the highest impact and highest incidence among elderly people: cataract, glaucoma, age-related macular degeneration or ARMD, and diabetic retinopathy. The focus is on the research regarding geriatric issues specific to these disorders.

ASSESSING VISUAL LOSS IN AGE

SCOPE OF THE PROBLEM

Ophthalmologists are aware that visual loss is common in the elderly population and that the incidence rates of blinding disorders (eg, cataract, ARMD, glaucoma, and diabetic retinopathy) increase with increasing age. ^{34–56} Visual impairment defined by Snellen acuity worse than 20/40 occurs in as many as 21% of persons aged 75 years or older. The Salisbury Eye Evaluation (SEE) project, which studied 2520 individuals aged 65 to 84, found the prevalence of visual acuity worse than 20/40 but better than 20/200 to be 11.4% in the white Americans and 16.4% in the black Americans studied. ³³ The Beaver Dam Eye Study, which examined 4926 persons aged 43 to 86 years, found that a best-corrected visual acuity worse than 20/40 occurred in 21.1% of those aged 75 years and older, in 5.0% of those between 64 and 74, in 0.9% of those between 55 and 64, and in 0.8% of those between 43 and 54. ^{7,49–51} Female gender was found to be an independent predictor of poor visual acuity. The Melbourne (Australia) Visual Impairment Project reported visual acuity less than 20/60 in 1.34% of 3271 persons. Of those with visual impairment, 89% were 60 years or older, and in the multiple regression analysis, age was found to be the only significant predictor of visual impairment. ⁸⁹

MEASURES AND LEVELS OF VISUAL LOSS

Although Snellen testing is the standard measure of visual acuity in most ophthalmology clinics, there are other quantitative measures of visual acuity. In the Snellen system, letter size is defined as the distance at which the overall letter height subtends 5 minutes of arc. Snellen acuity can be converted to decimal acuity. Visual acuity can be specified in terms of minimum angle of resolution (MAR), calculated by dividing the letter size by the test distance. A derivative of MAR is the logarithm of MAR (logMAR). Other non-Snellen measures include the Bailey-Lovie logMAR chart and the early treatment diabetic retinopathy study (ETDRS) chart.² Many ophthalmologic clinical trials have adopted these non-Snellen measures of acuity because they can provide more quantitative and comparative data in studies of visual function.

The Snellen measure of visual acuity has also been used to define levels of visual impairment, blindness, and low vision. *Visual impairment* is usually defined as best-cor-

rected Snellen visual acuity worse than 20/40 but better than 20/200. *Legal blindness* is defined as best-corrected visual acuity of 20/200 or worse or a visual field diameter less than 10 degrees. *Low vision* is defined as visual acuity less than 20/60 in the better eye. ^{3–5}

MEASURING IMPACT OF LOSS ON VISUAL FUNCTION

The most common causes of visual impairment in elderly persons are age-related cataract, ARMD, glaucoma, and diabetic retinopathy. Of all persons aged 75 years and over, 52% have advanced cataracts, 6,7 25% have nonexudative ARMD, 5% have exudative ARMD, and 2% to 10% have glaucoma. $^{6-8}$ Many studies have devised measures of functional outcome following cataract extraction. $^{9-30}$ Although the standard measure of visual function in eye research has been Snellen visual acuity, other non-Snellen measures of visual function may be more important in determining the functional impact of visual loss in elderly persons.

Rumsey correlated visual complaints with objective visual tests in 50 older adults and in 20 middle-aged adults and found that decrements in visual acuity, decreased contrast sensitivity, increased glare sensitivity, diminished color vision, and loss of stereopsis were all more apparent in the older group. ³¹ These results indicate that answers to task-specific questions may provide greater insight into older adults' visual performance in their normal environment than simple measurement of Snellen visual acuity alone can provide.

Using a visual-functioning index (VF-7), Uusitalo et al measured functional impairment in 168 patients with cataracts. ³⁰ The functional items were nighttime driving; reading small print; watching television; seeing steps, stairs, or curbs; reading traffic, street, or store signs; cooking; and doing fine handwork. The correlation among changes in the VF-7 score and visual acuity in the operated eye was 0.17. The correlation between changes in the VF-7 and patient satisfaction after cataract surgery was high (r = 0.56), and the VF-7 was a strong predictor of patient satisfaction after cataract surgery. Improved Snellen acuity has been the traditional outcome measure for successful cataract surgery, but these researchers' findings support the use of measures of postoperative functional outcomes and of patient satisfaction.

Rubin et al described the correlation between psychophysical measures of visual impairment and self-reported difficulty with everyday visual tasks in a population-based sample of persons aged 65 years and older. ^{32,33} Visual acuity, contrast and glare sensitivity, stereoacuity, and visual fields were found to be significant independent risk factors for self-reported visual disability. Visual impairment defined by Snellen acuity alone was not the only association with subjective disability, and additional vision measures were recommended to better understand the functional impact of vision loss.

MEASURING IMPACT OF LOSS ON FUNCTIONAL ABILITY

In a study of 1210 community-dwelling women aged 75 years and older that compared women with low visual acuity or low contrast sensitivity and women with good vision, the women with poor vision were found to be significantly more likely to be physically dependent.⁹⁰ The researchers concluded that testing contrast sensitivity in addition to Snellen acuity would allow better prediction of impairment in ADLs. McClure et al demonstrated that specific levels of objective vision loss measured by acuity, reading index,

and contrast sensitivity corresponds with subjective functional difficulty in the performance of daily living tasks.⁹¹

Assessment instruments that provide more information about visual function than the standard Snellen acuity testing can provide have been developed. For example, a health-related quality-of-life (HRQOL) instrument measures the ability to engage in ADLs (eg, self-care, driving, working) and the self-perception of well-being (eg, pain, energy, and self-image). The Medical Outcomes Study Short Form 36-item health survey (SF-36) is the most widely used HRQOL instrument. The SF-36 measures eight aspects of HRQOL, including general health perceptions, physical functioning, role limitations, bodily pain, mental functioning (eg, mental health, energy or fatigue), and emotional function (eg, role limitations, social functioning).⁹² Targeted HRQOL measures specific for ocular diseases have been developed. These include the Visual Functioning Scale (VF-14), which measures the person's ability to perform 14 vision-dependent activities. The Activities of Daily Vision Scale (ADVS), developed for evaluating cataracts, rates difficulty with 20 common visual activities (eg driving at night, reading newsprint, reading labels). The National Eye Institute Visual Functioning Questionnaire (NEI-VFQ) was developed to assess functional impairment in eye disorders and is similar to the ADVS in content. This instrument is a 25-item questionnaire that includes items for distance and near vision, eye pain, driving, emotional well-being, social and role functioning, and dependency. These instruments define overall functioning in patients with ocular disease, and assessments of treatment outcome should include at least one of them. 17,18,93,94

Some researchers have used these instruments to measure the impact of vision loss on function. Mangione et al reported that NEI-VFQ scores were the lowest for 90 persons with low vision and 108 with ARMD.⁹³ The median Snellen binocular visual acuity in those with low vision was 20/252 and in those with ARMD was 20/63. The scores for vision-specific difficulties, dependency, social function, and mental health were lowest in the low-vision group. Visual impairment was found to be associated with decreased overall function. Scott et al studied 156 low-vision patients using the NEI-VFQ, VF-14, and the SF-36.⁹⁵ These researchers found that patients' scores on four subscales of the NEI-VFQ improved after low-vision aids were prescribed and refractive error was corrected. Although the SF-36 was unchanged, the VF-14 score improved after treatment. Many researchers have suggested that at least one of the functional outcome tools (eg, NEI-VFQ, SF-36, VF-14) should be included in studies of visual intervention or treatment. ^{93,94,96–102}

Ophth 1 (Level B): Future research in the treatment of ocular disease in the older person or rehabilitation for older persons with low vision should, wherever possible, make use of tools for assessing functional outcomes.

VISUAL LOSS AND SPECIFIC GERIATRIC CONDITIONS

VISUAL LOSS AND FALLS

Falls are a common cause of morbidity and mortality in the elderly population. Each year approximately 25% to 35% of older persons fall, ^{64,73,74} and each year up to 7% of pa-

tients aged 75 and older require an emergency room visit after a fall. ^{58–75} Falls by elderly persons can be devastating, and more than 40% result in hospitalization. ^{67,68}

Studies have established that poor vision is a risk factor for falls. ^{6,58–74} Nevitt et al reported a threefold risk for multiple falls with poor vision. ⁶⁴ Decreased contrast sensitivity and poor depth perception are associated with an increased risk of falls and hip fractures, ⁵⁸ and impaired visual acuity is associated with an increased risk of wrist and humerus fractures. ⁶⁰ The Beaver Dam Eye Study found that 11% (943) of 2365 persons aged 60 years or older with acuity less than 20/25 but only 4.4% of those with normal visual acuity had experienced a fall in the prior year. ⁶

- *Ophth 2 (Level A)*: Elderly patients with visual impairment treated with low-vision rehabilitation or whose vision has improved following a specific intervention (eg, cataract surgery, refraction) should be compared with an untreated group or a treated group without visual improvement. The change in incidence of falls over time in the two groups should be prospectively studied.
- *Ophth 3 (Level B)*: Cross-sectional or prospective cohort studies should be performed to determine if certain ocular disorders are more or less likely to be associated with falls by elderly persons and whether multiple ocular disorders are synergistic or additive risk factors.
- *Ophth 4 (Level B)*: Time-series studies of correlations between level of visual function and likelihood of falls should be carried out in cohort studies.

Since visual impairment increases the risk of falls, elderly patients with known visual impairment should have access to services to make their home environment safer. Oph-thalmologists should be aware of these measures, including:

- increasing lighting and decreasing glare;
- increasing contrast at danger areas such as corners and on stair steps;
- removing floor obstacles, minimizing clutter, and reducing floor hazards (eg, anchoring loose rugs and eliminating uneven surfaces);
- utilizing well-designed hand rails and assistive furnishings (eg, use of non-skid flooring);
- using appropriate walking devices (stable walker and cane types);
- avoiding improper footwear (eg, high-heeled shoes).¹⁶
 - *Ophth 5 (Levels B, A)*: Prospective interventional studies are needed to establish whether interventions to reduce environmental hazards are cost-effective and practical. Prospective interventional randomized or nonrandomized studies should be performed to determine if the incidence of falls in older patients with visual impairment decreases among those for whom home safety improvements are performed.

VISUAL LOSS AND HEARING LOSS

In elderly persons, visual impairment commonly occurs with other impairments. For example, visual and hearing loss may both occur in the same patient, and the presence of both sensory impairments increases their functional impact. Appollonio et al demonstrated the predictive value of hearing and visual impairments for mortality in 1140 noninstitutionalized elderly persons.³⁸ Keller et al in a prospective study of 576 older persons demonstrated that visual and auditory impairment impacts functional status, and that combined vision and hearing impairments have a greater effect on function than do single sensory impairments. Moreover, they found that these two sensory impairments, hearing and visual loss, influence functional status independently of mental status and comorbid illness.⁸³ Klein et al in the Beaver Dam Study documented the common coexistence of ARMD and hearing loss.¹⁰³ Multiple studies have demonstrated that hearing loss and visual loss are interrelated deficits that may increase the functional impact of either sensory deficit alone.^{103–107} Overall, these results suggest that interventions to improve sensory function may improve functional independence as well.

- *Ophth 6 (Level B)*: Research is needed to quantify the effect of multisensory loss in elderly patients (eg, hearing and vision) on functional outcomes. Observational cohort studies should be performed to determine which ocular disorders (eg, age-related macular degeneration, cataract glaucoma) are more likely to be associated with hearing loss and whether or not these ocular disorders have an additive or synergistic effect on functional outcome.
- *Ophth 7 (Level A)*: Prospective, focused cohort studies with appropriate comparison groups or nonrandomizd controlled trials of interventions for multisensory loss, including visual or hearing rehabilitation, should be performed to test for improved functional outcomes.

VISUAL LOSS AND DEPRESSION

Visual disability can cause secondary grief, anxiety, and depressed mood. These nonvisual consequences of visual impairment can worsen or precipitate clinical depression in the elderly person. Appollonio et al showed that an uncorrected sensory deprivation is associated with a significant and independent impairment of mood, decreased self-sufficiency in instrumental ADLs, and impaired social relationships. ¹⁰⁸ In men with uncorrected sensory impairment, the unadjusted 6-year mortality rate was found to be almost twice that of the other two study groups. Rovner et al reported a correlation between disability, depression, and impaired vision in a small sample of community-dwelling older persons. ¹⁰⁹ Rovner and Ganguli further assessed the relationship of depression, impaired vision, and disability in a later study of 872 noninstitutionalized older patients. ¹¹⁰ They found impaired vision and depression both to be associated strongly with functional impairment and concluded that treating depression might reduce excess disability associated with impaired vision. Carabellese studied vision and depression in 1191 noninstitutionalized persons aged 70 to 75 years and found that visual impairment is significantly and independently associated with an increased risk for depression, decreased self-sufficiency in ADLs, and impaired social relationships.⁸⁰

- *Ophth 8 (Level B)*: Research is needed to establish what types and what level of visual impairment might be associated with clinical depression in elderly patients. Observational cohort studies should be performed to determine the interaction of visual impairment and depression on the health-related quality of life or other studies of function in older persons.
- *Ophth 9 (Level B)*: Interventional studies of the evaluation and treatment of depression in older patients with visual impairment should be performed to determine the best timing for intervention.
- *Ophth 10 (Level A)*: Interventional studies of the effect in elderly patients of specific treatments of visual loss on depression should be performed to determine if improvement in the vision-related depression might lead to improved health-related quality of life and overall functioning.

VISUAL LOSS AND DEMENTIA

Visual loss is associated with and may worsen dementia or delirium. ^{111–113} Uhlman et al studied 87 older patients with mild-to-moderate Alzheimer's disease and 87 nondemented age- and sex-matched control patients. ¹¹¹ The researchers found the prevalence of visual impairment to be higher in cases than in controls and visual impairment to be associated with both an increased risk for and an increased clinical severity of Alzheimer's disease. The increased risk of dementia in the existing cohort studies for Alzheimer's disease did not demonstrate a progressive dose-response relationship, and a cohort study alone does not establish a cause-and-effect relation.

- *Ophth 11 (Level B)*: Observational cohort studies should be performed to determine if there is any association between type or severity of visual loss and the major causes of dementia (eg, Alzheimer's disease, multi-infarct dementia).
- *Ophth 12 (Level B)*: Large population studies should be performed to determine if dementia and visual loss are associated in elderly persons and if the association is independent of other important variables (eg, age could explain the entire association).
- *Ophth 13 (Level A)*: If an association between dementia and visual loss is found (Ophth 12), especially a severity-related one, then interventional studies should be performed to determine if improvement or stabilization of vision might reduce the incidence or severity of dementia in older persons.
- *Ophth 14 (Level A)*: In elderly patients with visual loss and dementia, the type and timing of specific interventions should be compared to determine the most effective for improving visual function that leads to improved health-related quality of life or overall functioning.

VISUAL LOSS AND OVERALL FUNCTION

Several population-based studies have shown an association between visual impairment and overall function. In Established Populations for the Epidemiologic Studies of the Elderly, a population-based study of 5143 elderly persons, 26% of 577 individuals with limitation in ADLs were found to be visually impaired. ¹¹⁴ The Massachusetts Health Care Panel Study of noninstitutionalized elderly persons reported 289 with good vision and 207 with self-perceived visual impairment.⁷⁹ The poor-vision group was 2.3 times more likely than the group with good vision to need help grocery shopping and 1.68 times more likely to need help paying bills. In the Salisbury Eye Evaluation project, researchers found visual impairment to be an important predictor of lack of social or religious activities. ¹¹⁵ They also found visual loss to be associated with 1.82 times greater odds of significant difficulty on any ADL and to be associated with 2.45 greater odds of significant difficulty on any instrumental ADL. The Blue Mountains Eye Study found that visual impairment affects the independence of elderly persons, especially women. 77,78 Visually impaired individuals were found to be more likely to rely on community support services, more likely to rely on regular help for cleaning or shopping, and five times more likely to be unable to go out alone.

Marx et al surveyed 103 nursing-home residents for ADL function and found a strong link between low vision and ADL disability; they also found that residents' ADL dependency was significantly related to the presence of eye disorders. ¹¹⁶ Pillar et al evaluated hospitalized elderly blind patients with motor impairments admitted for physical rehabilitation and found functional independence to be less common in these patients than in those who were visually intact. ¹¹⁷ Maino reported that visually impaired elders are much more likely than their normal-sighted peers to have mobility restrictions. ¹¹⁸ Older persons with visual impairment were found to be three to four times more likely to have difficulty walking, going outside, and getting in and out of bed. These and other studies have shown that there is a relationship between visual impairment and loss of independence. ^{117–130} Research is now needed to determine if there is a relationship between the type and severity of visual loss and loss of overall function.

- *Ophth 15 (Level B)*: Single-time observational or time-series observational studies should be performed in elderly patients to determine the relationship between loss of independence or decreases in measures of overall function and the type (eg, cataract, glaucoma), timing of onset (eg, early or late), and severity of loss of vision.
- *Ophth 16 (Level A)*: Interventional studies should be performed to determine whether stabilization or improvement in vision or visual function (eg, with low-vision rehabilitation) in elderly patients leads to increased independence and improved overall functioning.

VISUAL LOSS AND DRIVING IMPAIRMENT

Visual loss impairs the older person's ability to drive. ^{7,20,131–136} As people age, visual functions such as acuity, visual field, and night vision deteriorate. This decline in vision is associated in part with the elderly age group's increase in vehicular accidents per mile driven. Kosnik et al showed that older persons who have recently given up driving report more visual problems than do their driving counterparts. ¹³¹ These researchers found driv-

ing problems to be related not only to decreased Snellen acuity but also to difficulties in dynamic vision, visual processing speed, visual search, light sensitivity, and near vision. Ball et al examined the association between visual impairment in 257 older drivers and the avoidance of challenging driving situations; they found that drivers with visual impairment report more avoidance behavior than do visually normal drivers.¹³³

There is a need for evidence of a significant predictive relationship between changes in vision function and automobile crashes. ¹³⁶ Although most states require vision screening for driver's license renewal, some do not. Among those states requiring vision screening, there is considerable variation in the frequency and level of testing. Efforts to determine the role of vision in driving, though suggestive, have not been useful in identifying at-risk older drivers. Researchers have observed that older drivers are often aware of their decreased functional capacity and voluntarily adjust their driving patterns by driving less frequently, for shorter distances, during daylight hours, more slowly, and during non-rush hours. Although not statistically significant, the decline in annual traffic fatality rates with increased state vision screening requirements suggests a possible beneficial effect of vision screening.

Ophth 17 (Level B): Single-time or time-series observational studies are needed to determine if mandatory vision screening of elderly drivers appears beneficial in decreasing or preventing traffic accidents.

Ophth 18 (Level A): Interventional cohort studies should be performed to determine whether improvement in vision decreases the frequency and severity of traffic accidents by elderly drivers.

Traditional measures of visual screening for driving ability (eg, Snellen acuity and perimetry) may not be sufficient to assess the elderly driver's predilection for traffic accidents. The useful field of view is one functional measure of visual field that correlates with driving ability and may be predictive of future vehicular accidents. Owsley et al in a comparison of 279 older adults with cataract and 105 patients without cataract showed that cataract adversely affects driving ability.²⁰ As with previous studies of elderly drivers with visual impairment, these patients were found to be avoiding potentially dangerous or challenging driving situations. The drivers with cataract were twice as likely to report reductions in days driven and number of destinations per week, driving slower than the general traffic flow, and preferring someone else to drive. They were five times more likely to have received advice about limiting their driving, four times more likely to report difficulty with challenging driving situations, and two times more likely to reduce their driving exposure. Cataract patients were also found to be 2.5 times more likely to have had an at-fault crash in the prior 5 years. McGwin et al found that impairment of useful field of view is associated with both self-reported and state-recorded car accidents; glaucoma was identified as a significant risk factor for state-recorded crashes.¹³⁴ Kline et al reported age-related visual problems that are related to types of automobile accidents more common among older drivers. ¹³² Although central visual loss and impaired driving have been well studied, peripheral vision loss also appears to be associated with impaired driving. There is a need to define the types and extent of peripheral vision loss that might impair driving.

Ophth 19 (Level B): Single-time or cross-sectional observational studies of a suitable cohort are needed to determine whether there is a relationship between the older person's driving performance and the type, severity, and onset of loss of vision.

- *Ophth 20 (Level B)*: Observational cohort studies should be performed to determine the interaction between visual loss and other comorbidities or risk factors for unsafe driving such as physical impairments, decreased hearing, and decreased cognition.
- *Ophth 21 (Level A)*: Interventional studies of treatments to improve vision or stabilize vision loss in older patients with visual impairment should be performed to determine whether improvement in vision decreases the frequency and severity of traffic accidents among elderly drivers.

VISUAL LOSS AND HOSPITALIZATION

It has been determined that impaired vision contributes to an increase in the average length of hospital stay of elderly patients. One study found that the average length of stay for visually impaired patients was 11.9 days but only 8.2 days for those without visual impairment.¹³⁷ Visually impaired patients also experience more problems after discharge.¹¹⁹ In hospitalized patients, vision impairment was found to be significantly more common among patients with delirium, and those with delirium were found to have increased mortality, institutionalization, and readmission rates after 1 year.¹¹² See also the discussion of delirium in the chapter on cross-cutting issues (Chapter 13).

- *Ophth 22 (Level B)*: Single-time or time-series observational studies are needed to establish the relationship in elderly patients of the type and severity of visual loss to the length of hospital stay and to the incidence and severity of in-hospital comorbidities (eg, delirium and depression).
- *Ophth 23 (Level A)*: Interventional studies of treatments to improve or stabilize vision prior to or during hospitalization should be performed to determine if such treatments decrease the length of hospital stay or reduce the incidence or severity of delirium in hospitalized elderly patients.

COMPREHENSIVE EYE EVALUATION AND SCREENING

Up to 40% of blindness among elderly persons is either preventable or treatable. ¹³⁸ However, no randomized controlled trials or cohort studies have addressed the timing of evaluations for visual impairment or the efficacy of interventions following screening. A meta-analysis of the literature on visual screening of elderly persons revealed no benefit to screening persons aged 65 years and older. ¹³⁹ The American Academy of Ophthalmology (AAO) Preferred Practice Pattern (PPP) for Comprehensive Adult Eye Evaluation nevertheless recommends an eye examination every 1 to 2 years for patients aged 65 years and older. ¹⁴⁰ The U.S. Preventive Services Task Force also recommends screening elderly persons for visual impairment with Snellen visual acuity. ¹⁴¹ These recommendations are

based upon the well-documented high prevalence rate of common and often asymptomatic eye pathology in the elderly age group, including cataract, ARMD, glaucoma, and diabetic retinopathy.¹⁴²

Ariyasu et al studied vision screening in 317 patients and found that near visual acuity of 20/40 or worse and distance visual acuity worse than 20/30 is significantly associated with eye pathology. ¹⁴³ These two vision tests were found to have a sensitivity and specificity of 0.73 to 0.75. The likelihood ratios for pathology were 2.8 for the near vision test and 2.7 for the distance vision test.

- *Ophth 24 (Level B)*: Prospective observational studies are needed to validate the current recommendations for visual screening and to establish the most cost-effective and reliable means for detecting treatable pathology in elderly persons. Prospective costeffectiveness studies of vision screening of elderly populations at risk are needed to establish the efficacy of such programs. Prospective observational studies should define the leading approaches to screening (eg, Snellen testing, J-scale, visual function scales, comprehensive examinations), and comparative studies should be performed to determine cost-effectiveness, validity, reliability, and feasibility.
- *Ophth 25 (Level A)*: Interventional studies should be performed in elderly persons to compare no screening with different screening methods, measuring efficacy on the basis of visual and functional outcome.

IMPORTANT EYE DISORDERS IN GERIATRIC POPULATIONS

CATARACT

Definition and Treatment

Cataract, defined as opacity in the lens, is the leading cause of blindness worldwide. Cataract is present in 14.3% of men and 23.5% of women between the ages of 65 and 74 years. ⁴⁹

No effective medical therapy of cataract exists, but ongoing research studies are addressing the question. Current studies have focused on the indications, techniques, and timing for surgical treatment. Surgical removal of a cataract, however, is not mandated by the mere presence of a lens opacity. The AAO PPP for cataract summarizes the indications for surgery. ¹⁰ Cataract surgery is generally indicated if vision is impaired by cataract, if that vision no longer meets the patient's needs, and if surgery provides a reasonable likelihood of improved visual function. Thus, the need for cataract surgery should be determined primarily by the functional status of the patient, and preoperative assessment should include the needs and preferences of the patient. Other specific indications for surgery are lens-induced disease such as phacomorphic or phacolytic glaucoma and cases when visualization of the fundus is necessary (eg, diabetic retinopathy) for adequate treatment of intraocular pathology.

Cataract Surgery and Functional Decline

There is a demonstrated association between decreased visual acuity from cataract and decreased overall well-being. ^{85,87} Bernth-Petersen interviewed patients with the Visual Function Index before and after cataract extraction and noted that at 1 year after surgery their reading capacity, distance vision, television watching, and other activities had significantly improved. ¹⁴⁴ This was the first study to assess the effect of other eye diseases on the functional outcome after cataract surgery. Applegate et al measured outcome after cataract surgery with multiple vision-specific and generic instruments. In this study, patients' ADLs were not found to have improved. ¹¹

The inability of these early studies to demonstrate improvement in functional status after cataract surgery may have been due to the insensitivity of generic health status instruments to change in vision-specific areas of functional improvement. The subsequent development of the ADVS, which asks persons to rate their difficulty with 20 common visual activities, addresses this problem for researchers interested in measuring visual function. Examples of visual activities included in the ADVS are ability to drive at night and ability to read ordinary newsprint and labels on medications. Open-ended interviews using the ADVS were performed with elderly persons with bilateral cataracts.⁹⁴ Improvements in ADVS scores after cataract extraction have been reported.^{17,18}

Two observational studies of outcome after cataract extraction used standardized questionnaires and reported improvements in vision-targeted functioning and generic health-related quality of life. ^{26,39} Javitt et al reported that 75% to 92% of patients with cataract improved in self-reported visual function after cataract surgery; the percentage who improved depended on whether patients had cataract extraction in their first, second, or both eyes during the period of study. ¹²² A second multicenter study found that 89% of patients reported improvement on the VF-14 after cataract extraction. ²⁵ Even though the ADVS and VF-14 cover similar content, only 77% of the patients in a study by Mangione et al had a positive change on the ADVS. ¹⁸ The proportion of patients who improved in the latter study may have been lower because of greater ocular and medical comorbidity and older age of the patients.

Brenner et al reported a positive correlation between visual function and improvements in mental health, current life satisfaction, and social functioning. ³⁹ Steinberg et al administered the Sickness Impact Profile (SIP), a multidimensional survey designed to measure the behavioral impact of illness, ¹²⁵ to cataract patients. ²⁶ Although 89% had improved vision-targeted VF-14 scores, only 67% had improved SIP scores. Monestam and Wachtmeister found that visual problems while driving declined from 82% preoperatively to 5% after surgery and that problems estimating distance decreased from 37% to 6%. ¹⁹ These researchers assessed the impact of cataract surgery on low-vision patients; 81% reported an improved ability to perform visually demanding tasks after cataract surgery. The number of patients who were unable to read newspaper-size print decreased from 44% to 21% after surgery. Patients with loss of peripheral visual fields also gained orientation ability.

Keeffe et al developed an instrument to describe and quantify handicap caused by vision impairment. ⁸² They used an item pool derived from focus groups and from a review of vision-related quality-of-life questionnaires. They administered the 76-item Impact of Vision Impairment to 95 people and found an association between visual acuity and the type and degree of handicap on subscales. The findings from numerous studies suggest that

there is a functional benefit from cataract extraction: Those with the greatest improvement in visual functional status have less decline in generic health-related quality of life.

- *Ophth 26 (Level A)*: Interventional studies with elderly patients are needed to determine if there are differences in the amount of functional improvement that are based on the timing of cataract surgery, the initial and final visual outcome, whether one or both eyes are operated on, and the age of the patient at the time of the surgery.
- *Ophth 27 (Level B)*: Meta-analyses of existing data from previously performed interventional studies and clinical trials of cataract extraction should be performed to provide age-specific and age-stratified data for the elderly age group and to identify any age-specific differences in functional outcome.

AGE-RELATED MACULAR DEGENERATION

Definition and Treatment

ARMD is defined by the AAO PPP as a disorder of the macular that most often occurs in patients older than 50 years. Of persons aged 75 years and older, 25% have nonexudative ARMD and 5% have exudative. ⁶⁻⁸ ARMD is characterized by the following:

- the presence of drusen;
- retinal pigment epithelial (RPE) hypopigmentation or hyperpigmentation;
- geographic atrophy of the RPE and choriocapillaris;
- exudative neovascular maculopathy with choroidal neovascularization, serous or hemorrhagic detachments of the sensory retina or RPE, hard exudates, and subretinal or sub-RPE fibrovascular proliferation and disciform scar;
- the presence of no other cause for these findings. 34

There is no known effective medical or surgical treatment for the nonexudative form of ARMD. ^{91,145–153} Current research is focusing on the pathogenesis, prevention, and treatment of ARMD. The exudative form of ARMD may benefit from laser therapy to treat the underlying subretinal neovascularization. ^{150–153}

Functional Impairment

Williams et al studied 86 elderly patients with ARMD and legal blindness in at least one eye.¹⁵⁴ Participants completed the Quality of Well-being Scale, the Instrumental Activities of Daily Living index, self-rated general health status questionnaire, and the Profile of Mood States. Persons with ARMD were found to suffer significant emotional distress and profoundly reduced quality of life, and they required assistance with key ADLs.

The effects of ARMD in one eye may affect binocular function. Faubert and Overbury studied 59 older adults with ARMD and found that in almost half the cases spatial contrast sensitivity is worse when both eyes are used together. ¹⁵⁵ "Binocular inhibition" was not found to be related to the contrast sensitivity of the better eye or to visual acuity.

Mangione et al studied 201 RMD patients and found that severity of ARMD is associated with poorer scores on the ADVS and is most significant for near vision and driving.⁵³

Although there are good data on the potential for treating ARMD with laser photocoagulation, data on the visual outcomes from therapy, particularly for subfoveal neovascularization, have been limited. Research on the cause, prevention, and treatment of ARMD is ongoing. Although visual improvement may be limited currently for the treatments for ARMD, visual preservation or stabilization may be helpful.

- *Ophth 28 (Level A)*: Interventional studies are needed to define the efficacy, cost-effectiveness, and functional outcomes of specific treatments for age-related macular degeneration.
- *Ophth 29 (Level A)*: Interventional studies are needed to determine the differences made, if any, by the timing of the treatment of age-related macular degeneration, with results stratified by age of the patient or timing of onset.
- *Ophth 30 (Level B)*: Meta-analyses of existing data from interventional and clinical studies on age-related macular degeneration should be performed to provide age-specific and age-stratified data regarding type, timing of therapy, and visual and functional outcome.
- *Ophth 31 (Level B)*: All interventional studies of age-related macular degeneration should include demonstration of improvement in function as well as in visual acuity.

GLAUCOMA

Definition and Treatment

Glaucoma is a term used to describe a number of disorders that result in optic nerve damage due in part to elevated intra-ocular pressure. ^{35,156} This damage produces gradual and progressive visual field loss. Glaucoma is the third most common cause of visual loss and affects 2.5% of the population aged 40 years or over. The incidence of glaucoma increases with age and disproportionately affects elderly black Americans; 10% of black Americans but only 2% of white Americans have glaucoma. The most common type of glaucoma is primary open-angle glaucoma (POAG).

The AAO PPP defines POAG as a multifactorial optic neuropathy in which there is characteristic acquired loss of retinal ganglion cells and atrophy of the optic nerve. The disease is generally adult onset, chronic, and bilateral but often asymmetric. The angle is open and normal appearing, and there is no secondary cause for glaucoma. There is evidence of progressive optic nerve damage from changes in the optic disc and retinal nerve fiber layer, and visual field defects are characteristic.

There is no cure for POAG. Medical treatment with topical or systemic agents to lower intra-ocular pressure in POAG is the first line of therapy. The AAO PPP for POAG, derived from an expert consensus panel review of the available literature, recommends a 20% reduction in intra-ocular pressure for POAG patients with progressive visual field loss or optic nerve damage.³⁵ The recommended follow-up schedule should be based upon stabilization of intra-ocular pressure within a 3-month maximum, with adjustment of therapy until the target intra-ocular pressure is reached. The goals of medical treatment are

to slow or halt progression of visual loss, to prevent further damage to the optic nerve, and to lower intraocular pressure. Although most patients with POAG have elevated intra-ocular pressure, some do not but still sustain visual loss and optic nerve cupping. This condition is known as *normal* or *low-tension* glaucoma. The Collaborative Normal-Tension Glaucoma Study Group demonstrated in a multicenter randomized controlled trial that treatment of intra-ocular pressure is helpful. This study found a 20% reduction in rate of visual field loss at 3 years and a 40% reduction at 5 years if intra-ocular pressure was reduced by 30% in comparison with untreated eyes. ^{42,43} The AAO PPP recommends that the choice of treatment take into consideration quality of life, patient's physical, visual, medical, psychologic, and social circumstances. ³⁵

POAG patients who fail, are intolerant to, or are nonadherent with medical therapy may require surgical treatment. The goal of surgical therapy in glaucoma is to lower the intra-ocular pressure of an eye. Although surgery may result in lower eye pressures, eyes may continue to have progressive glaucomatous damage after surgery.

Functional Impact

The older person's HRQOL is affected by glaucoma. Sherwood et al reported the negative impact of glaucoma on quality of life.¹²⁸ Wilson et al measured functional status and well-being of glaucoma patients with the SF-36 questionnaire.⁷⁶ Both studies reported lower scores on general health instruments and quality of life in glaucoma patients than in control patients. Parrish et al and Guttierrez et al described decreased scores on the NEI-VFQ, the VF-14, and the ADVS.^{99,121} Scores on the VF-14 and the NEI-VFQ were associated with visual field impairment. ADVS scores were worse in glaucoma patients. All these studies indicate loss of function in multiple domains.

- *Ophth 32 (Level A)*: Interventional studies are needed to determine if the type and timing of treatments of glaucoma alters efficacy and if efficacy in elderly patients improves functional outcome.
- *Ophth 33 (Level A)*: Interventional studies are needed to determine the cost-effectiveness and durability of stabilization or improvement of vision in elderly glaucoma patents.
- *Ophth 34 (Level A)*: Interventional studies should be performed to determine if preventive measures or screening for glaucoma in older persons is effective and improves functional outcome.
- *Ophth 35 (Level B)*: Observational studies are needed to determine if treatment efficacy and functional outcome for glaucoma therapy differ by age.
- *Ophth 36 (Level B)*: Meta-analyses of existing data from interventional and clinical studies on surgical and medical treatment for glaucoma should be performed to provide age-specific and age-stratified data on functional outcome.

DIABETIC RETINOPATHY

Diabetic retinopathy is defined as the retinal changes caused by diabetes mellitus. Diabetes type 1 or 2 may produce diabetic retinopathy, and the incidence of diabetic retinopathy

increases with the duration of systemic disease. There are two types of diabetic retinopathy, nonproliferative and proliferative. The nonproliferative form causes retinal hemorrhages and exudates. Leakage of fluid from microaneurysms may produce visual loss as a consequence of diabetic macular edema. Type 2 diabetes is more likely to have macular edema. The proliferative form occurs as a result of new blood vessel formation (neovascularization) in response to retinal ischemia. These new blood vessels are friable and may bleed, leading to vitreous hemorrhage and secondary visual loss. Traction may develop on the underlying retina and result in a tractional retinal detachment. Neovascularization may develop on the iris or the angle and lead to neovascular glaucoma.

Diabetic retinopathy is the fourth most common cause of visual loss in the elderly age group. ^{44–48,157–159} Good control of blood glucose is important in the treatment and prevention of diabetic retinopathy. In the Diabetes Control and Complications Trial, patients with type 1 diabetes mellitus were randomized to conventional therapy or to intensive therapy with the aim of achieving near-normal blood glucose and glycosylated hemoglobin concentrations. ⁴⁴ An average of 4 years after randomization, the proportion of patients who had worsening retinopathy, including proliferative retinopathy, macular edema, and the need for laser therapy, was lower in the intensive-therapy group than in the conventional-therapy group. Comorbid conditions such as hypertension and hyperlipidemia can worsen diabetic retinopathy and should also be treated. ¹⁵⁹

Multiple studies have demonstrated that laser treatment significantly reduces the incidence and severity of visual loss and blindness due to proliferative diabetic retinopathy and macular edema. ^{44–48} The Diabetic Retinopathy Study showed that laser treatment with panretinal photocoagulation for proliferative diabetic retinopathy reduces blindness by up to 60%. ⁴⁵ Miller et al studied the impact of diabetes on disability and physical functioning in 116 diabetic inner-city black Americans aged 70 years and older and found that impairments in visual function explains part of the association between diabetic status and poor general health, disability, and falls. ¹⁶⁰

- *Ophth* 37 (*Level B*): Observational studies should be performed to determine the functional impact of diabetic retinopathy on the health-related quality of life of older diabetic patients.
- *Ophth 38 (Level A)*: Interventional studies are needed to determine whether specific preventive strategies (eg, tight diabetic control measures or diabetic retinopathy screening programs) and treatment measures improve functional outcomes in older diabetic patients.
- *Ophth 39 (Level B)*: Observational studies are needed to determine if the age of the patient, age at onset of diagnosis, and age at initiation of treatment are important factors in functional outcome in diabetic retinopathy.
- *Ophth 40 (Level B)*: Meta-analyses of data from existing and future interventional studies on the treatment of diabetes, including diabetic control, laser treatment for proliferative diabetic retinopathy

and diabetic macular edema, and surgical treatment, should be performed to provide age-specific and age-stratified data on functional outcome.

LOW VISION

The AAO PPP on low vision defines moderate visual impairment as best corrected vision of less than 20/60 and profound visual loss as less than 20/400 or visual field diameter less than 10 degrees. ³⁶ Low vision is defined as profound visual impairment in one eye or at least moderate visual impairment in both eyes. Studies have shown that profound visual loss is a significant psychologic loss for patients. Low vision ranks only behind arthritis and heart disease for impact on function in the elderly age group. Visual loss is often rated as the elderly patient's worst problem, even in the context of other chronic disabling conditions such as cardiac disease. Fletcher et al have emphasized that comprehensive low-vision rehabilitation programs can have dramatic results in increasing the independence and productivity of affected persons; numerous studies document that low-vision rehabilitation improves patient independence, performance of ADLs, and quality of life. ^{3-5,161,162} The ACOVE (Assessing Care of Vulnerable Elders) report documented that 74% of patients undergoing low-vision services improve their overall functioning, including their ability to cook, read, drive, decrease their dependence on others, and improve productivity at work.¹³⁸ Scott et al investigated the functional status and quality of life of patients at a low-vision clinic and evaluated the impact of low-vision services.⁹⁵ Using the SF-36, VF-14, and NEI-VFQ, these researchers demonstrated that low-vision clinic patients perceive marked impairment of functional status and quality of life. Elliott et al studied the demographic characteristics of 4744 low-vision patients, of whom 71% were aged 65 or over and 55% were aged 75 or over; ARMD was the primary diagnosis in 75%, and 46% had cataract. 163

Ophth 41 (Level A): Interventional studies should be performed in elderly persons to determine if the types and visual outcome effectiveness of low-vision therapies are important factors in functional outcomes.

RECOMMENDED RESEARCH STRATEGIES

This review of recent literature on geriatric ophthalmology emphasizes functional outcomes, especially with regard to the four major causes of visual impairment in elderly persons. In setting their own research agendas, researchers in ophthalmology are invited to use this needs assessment to identify the types and scope of studies needed to improve the ophthalmic care of elderly patients. The following recommendations are based upon this review of the literature:

• Existing data from interventional studies and clinical trials in ophthalmology should be systematically "mined" for age-specific and age-stratified information in outcomes among elderly patients. The timing or efficacy for specific interventions may be partly dependent on age.

- All new research should be aimed at producing age-specific and age-stratified data. In addition, editors and editorial boards of the major ophthalmology journals should consider requiring such data in reports of ongoing publications and research.
- Studies should be directed at age-specific and age-stratified outcomes. Interventional studies should include functional assessment and functional outcomes in addition to visual assessment and visual outcomes.

KEY RESEARCH QUESTIONS IN GERIATRIC OPHTHALMOLOGY

Ophth KQ1: Does visual improvement or stabilization, including low-vision rehabilitation, reduce the severity, incidence, and prevalence of depression, dementia, delirium, falls, driving accidents, loss of function or quality of life, and hospital complications in the elderly population?

Hypothesis-generating: Observational cohort studies would document whether visual loss impacts these conditions and disorders of elderly persons. This could be achieved through surveys of existing patients with visual loss prospectively.

Hypothesis-testing: We recommend that interventional studies be performed to determine if visual improvement or low-vision rehabilitation reduces the severity of, the incidence of, and the prevalence of the listed disorders in the elderly population. These studies could be nonrandomized controlled trials using nonresponders as a comparison group. Ethical issues regarding the withholding of treatments to improve visual function might exclude the feasibility of a randomized trial. In the case of low-vision rehabilitation, because these services are currently not universally available or accepted, comparison groups of treated and untreated patients would be readily available.

Ophth KQ2: What is the best timing for and what are the best methods for intervention in visual loss in the elderly person, and what are the best outcome measures for documenting success?

Hypothesis-generating: We recommend that existing data from clinical trials and interventional studies be re-examined by meta-analysis to determine if age-specific and age-stratified recommendations from these trials are valid for elderly persons.

Hypothesis-testing: We recommend interventional studies to determine the best timing for and the specific methods for intervention in visual loss, and we recommend the use of outcome measures that include the functional impact of visual loss or visual improvement in elderly persons. Interventional studies on the efficacy of preoperative and prehospitalization visual screening and subsequent vision treatments should be performed. Functional measures should be included as primary or secondary outcome measures for these studies.

Ophth KQ3: What are the risk factors for functional vision impairment in the elderly person and what screening intervals and methods and what instruments for measuring visual function would be best for identifying an older person's risks for such impairment?

Hypothesis-generating: We recommend observational cohort studies to determine the risk factors for functional visual impairment in the elderly person.

Hypothesis-testing: We recommend interventional studies in elderly persons to determine the best intervals for visual screening, the best methods for visual screening, the best measures of visual function, and the most valid and reliable instruments for measuring function.

REFERENCES

- 1. Bierman A, Spector W, Atkins D, et al. Improving the Health Care of Older Americans. A Report of the AHRQ Task Force on Aging. Rockville, MD: Agency for Healthcare Research and Quality, 2001. AHRQ Publication No. 01-0030.
- Bailey IL. New procedures for detecting early vision losses in the elderly. Optom Vis Sci 1993;70:299-305.
- 3. Castor TD, Carter TL. Low vision: physician screening helps to improve patient function. Geriatrics 1995;50:51-52, 55-57; quiz 58-59.
- 4. Fletcher DC, Shindell S, Hindman T, Schaffrath M. Low vision rehabilitation. Finding capable people behind damaged eyeballs. West J Med 1991;154:554-556.
- 5. Fletcher DC. Low vision: the physician's role in rehabilitation and referral. Geriatrics 1994;49:50-53.
- Klein BE, Klein R, Lee KE, Cruickshanks KJ. Performance-based and self-assessed measures of visual function as related to history of falls, hip fractures, and measured gait time. The Beaver Dam Eye Study. Ophthalmology 1998;105:160-164.
- 7. Klein R, Klein BE, Linton KL, De Mets DL. The Beaver Dam Eye Study: visual acuity. Ophthalmology 1991;98:1310-1315.
- 8. Tielsch JM, Javitt JC, Coleman A, et al. The prevalence of blindness and visual impairment among nursing home residents in Baltimore. N Engl J Med 1995;332:1205-1209.
- 9. Tielsch JM, Steinberg EP, Cassard SD, et al. Preoperative functional expectations and postoperative outcomes among patients undergoing first eye cataract surgery. Arch Ophthalmol 1995;113:1312-1318.
- 10. American Academy of Ophthalmology. Preferred Practice Patterns. Cataract in the Adult Eye. 1996.
- 11. Applegate WB, Miller ST, Elam JT, et al. Impact of cataract surgery with lens implantation on vision and physical function in elderly patients. JAMA 1987;257:1064-1066.
- 12. Bruce DW, Gray CS. Beyond the cataract: visual and functional disability in elderly people. Age Ageing 1991;20:389-391.
- 13. Cataract Management Guideline Panel. Clinical Practice Guideline Number 4. Cataract in adults: management of functional impairment. Rockville MD: Department of Health and Human Services, Public Health Service, 1993. AHCPR Pub 93-0542.
- 14. Crabtree HL, Hildreth AJ, O'Connell JE, et al. Measuring visual symptoms in British cataract patients: the cataract symptom scale. Br J Ophthalmol 1999;83:519-523.
- 15. Javitt JC, Steinberg EP, Sharkey P, et al. Cataract surgery in one eye or both. A billion dollar per year issue. Ophthalmology 1995;102:1583-1592; discussion 1592-1583.

- Lee AG, Beaver HA, Teasdale T. The Aging Eye (CD-ROM). Houston, TX: Baylor College of Medicine, 2001.
- 17. Mangione CM, Orav EJ, Lawrence MG, et al. Prediction of visual function after cataract surgery. A prospectively validated model. Arch Ophthalmol 1995;113:1305-1311.
- Mangione CM, Phillips RS, Lawrence MG, et al. Improved visual function and attenuation of declines in health-related quality of life after cataract extraction. Arch Ophthalmol 1994;112:1419-1425.
- 19. Monestam E, Wachtmeister L. Impact of cataract surgery on car driving: a population based study in Sweden. Br J Ophthalmol 1997;81:16-22.
- 20. Owsley C, Stalvey B, Wells J, Sloane ME. Older drivers and cataract: driving habits and crash risk. J Gerontol A Biol Sci Med Sci 1999;54:M203-M211.
- 21. Powe NR, Schein OD, Gieser SC, et al. Synthesis of the literature on visual acuity and complications following cataract extraction with intraocular lens implantation. Cataract Patient Outcome Research Team. Arch Ophthalmol 1994;112:239-252.
- Powe NR, Tielsch JM, Schein OD, et al. Rigor of research methods in studies of the effectiveness and safety of cataract extraction with intraocular lens implantation. Cataract Patient Outcome Research Team. Arch Ophthalmol 1994;112:228-238.
- 23. Schein OD, Steinberg EP, Cassard SD, et al. Predictors of outcome in patients who underwent cataract surgery. Ophthalmology 1995;102:817-823.
- Schein OD, Bass EB, Sharkey P, et al. Cataract surgical techniques. Preferences and underlying beliefs. Arch Ophthalmol 1995;113:1108-1112.
- 25. Steinberg EP, Tielsch JM, Schein OD, et al. National study of cataract surgery outcomes. Variation in 4-month postoperative outcomes as reflected in multiple outcome measures. Oph-thalmology 1994;101:1131-1140; discussion 1140-1131.
- 26. Steinberg EP, Tielsch JM, Schein OD, et al. The VF-14. An index of functional impairment in patients with cataract. Arch Ophthalmol 1994;112:630-638.
- 27. Bass EB, Steinberg EP, Luthra R, et al. Do ophthalmologists, anesthesiologists, and internists agree about preoperative testing in healthy patients undergoing cataract surgery? Arch Ophthalmol 1995;113:1248-1256.
- 28. Superstein R, Boyaner D, Overbury O. Functional complaints, visual acuity, spatial contrast sensitivity, and glare disability in preoperative and postoperative cataract patients. J Cataract Refract Surg 1999;25:575-581.
- 29. Tobacman JK, Zimmerman B, Lee P, et al. Visual function impairments in relation to gender, age, and visual acuity in patients who undergo cataract surgery. Ophthalmology 1998;105:1745-1750.
- 30. Uusitalo RJ, Brans T, Pessi T, Tarkkanen A. Evaluating cataract surgery gains by assessing patients' quality of life using the VF-7. J Cataract Refract Surg 1999;25:989-994.
- 31. Rumsey KE. Redefining the optometric examination: addressing the vision needs of older adults. Optom Vis Sci 1993;70:587-591.
- 32. Rubin GS, Roche KB, Prasada-Rao P, Fried LP. Visual impairment and disability in older adults. Optom Vis Sci 1994;71:750-760.
- Rubin GS, West SK, Munoz B, et al. A comprehensive assessment of visual impairment in a population of older Americans. The SEE Study. Salisbury Eye Evaluation Project. Invest Ophthalmol Vis Sci 1997;38:557-568.
- American Academy of Ophthalmology. Preferred Practice Patterns. Age-related Macular Degeneration. Limited Revision. 2001.
- American Academy of Ophthalmology. Preferred Practice Patterns. Primary Open Angle Glaucoma. 2000.
- 36. American Academy of Ophthalmology. Preferred Practice Patterns. Vision Rehabilitation for Adults. 2001.

- 37. Albrecht KG, Lee PP. Conformance with preferred practice patterns in caring for patients with glaucoma. Ophthalmology 1994;101:1668-1671.
- Appollonio I, Carabellese C, Magni E, et al. Sensory impairments and mortality in an elderly community population: a six-year follow-up study. Age Ageing 1995;24:30-36.
- Brenner MH, Curbow B, Javitt JC, et al. Vision change and quality of life in the elderly. Response to cataract surgery and treatment of other chronic ocular conditions. Arch Ophthalmol 1993;111:680-685.
- Campbell VA, Crews JE, Moriarty DG, et al. Surveillance for sensory impairment, activity limitation, and health-related quality of life among older adults—United States, 1993-1997. Mor Mortal Wkly Rep CDC Surveill Summ 1999;48:131-156.
- 41. Carter TL. Age-related vision changes: a primary care guide. Geriatrics 1994;49:37-42, 45; quiz 46-37.
- Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol 1998;126:487-497.
- 43. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol 1998;126:498-505.
- 44. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000;342:381-389.
- 45. The Diabetic Retinopathy Study Research Group. Indications for photocoagulation treatment of diabetic retinopathy: Diabetic Retinopathy Study Report No. 14. Int Ophthalmol Clin 1987;27:239-253.
- The Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report No. 8. Ophthalmology 1981;88:583-600.
- 47. The Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study Report No. 4. Int Ophthalmol Clin 1987;27:265-272.
- 48. The Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS Report No. 9. Ophthalmology 1991;98:766-785.
- 49. Klein BE, Klein R, Linton KL. Prevalence of age-related lens opacities in a population. The Beaver Dam Eye Study. Ophthalmology 1992;99:546-552.
- 50. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology 1992;99:933-943.
- 51. Klein R. Age-related eye disease, visual impairment, and driving in the elderly. Hum Factors 1991;33:521-525.
- 52. Tielsch JM, Sommer A, Katz J, et al. Socioeconomic status and visual impairment among urban Americans. Baltimore Eye Survey Research Group. Arch Ophthalmol 1991;109: 637-641.
- 53. Mangione CM, Gutierrez PR, Lowe G, et al. Influence of age-related maculopathy on visual functioning and health-related quality of life. Am J Ophthalmol 1999;128:45-53.
- Olsen CL, Kassoff A, Gerber T. The care of diabetic patients by ophthalmologists in New York State. Ophthalmology 1989;96:739-745.
- 55. Perry DP. ARMD is robbing older people blind-and stealing their independence, too. J Am Optom Assoc 1999;70:7-9.
- 56. Salive ME, Guralnik J, Christen W, et al. Functional blindness and visual impairment in older adults from three communities. Ophthalmology 1992;99:1840-1847.
- 57. Jette AM, Branch LG. Impairment and disability in the aged. J Chronic Dis 1985;38:59-65.

- Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med 1995;332:767-773.
- 59. Cwikel J. Falls among elderly people living at home: medical and social factors in a national sample. Isr J Med Sci 1992;28:446-453.
- Kelsey JL, Browner WS, Seeley DG, et al. Risk factors for fractures of the distal forearm and proximal humerus. The Study of Osteoporotic Fractures Research Group (published erratum appears in Am J Epidemiol 1992 135:1183). Am J Epidemiol 1992;135:477-489.
- 61. Lord SR, McLean D, Stathers G. Physiological factors associated with injurious falls in older people living in the community. Gerontology 1992;38:338-346.
- 62. Melton LJ, 3rd, Riggs BL. Risk factors for injury after a fall. Clin Geriatr Med 1985;1: 525-539.
- 63. Myers AH, Robinson EG, Van Natta ML, et al. Hip fractures among the elderly: factors associated with in-hospital mortality. Am J Epidemiol 1991;134:1128-1137.
- Nevitt MC, Cummings SR, Kidd S, Black D. Risk factors for recurrent nonsyncopal falls. A prospective study. JAMA 1989;261:2663-2668.
- Nevitt MC, Cummings SR, Hudes ES. Risk factors for injurious falls: a prospective study. J Gerontol 1991;46:M164-M170.
- 66. O'Loughlin JL, Robitaille Y, Boivin JF, Suissa S. Incidence of and risk factors for falls and injurious falls among the community-dwelling elderly. Am J Epidemiol 1993;137:342-354.
- 67. Sattin RW, Lambert Huber DA, DeVito CA, et al. The incidence of fall injury events among the elderly in a defined population. Am J Epidemiol 1990;131:1028-1037.
- 68. Sattin RW. Falls among older persons: a public health perspective. Annu Rev Public Health 1992;13:489-508.
- 69. Sorock GS. Falls among the elderly: epidemiology and prevention. Am J Prev Med 1988;4: 282-288.
- Speechley M, Tinetti M. Falls and injuries in frail and vigorous community elderly persons. J Am Geriatr Soc 1991;39:46-52.
- 71. Tinetti ME. Instability and falling in elderly patients. Semin Neurol 1989;9:39-45.
- 72. Tinetti ME, Powell L. Fear of falling and low self-efficacy: a case of dependence in elderly persons. J Gerontol 1993;48 Spec No:35-38.
- 73. Tinetti ME, Doucette J, Claus E, Marottoli R. Risk factors for serious injury during falls by older persons in the community. J Am Geriatr Soc 1995;43:1214-1221.
- Tinetti ME, McAvay G, Claus E. Does multiple risk factor reduction explain the reduction in fall rate in the Yale FICSIT Trial? Frailty and Injuries Cooperative Studies of Intervention Techniques. Am J Epidemiol 1996;144:389-399.
- 75. Tobis JS, Block M, Steinhaus-Donham C, et al. Falling among the sensorially impaired elderly. Arch Phys Med Rehabil 1990;71:144-147.
- Wilson MR, Coleman AL, Yu F, et al. Functional status and well-being in patients with glaucoma as measured by the Medical Outcomes Study Short Form-36 questionnaire. Ophthalmology 1998;105:2112-2116.
- Wang JJ, Mitchell P, Smith W, et al. Impact of visual impairment on use of community support services by elderly persons: the Blue Mountains Eye Study. Invest Ophthalmol Vis Sci 1999;40:12-19.
- 78. Wang JJ, Mitchell P, Smith W. Vision and low self-rated health: the Blue Mountains Eye Study. Invest Ophthalmol Vis Sci 2000;41:49-54.
- 79. Branch LG, Horowitz A, Carr C. The implications for everyday life of incident self-reported visual decline among people over age 65 living in the community. Gerontologist 1989;29: 359-365.
- 80. Carabellese C, Appollonio I, Rozzini R, et al. Sensory impairment and quality of life in a community elderly population. J Am Geriatr Soc 1993;41:401-407.

- Keeffe JE, Lam D, Cheung A, et al. Impact of vision impairment on functioning. Aust N Z J Ophthalmol 1998;26 Suppl 1:S16-S18.
- Keeffe JE, McCarty CA, Hassell JB, Gilbert AG. Description and measurement of handicap caused by vision impairment. Aust N Z J Ophthalmol 1999;27:184-186.
- Keller BK, Morton JL, Thomas VS, Potter JF. The effect of visual and hearing impairments on functional status. J Am Geriatr Soc 1999;47:1319-1325.
- Kelly M. Consequences of visual impairment on leisure activities of the elderly. Geriatr Nurs 1995;16:273-275.
- Lee PP, Smith JP, Kington R. The relationship of self-rated vision and hearing to functional status and well-being among seniors 70 years and older. Am J Ophthalmol 1999;127:447-452.
- Lee PP, Spritzer K, Hays RD. The impact of blurred vision on functioning and well-being. Ophthalmology 1997;104:390-396.
- 87. Lee PP, Whitcup SM, Hays RD, et al. The relationship between visual acuity and functioning and well-being among diabetics. Qual Life Res 1995;4:319-323.
- Thompson JR, Gibson JM, Jagger C. The association between visual impairment and mortality in elderly people. Age Ageing 1989;18:83-88.
- 89. Livingston PM, Lee SE, McCarty CA, Taylor HR. A comparison of participants with non-participants in a population-based epidemiologic study: the Melbourne Visual Impairment Project. Ophthalmic Epidemiol 1997;4:73-81.
- 90. Dargent-Molina P, Hays M, Breart G. Sensory impairments and physical disability in aged women living at home. Int J Epidemiol 1996;25:621-629.
- McClure ME, Hart PM, Jackson AJ, et al. Macular degeneration: do conventional measurements of impaired visual function equate with visual disability? Br J Ophthalmol 2000;84:244-250.
- 92. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-483.
- Mangione CM, Berry S, Spritzer K, et al. Identifying the content area for the 51-item National Eye Institute Visual Function Questionnaire: results from focus groups with visually impaired persons. Arch Ophthalmol 1998;116:227-233.
- 94. Mangione CM, Phillips RS, Seddon JM, et al. Development of the 'Activities of Daily Vision Scale'. A measure of visual functional status. Med Care 1992;30:1111-1126.
- 95. Scott IU, Smiddy WE, Schiffman J, et al. Quality of life of low-vision patients and the impact of low-vision services. Am J Ophthalmol 1999;128:54-62.
- Cassard SD, Patrick DL, Damiano AM, et al. Reproducibility and responsiveness of the VF-14. An index of functional impairment in patients with cataracts. Arch Ophthalmol 1995;113:1508-1513.
- 97. Hart PM, Chakravarthy U, Stevenson MR, Jamison JQ. A vision specific functional index for use in patients with age related macular degeneration. Br J Ophthalmol 1999;83:1115-1120.
- Horowitz A. Vision impairment and functional disability among nursing home residents. Gerontologist 1994;34:316-323.
- 99. Parrish RK, Gedde SJ, Scott IU, et al. Visual function and quality of life among patients with glaucoma. Arch Ophthalmol 1997;115:1447-1455.
- 100. Ross CK, Stelmack JA, Stelmack TR, et al. Development and sensitivity to visual impairment of the Low Vision Functional Status Evaluation (LVFSE). Optom Vis Sci 1999;76:212-220.
- 101. Turco PD, Connolly J, McCabe P, Glynn RJ. Assessment of functional vision performance: a new test for low vision patients. Ophthalmic Epidemiol 1994;1:15-25.
- Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179-186.
- Klein R, Cruickshanks KJ, Klein BE, et al. Is age-related maculopathy related to hearing loss? Arch Ophthalmol 1998;116:360-365.

- 104. Bagley M. Helping older adults to live better with hearing and vision losses. J Case Manag 1998;7:147-152.
- 105. Guralnik JM. The impact of vision and hearing impairments on health in old age. J Am Geriatr Soc 1999;47:1029-1031.
- 106. Rudberg MA, Furner SE, Dunn JE, Cassel CK. The relationship of visual and hearing impairments to disability: an analysis using the longitudinal study of aging. J Gerontol 1993;48:M261-M265.
- 107. Rubin GS, Bandeen-Roche K, Huang GH, et al. The association of multiple visual impairments with self-reported visual disability: SEE project. Invest Ophthalmol Vis Sci 2001;42: 64-72.
- 108. Appollonio I, Carabellese C, Frattola L, Trabucchi M. Effects of sensory aids on the quality of life and mortality of elderly people: a multivariate analysis. Age Ageing 1996;25:89-96.
- 109. Rovner BW, Zisselman PM, Shmuely-Dulitzki Y. Depression and disability in older people with impaired vision: a follow-up study. J Am Geriatr Soc 1996;44:181-184.
- Rovner BW, Ganguli M. Depression and disability associated with impaired vision: the MoVies Project. J Am Geriatr Soc 1998;46:617-619.
- 111. Uhlmann RF, Larson EB, Koepsell TD, et al. Visual impairment and cognitive dysfunction in Alzheimer's disease. J Gen Intern Med 1991;6:126-132.
- 112. George J, Bleasdale S, Singleton SJ. Causes and prognosis of delirium in elderly patients admitted to a district general hospital. Age Ageing 1997;26:423-427.
- 113. Steinman SB, Steinman BA, Trick GL, Lehmkuhle S. A sensory explanation for visual attention deficits in the elderly. Optom Vis Sci 1994;71:743-749.
- 114. Salive ME, Guralnik J, Glynn RJ, et al. Association of visual impairment with mobility and physical function. J Am Geriatr Soc 1994;42:287-292.
- 115. West SK, Munoz B, Rubin GS, et al. Function and visual impairment in a population-based study of older adults. The SEE project. Salisbury Eye Evaluation. Invest Ophthalmol Vis Sci 1997;38:72-82.
- 116. Marx MS, Werner P, Cohen-Mansfield J, Feldman R. The relationship between low vision and performance of activities of daily living in nursing home residents. J Am Geriatr Soc 1992;40:1018-1020.
- 117. Pillar T, Gaspar E, Dickstein R. Physical rehabilitation of the elderly blind patient. Int Disabil Stud 1990;12:75-77.
- 118. Maino JH. Visual deficits and mobility. Evaluation and management. Clin Geriatr Med 1996;12:803-823.
- 119. Boter H, Mistiaen P, Duijnhouwer E, Groenewegen I. The problems of elderly patients at home after ophthalmic treatment. J Ophthalmic Nurs Technol 1998;17:59-65.
- 120. Cate Y, Baker SS, Gilbert MP. Occupational therapy and the person with diabetes and vision impairment. Am J Occup Ther 1995;49:905-911.
- 121. Gutierrez P, Wilson MR, Johnson C, et al. Influence of glaucomatous visual field loss on health-related quality of life. Arch Ophthalmol 1997;115:777-784.
- 122. Javitt JC, Brenner MH, Curbow B, et al. Outcomes of cataract surgery. Improvement in visual acuity and subjective visual function after surgery in the first, second, and both eyes. Arch Ophthalmol 1993;111:686-691.
- 123. Jayamanne DG, Allen ED, Wood CM, Currie S. Correlation between early, measurable improvement in quality of life and speed of visual rehabilitation after phacoemulsification. J Cataract Refract Surg 1999;25:1135-1139.
- 124. Lundstrom M, Fregell G, Sjoblom A. Vision related daily life problems in patients waiting for a cataract extraction. Br J Ophthalmol 1994;78:608-611.
- 125. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care 1981;19:787-805.

- 126. Nelson P, Aspinall P, O'Brien C. Patients' perception of visual impairment in glaucoma: a pilot study. Br J Ophthalmol 1999;83:546-552.
- 127. Phillips KE, Russello SM, Bonesi J, Garcon R. Functional visual problems: training home care aides to identify early signs. Caring 1997;16:54, 56-60, 62-54.
- 128. Sherwood MB, Garcia-Siekavizza A, Meltzer MI, et al. Glaucoma's impact on quality of life and its relation to clinical indicators. A pilot study. Ophthalmology 1998;105:561-566.
- 129. Swagerty DL. The impact of age-related visual impairment on functional independence in the elderly. Kans Med 1995;96:24-26.
- 130. Wahl HW, Schilling O, Oswald F, Heyl V. Psychosocial consequences of age-related visual impairment: comparison with mobility-impaired older adults and long-term outcome. J Gerontol B Psychol Sci Soc Sci 1999;54:P304-P316.
- Kosnik WD, Sekuler R, Kline DW. Self-reported visual problems of older drivers. Hum Factors 1990;32:597-608.
- 132. Kline DW, Kline TJ, Fozard JL, et al. Vision, aging, and driving: the problems of older drivers. J Gerontol 1992;47:P27-P34.
- 133. Ball K, Owsley C, Stalvey B, et al. Driving avoidance and functional impairment in older drivers. Accid Anal Prev 1998;30:313-322.
- 134. McGwin G, Owsley C, Ball K. Identifying crash involvement among older drivers: agreement between self-report and state records. Accid Anal Prev 1998;30:781-791.
- 135. Owsley C, Ball K, McGwin G, Jr., et al. Visual processing impairment and risk of motor vehicle crash among older adults. JAMA 1998;279:1083-1088.
- 136. Shipp MD, Penchansky R. Vision testing and the elderly driver: is there a problem meriting policy change? J Am Optom Assoc 1995;66:343-351.
- 137. Morse AR, Yatzkan E, Berberich B, Arons RR. Acute care hospital utilization by patients with visual impairment. Arch Ophthalmol 1999;117:943-949.
- 138. Wenger NS, Shekelle PG. Assessing care of vulnerable elders: ACOVE project overview. Ann Intern Med 2001;135:642-646.
- Smeeth L, Iliffe S. Community screening for visual impairment in the elderly. Cochrane Database Syst Rev 2000:CD001054.
- 140. American Academy of Ophthalmology. Preferred Practice Patterns. Comprehensive Adult Medical Eye Evaluation. 2000.
- 141. U.S. Preventive Services Task Force. Recommendations for screening for visual impairment. In Guide to Clinical Preventive Services, 2nd ed. Baltimore MD: Williams & amp; Wilkins, 1996, pp 373-382.
- 142. Rahmani B, Tielsch JM, Katz J, et al. The cause-specific prevalence of visual impairment in an urban population. The Baltimore Eye Survey. Ophthalmology 1996;103:1721-1726.
- 143. Ariyasu RG, Lee PP, Linton KP, et al. Sensitivity, specificity, and predictive values of screening tests for eye conditions in a clinic-based population. Ophthalmology 1996;103:1751-1760.
- 144. Bernth-Petersen P. Visual functioning in cataract patients. Methods of measuring and results. Acta Ophthalmol (Copenh) 1981;59:198-205.
- 145. Verteporfin Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization–verteporfin in photodynamic therapy report 2. Am J Ophthalmol 2001;131:541-560.
- 146. Verteporfin Study Group. Photodynamic therapy with verteporfin for age-related macular degeneration. American Academy of Ophthalmology. Ophthalmology 2000;107:2314-2317.
- 147. Dahlin-Ivanoff S, Klepp KI, Sjostrand J. Development of a health education programme for elderly with age-related macular degeneration: a focus group study. Patient Educ Couns 1998;34:63-73.

- 148. Fine AM, Elman MJ, Ebert JE, et al. Earliest symptoms caused by neovascular membranes in the macula. Arch Ophthalmol 1986;104:513-514.
- 149. Fine SL. Early detection of extrafoveal neovascular membranes by daily central field evaluation. Ophthalmology 1985;92:603-609.
- Gelfand YA, Linn S, Miller B. The application of the macular photocoagulation study eligibility criteria for laser treatment in age-related macular degeneration. Ophthalmic Surg Lasers 1997;28:823-827.
- 151. Klein ML, Jorizzo PA, Watzke RC. Growth features of choroidal neovascular membranes in age-related macular degeneration. Ophthalmology 1989;96:1416-1419; discussion 1420-1411.
- 152. Macular Photocoagulation Study Group. Visual outcome after laser photocoagulation for subfoveal choroidal neovascularization secondary to age-related macular degeneration. The influence of initial lesion size and initial visual acuity. Arch Ophthalmol 1994;112:480-488.
- 153. Vander JF, Morgan CM, Schatz H. Growth rate of subretinal neovascularization in age-related macular degeneration. Ophthalmology 1989;96:1422-1426; discussion 1426-1429.
- 154. Williams RA, Brody BL, Thomas RG, et al. The psychosocial impact of macular degeneration. Arch Ophthalmol 1998;116:514-520.
- 155. Faubert J, Overbury O. Binocular vision in older people with adventitious visual impairment: sometimes one eye is better than two. J Am Geriatr Soc 2000;48:375-380.
- 156. Hertzog LH, Albrecht KG, LaBree L, Lee PP. Glaucoma care and conformance with preferred practice patterns. Examination of the private, community-based ophthalmologist. Ophthalmology 1996;103:1009-1013.
- 157. Ferris F. Early photocoagulation in patients with either type I or type II diabetes. Trans Am Ophthalmol Soc 1996;94:505-537.
- 158. Ferris FL, 3rd. How effective are treatments for diabetic retinopathy? JAMA 1993;269: 1290-1291.
- 159. Lee ET, Keen H, Bennett PH, et al. Follow-up of the WHO Multinational Study of Vascular Disease in Diabetes: general description and morbidity. Diabetologia 2001;44 Suppl 2:S3-S13.
- 160. Miller DK, Lui LY, Perry HM, et al. Reported and measured physical functioning in older inner-city diabetic African Americans. J Gerontol A Biol Sci Med Sci 1999;54:M230-M236.
- 161. D'Ilura T, McInerney R, Horowitz A. An evaluation of low vision services. J Vis Impair Blindness 1995;Nov-Dec:487-493.
- Monestam E, Wachtmeister L. The impact of cataract surgery on low vision patients. A population based study. Acta Ophthalmol Scand 1997b;75:569-576.
- 163. Elliott DB, Trukolo-Ilic M, Strong JG, et al. Demographic characteristics of the vision-disabled elderly. Invest Ophthalmol Vis Sci 1997;38:2566-2575.