Evaluation of photodynamic therapy for the treatment of exudative age-related macular degeneration (ARMD) with subfoveal neovascularization

AGENCE D'ÉVALUATION DES TECHNOLOGIES
ET DES MODES D'INTERVENTION EN SANTÉ

Québec

Evaluation of photodynamic therapy for the treatment of exudative age-related macular degeneration (ARMD) with subfoveal neovascularization

Report prepared for AETMIS
by Kathy Larouche and Sophie Rochon

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MISSION

The mission of the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) is to contribute to improving the Québec health-care system and to participate in the implementation of the Québec government's scientific policy. To accomplish this, the Agency advises and supports the Minister of Health and Social Services as well as the decision-makers in the health care system, in matters concerning the assessment of health services and technologies. The Agency makes recommendations based on scientific reports assessing the introduction, diffusion and use of health technologies, including technical aids for disabled persons, as well as the modes of providing and organizing services. The assessments take into account many factors, such as efficacy, safety and efficiency, as well as ethical, social, organizational and economic implications.

FOREWORD

EVALUATION OF PHOTODYNAMIC THERAPY FOR THE TREATMENT OF EXUDATIVE AGE-RELATED MACULAR DEGENERATION WITH SUBFOVEAL NEOVASCULARIZATION

In Western countries, age-related macular degeneration (ARMD) is the leading cause of blindness in people over the age of 55. This disease is characterized mainly by degenerative changes in the macular region of the retina that result in a gradual decrease in central vision. In Québec, it is estimated that about 37,200 people are affected, hence the need for effective therapeutic modalities to treat the disease.

It was in this context that ophthalmologists in the New Technologies Axis of the Vision Network, which is sponsored by the *Fonds de la recherche en santé du Québec* (FRSQ), asked the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) to assess the efficacy of photodynamic therapy for the treatment of ARMD. There was also the need to examine the costs associated with this therapeutic modality in Québec and to look at the organization of the care and services involved.

AETMIS's assessment is based on a rigorous examination of the existing scientific data. According to this assessment, the efficacy of photodynamic therapy with verteporfin photosensitizer is well established for two forms of ARMD: 1) exudative subfoveal ARMD with predominantly classic neovascularization, and 2) exudative subfoveal ARMD with pure occult neovascularization. AETMIS also concludes that, given the potentially rapid progression of neovascular ARMD, its early detection could help reduce severe, irreversible vision loss and consequently major expenses, by the public system, for managing this disease and its sequelae.

The report proposes several options for detecting the disease earlier. The optimal implementation of this technology will, however, require major changes to the organization of the care and services in the area of ocular health. Lastly, AETMIS presents various recommendations that urge ministerial and professional authorities to recognize ARMD as a major public health problem and to encourage initiatives for the population-based management of ARMD in the broader context of managing preventable blindness.

In submitting this report, AETMIS wishes to provide the best possible information to the policymakers in Québec's health-care system to assist them in taking action on this important problem.

Dr. Luc Deschênes
Chairman and Chief Executive Officer

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CONFLICT OF INTEREST

None declared.

SUMMARY

PROBLEM AND OBJECTIVES

Over the past few decades, most industrialized countries have experienced an increase in their elderly populations. This inversion of the age pyramid is leading to an increased incidence of many diseases, including age-related macular degeneration (ARMD). ARMD is characterized by degenerative lesions in the macular region of the retina resulting in a gradual decrease in vision that can lead to a loss of central vision. In fact, this disease is the leading cause of blindness in Western countries. Its prevalence is approximately 0.2% in people aged 55 to 64 and climbs to more than 13% in the over-85 population. Based on epidemiological data, the number of affected individuals in Québec can be estimated at approximately 37,200.

ARMD has been divided into three histopathologic forms: an early form, also known as age-related maculopathy (ARM) or pre-ARMD (it should be noted that the early form is not included in the prevalence and incidence data provided in this report), and two advanced or progressive forms, called atrophic and neovascular (or exudative) forms. At the present time, only the neovascular form is treatable. It accounts for about 47% of the cases of advanced ARMD, which, in Quebec, number close to 16,000. This disease therefore generates significant social costs, hence the need for effective therapeutic modalities to treat it.

It was in this context that ophthalmologists representing the New Technologies Axis of the Vision Network, which is sponsored by the *Fonds de la recherche en santé du Québec* (FRSQ), asked the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) to assess the efficacy of photodynamic therapy (PDT) with verteporfin photosensitizer for the treatment of ARMD. This report also looks at the costs associated with this therapeutic modality and examines, on an exploratory basis, the organization of the care and services involved.

RESEARCH METHODOLOGY

A literature search was conducted in the PubMed, Current Content Search and Cochrane Library databases by combining the terms *macular degeneration*, *photodynamic therapy* and *verteporfin* (Visudyne®); *Amsler grid; antioxidant*; *vitamin*; *risk factors*; *side effects* and *fluorescein angiography* for the period from 1975 to June 2004. We also used reports from several health technology assessment agencies that have examined PDT, abstracts of papers presented at international scientific conferences, a number of Web sites, and interviews with experts in ophthalmology and visual rehabilitation.

The decision tree for the economic analysis was designed for the purpose of predicting the costs and effects of PDT in individuals with ARMD. The population selected for this Markov-type model includes all Quebecers who were over the age of 55 in 2001 (1,730,000). The incidence data for the disease are applied to this cohort. Two options are compared in the model: a *treatment* option and a *no-treatment* option. To include all the possible treatment scenarios, the time horizon in this model was set at eight years, and the outcomes used are the *loss* and *non-loss* of three lines of vision. It will be noted that visual rehabilitation costs are included in both options on the basis of the patient's visual acuity.

The exploratory study of the organization of the care and services provided to ARMD patients was conducted in the summer 2002 using a qualitative approach based on semi-structured telephone interviews with eye specialists at all of the university and community hospitals and at certain private clinics in Québec that offer PDT, and with receptionists and nurses who work at these facilities.

PHOTODYNAMIC THERAPY

Photodynamic therapy involves irradiating, with low-intensity light, a tissue that has been subjected to a photosensitizer. At present, the only photosensitizer approved for the treatment of ARMD is verteporfin (Visudyne®). Generally, photosensitizers cause cytotoxic damage only when activated by an appropriate light source, and the damage is limited to a relatively precise area. Verteporfin also offers the advantage of rapid hepatic elimination, which limits the duration of visual or cutaneous photosensitization. Verteporfin is especially effective in ophthalmology, since it is light-activated by a mono-chromatically red diode laser that easily penetrates blood and fibrous tissues. It can therefore act on choroidal neovasculature and ultimately cause its destruction.

EFFICACY OF PHOTODYNAMIC THERAPY

The examination of the clinical efficacy of PDT with verteporfin photosensitizer is based on the results of two randomized, double-blind, multicentre clinical studies: the TAP study (Treatment of Age-related Macular Degeneration with Photodynamic Therapy) and the VIP study (Visudyne in Photodynamic Therapy). Overall, the clinical protocols in these two studies were very rigorous, and the results for the main outcome measures were significant. The TAP and VIP studies showed that PDT can effectively slow the progression of two forms of ARMD:

1) Subfoveal neovascular ARMD with more than 50% classic neovascularization, and
2) Subfoveal neovascular ARMD with pure occult neovascularization.

The efficacy of PDT has been demonstrated for these two forms of ARMD when the patient's visual acuity is at least 6/60 in the eye to be treated.

Overall, PDT reduces moderate to severe loss of visual acuity in individuals with these two forms of ARMD. It also reduces the number of individuals who become legally blind (visual acuity less than 6/60) after two years.

For patients with minimally classic ARMD (< 50% classic neovascularization), we cannot, from the existing studies, draw any conclusions regarding the efficacy of PDT.

No study has compared photodynamic therapy with other therapeutic modalities for treating subfoveal neovascular ARMD, since the other modalities (with the exception of laser photocoagulation) are still in the clinical trial stage. Laser photocoagulation is, however, effective in treating patients with extrafoveal and juxtafoveal neovascular ARMD, but this technique cannot be used for subfoveal neovascular ARMD because the laser destroys the retina immediately adjacent to the target area, which would cause a loss of central visual acuity.

PREVENTION OF ARMD

The AREDS study (Age-Related Eye Disease Study Research Group) examined the effect of the daily use of dietary antioxidant (vitamins C and E and beta-carotene) and zinc supplements by individuals with ARMD. The results of this randomized, double-blind, multicentre study showed that the recommended supplements can be effective in preventing the onset or progression of the disease in patients at risk for a progressive form of ARMD (patients with age-related maculopathy [ARM] with large drusen or with unilateral neovascular ARMD). However, there is no evidence to support the use of these supplements when the disease has not been detected in at least one eye. Furthermore, under no circumstances should patients take them without first having consulted a physician, since considerable side effects can occur in certain types of individuals.

RESULTS OF THE ECONOMIC ANALYSIS

In the economic analysis, we basically compare the PDT *treatment* option with the *no-treatment* option by calculating the total cost of the services involved in diagnosing, treating, following and managing poor eyesight and blindness, and the utility associated with the *loss* or *non-loss* of visual acuity. The results of this analysis are favourable with regard to the use of photodynamic therapy in exudative ARMD with predominantly classic or pure occult neovascularization. An estimate of the incremental cost-utility ratio per QALY (quality-adjusted life-year), calculated on the basis of an 8-year time horizon, yields the following figures:

- For patients with classic neovascularization: $33,880;
- For patients with classic neovascularization and those with pure occult neovascularization: $43,253.

The net annual budget impact is approximately $17.3 million if all the prevalent and incident cases are taken into account, but only $300,000 if only the incident cases are considered (1,261 patients eligible for treatment over a 2-year period).

Given the potentially rapid progression of neovascular ARMD, its early detection could considerably lower the risk of severe, irreversible vision loss and thus avoid considerable expenses to the public system by reducing the costs associated with the rehabilitation and treatment of the other problems associated with vision loss (depression, falls, etc.). This improvement has repercussions on the cost-utility ratios. Thus:

- For patients with ARMD with 50% classic neovascularization, the cost-utility ratio decreases from $33,880 to $20,701 per QALY;
- For patients with 50% classic neovascularization and those with pure occult neovascularization, the cost-utility ratio decreases from $43,253 to $22,813.

ACCESS TO OPHTHALMOLOGIC SERVICES

Different sources of information, including an exploratory study on the organization of the care and services relating to photodynamic therapy (PDT), yielded several observations on this important issue:

- ARMD patients cannot always access photodynamic therapy within a reasonable amount of time.
- Problems accessing eye specialists (ophthalmologists and retinologists) and fluorescein angiography lengthen the waiting time for obtaining a first treatment with PDT.
- The amount of time between the onset of macular degeneration and when the individual notices it can also be very long, which can contribute to a greater deterioration in vision.
- Also, in 2003, for budgetary reasons, some hospital patients who were receiving this treatment were transferred to the private sector. Since these patients have to assume a considerable portion of the cost of the drugs, access to photodynamic therapy is becoming even more limited.

CONCLUSION

From the evidence accumulated on photodynamic therapy with verteporfin photosensitizer we can conclude that this technology is effective in slowing the progression of subfoveal neovascular ARMD with predominantly classic neovascularization or pure occult neovascularization. Further-more, the estimated budget impact for a Québec cohort is acceptable if the improvement in quality of life is taken into account. However, a major reorganization of services and ocular health care should be considered in the near future to permit the optimal implementation of this technology, to reduce waiting times for this treatment and to deal with the demand that will be increasing in the coming years. Furthermore, measures aimed at promoting

the early detection of ARMD in the population, both at the individual and primary-care levels, could reduce the risk of severe, irreversible vision loss and thus reduce the social costs of this disease.

RECOMMENDATIONS

AETMIS recommends that:

1) Photodynamic therapy be considered a technology that can effectively slow the progression of certain forms of ARMD;
2) ARMD be recognized by the policymakers in Québec's health-care system as an important public health problem;
3) Québec-based initiatives for the population-based management of ARMD be part of a broader effort to manage preventable blindness;
4) The planning and implementation, in the wake of this report, of the next few steps in the broader context of managing preventable blindness be facilitated by the creation of a task force charged with proposing a concrete plan to the *Ministère de la Santé et des Services sociaux*;
5) The Vision Network/FRSQ consider the possibility of giving priority to the carrying out of studies evaluating the validity of the Amsler grid or other detection tools in the context of ARMD screening;
6) The Vision Network/FRSQ undertake more-thorough studies to determine, with the necessary rigour, the needs relating to the organization of the care and services pertaining to ARMD and preventable blindness in Québec.

LIST OF ABBREVIATIONS

AETMIS	*Agence d'évaluation des technologies et des modes d'intervention en santé*
AHQ	*Association des hôpitaux du Québec*
AI	Adequate intake
ARM	Age-related maculopathy
ARMD	Age-related macular degeneration
ANAES	*Agence nationale d'accréditation et d'évaluation en santé* (France)
AQDM	*Association québécoise de la dégénérescence maculaire*
AREDS	Age-Related Eye Disease Study Research Group
ARVO	Association for Research in Vision and Ophthalmology
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer
bFGF	Basic fibroblast growth factor
CARET	Beta-Carotene and Retinol Efficacy Trial
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CI	Confidence interval
CNV	Choroidal neovascularization/choroidal neovasculature
CS	Contrast sensitivity
DHA	Dehydroascorbic acid
DRI	Dietary reference intake
EAR	Estimated average requirement
ETDRS	Early Treatment Diabetic Retinopathy Study
FNB	Food and Nutrition Board
FRSQ	*Fonds de la recherche en santé du Québec*
HSP	Heat shock proteins
ICD-9	International Classification of Diseases (9th edition)
IHCMG	Illuminated high-contrast macular grid
INAHTA	International Network of Agencies for Health Technology Assessment
IPE	Iridial pigment epithelium
IU	International unit
JAT	Japanese ARMD Trial
LC	Low contrast
MAR	Minimum angle resolution

MPS	Macular Photocoagulation Study
MSAC	Medical Services Advisory Committee
MSSS	*Ministère de la Santé et des Services sociaux*
NEI	National Eye Institute (United States)
NICE	National Institute for Clinical Excellence (United Kingdom)
PDT	Photodynamic therapy
QALY	Quality-adjusted life-year
RAE	Retinol activity equivalent
RAMQ	*Régie de l'assurance maladie du Québec*
RDA	Recommended dietary allowance
RPE	Retinal pigment epithelium
SD_{REQ}	Standard deviation of requirements
SLO	Scanning laser ophthalmoscope
SMM	Norwegian Centre for Health Technology Assessment
SST	Submacular Surgery Trial
TAP	Treatment of Age-related Macular Degeneration with Photodynamic Therapy
TTT	Transpupillary thermotherapy
UL	Tolerable upper intake level
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VIO	Visudyne in Occult
VIP	Visudyne in Photodynamic Therapy
VIT	Verteporfin in Italy
WHO	World Health Organization

GLOSSARY

Atrophy
A decrease in the weight or size of an organ, tissue or cell. It may be physiological or pathological (hereditary, congenital or degenerative).

Contrast sensitivity
The ability to detect changes in lighting between two areas or to discriminate between an object and its background under varying degrees of lighting.

Drusen
Small, yellowish-white formations of acellular debris located either on the optic disc (in which they appear to be embedded and are accompanied by papilledema) or on Bruch's membrane (where they are clustered in the macular region).

Exudate
A serous or albuminous body fluid of inflammatory origin formed when serum passes through the vascular walls in the adjacent tissues.

Fibroblast
The stationary cell of connective tissue. It is very elongated or star-shaped and plays a role in the formation of collagen, reticulin and elastic fibers.

Fluorescein angiography
The photographing of vessels after the intra-arterial or intravenous injection of fluorescein.

Fovea
The part of the retina located at the centre of the macula. It consists solely of cones.

Macula
The posterior part of the retina, being a yellowish, horizontally oriented oval spot (2 mm wide and 1.5 mm high). At its centre is a funnel-shaped depression, the very centre of which is the fovea.

Photosensitizer
A compound capable of storing light energy, of being activated by light energy and of thus lending itself to numerous biochemical combinations.

Scotoma
A gap or blind spot in the visual field due to the presence of insensitive points on the retina.

Verteporfin
A monoacid benzoporphyrin derivative that is activated at a wavelength of approximately 690 nm. This compound can act as a photosensitizer.

Visual acuity
The discriminating power of the eye. Visual acuity can be defined as the minimum angle (or size) that a letter or form projected at a given distance from the eye must have for two separate black points, lines or spaces that make up the letter or form, to be discriminated by the retinal photoreceptors.

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1 PROBLEM

Age-related macular degeneration (ARMD) is a degenerative change in the retina that mainly affects people over the age of 55. It is the leading cause of poor vision in Western countries and leads to a gradual decrease in eyesight that can result in a loss of central vision. Affected individuals do not become totally blind, but they do lose all of the visual field needed to perform tasks requiring fine detail perception. Thus, they usually maintain a certain degree of autonomy and can move about, but they are unable to read, watch television or drive a car.

It is estimated that a half-million new cases of the most severe form of ARMD (neovascular) are diagnosed worldwide each year [Brown and Mellish, 2001]. With the aging of the population, this figure could triple within 25 years and thus generate significant social costs [Bressler, 2004; Sharma, 2001]. Until quite recently, there was no treatment for effectively slowing the progression of the disease. Over the past few years, however, several new therapeutic options for controlling neovascular ARMD have been tested. Photodynamic therapy with verteporfin photosensitizer is a technique used to slow the progression of the disease and the subsequent loss of vision. The main studies on this subject have shown that this technology is especially suited for patients with the exudative form of the disease with predominantly classic neovascularization or with occult neovascularization with no classic component [Bressler, 2001; VIP Study Group, 2001].

2 OBJECTIVES

The ophthalmologists representing the New Technologies Axis of the Vision Network, which is sponsored by the *Fonds de la recherche en santé du Québec* (FRSQ), asked the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) to examine the efficacy of photodynamic therapy for the treatment of ARMD. There was another aspect to this request, namely, informing optometrists, general practitioners and patients of the importance of diagnosing the disease as early as possible in order to treat it, if possible, and to thus avoid a substantial loss of visual acuity.

There are two main objectives to this report. One is to describe the pathophysiology and symptoms of and the treatments for age-related macular degeneration. The other is to assess the efficacy, acceptability and safety of photodynamic therapy with verteporfin photosensitizer and to examine the costs involved. The report will also look at the organization of the care and services relating to this therapeutic modality, although it is, in this case, only a preliminary examination, with its inherent limitations.

3 SEARCH METHOD

We examined the scientific literature on ARMD (*macular degeneration, ARMD*), photodynamic therapy (*photodynamic therapy*) and verteporfin (Visudyne®) (verteporfin OR Visudyne) published between January 1993[1] and June 2004 and indexed in the PubMed, Current Content Search and Cochrane Library databases. We also included abstracts of papers given at international conferences: ARVO (Association for Research in Vision and Ophthalmology) 2000, 2001 and 2002, and SOE (*Société ophtalmologique européenne*) 2001. We also documented certain aspects, by using the following keywords: *grid* AND *Amsler*; *antioxidant*; *vitamins*; and *side effects* AND *fluorescein*. We conducted these more-pointed searches for the period from 1975 to 2003.

We searched the International Network of Agencies for Health Technology Assessment (INAHTA) database and examined the agency reports on photodynamic therapy and ARMD thus identified: CCOHTA (Canadian Coordinating Office for Health Technology Assessment), SMM (Norwegian Centre for Health Technology Assessment), ANAES (*Agence nationale d'accréditation et d'évaluation en santé*), MSAC (Medical Services Advisory Committee) and NICE (National Institute for Clinical Excellence).

We also consulted several Web sites: Novartis, Visudyne® (Novartis Ophthalmics, Canada), the National Eye Institute (NEI), the *Régie de l'assurance maladie du Québec* (RAMQ), the *Fondation des aveugles du Québec*, and the *Association québécoise de la dégénérescence maculaire* (AQDM). Lastly, we conducted semistructured interviews with experts in the field of ophthalmology and visual rehabilitation (*Institut Nazareth et Louis-Braille*).

For the exploratory study of the organization of the care and services provided to ARMD patients, we used a qualitative approach based on semistructured telephone interviews with retinologists (n = 7) and ophthalmologists (n = 3) at all the university and community hospitals and private clinics in Québec that offer photodynamic therapy[2] and with the receptionists and nurses (n = 10) who work at these facilities. These practice locations are in various Québec's administrative regions. The interview guide contained a series of questions aimed at learning more about the practice, waiting times and the typical medical itinerary of a patient who thinks he/she has an eye problem. All the answers were recorded in writing and subsequently tabulated. This exploratory study took place in the summer of 2002.

1. We chose 1993 as the starting point because this was the year when research on photodynamic therapy began.

2. According to the data provided in June 2002 by the pharmaceutical company Norvartis Ophthalmics Canada, the manufacturer of verteporfin.

4 MACULAR DEGENERATION

4.1 THE RETINA, MACULA AND FOVEA

The retina is the tissue that lines the inner wall of the eye (Figure 1). Actually, it is an extremely complex structure consisting of about nine layers of cells, including a layer of highly-organized photoreceptor cells (cones and rods) within and around which are several other types of cells [Hogan et al., 1971]. It is in this photosensitive tissue that light signals are converted to nerve signals. They are subsequently transmitted to the brain via the optic nerve, where they are converted to visual images [Hogan et al., 1971].

In the centre of the retina is a circular area about 5 to 6 mm in diameter called the macula (yellow spot). The macula is responsible for central vision and has a high concentration of photoreceptor cells. Central vision is essential for performing most of our daily activities, such as reading and driving and for distinguishing facial features. However, although the macula is responsible for central vision, the perception of subtle, fine detail is dependent on a tiny area within the macular region called the fovea [Fine and Yanoff, 1979] (Figure 2).

FIGURE 1

Schematic representation of a longitudinal section of the eye

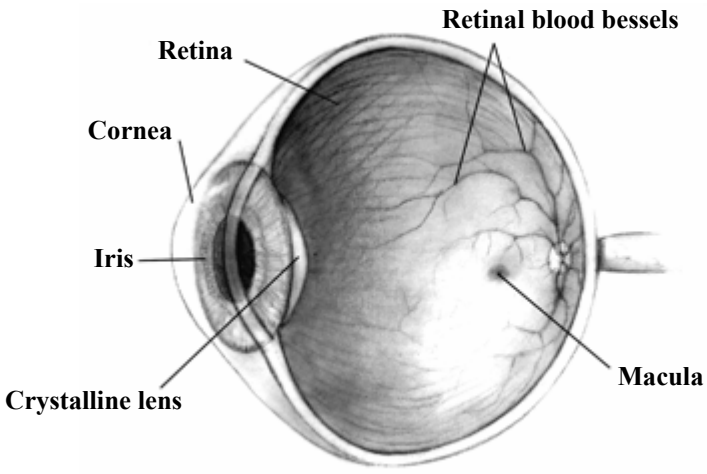

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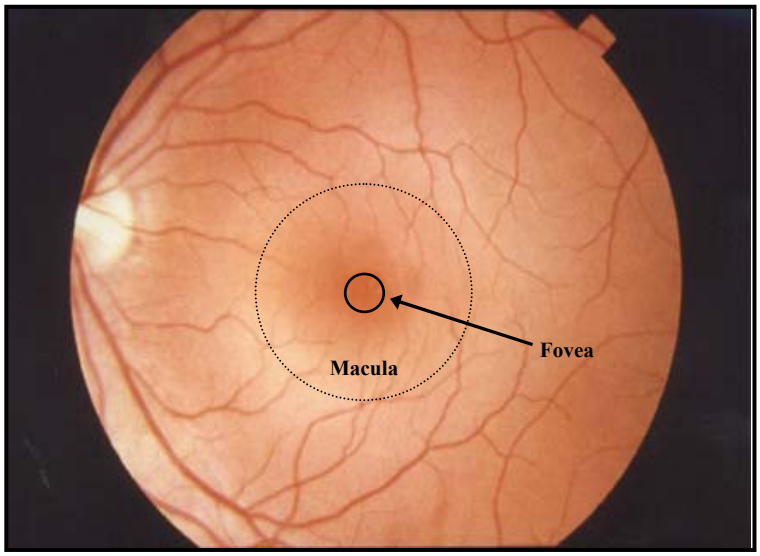
FIGURE 2

Photograph of a normal optic fundus



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When light rays enter the eye, they first go through the transparent structures, including the cornea, crystalline lens and vitreous body. Subsequently, the rays converge on the fovea. This small area lying within the vascular arcades is distinct from the rest of the retina in that it consists solely of cones. These photoreceptor cells become activated in full light and provide very precise detail and colour vision [Fine and Yanoff, 1979; Hogan et al., 1971]. It is for this reason that the images of the objects we observe form on the fovea and that it is the only area of the retina capable of providing visual acuity (VA) of 6/6[3].

The rest of the retina, including that portion of the macula outside the fovea, has, in addition to cones, another type of photoreceptor cell called a rod. Rods are at the basis of peripheral and twilight vision. They are more sensitive to light than cones but only provide blurred and colorless images. The concentration of rods is stable, whereas the concentration of cones decreases as the distance from the macula increases [Hogan et al., 1971].

The pathophysiology of ARMD is complex, and several types of cells located outside the retina seem to play an important role in the occurrence of the disease (Figure 3). The photoreceptors (cones and rods) are surrounded by extensions of the cells of the retinal pigment epithelium (RPE), which nourishes them and keeps them in place. Under the layer of retinal pigment epithelial cells is an elastic, acellular collagen membrane called Bruch's membrane. This membrane serves as a diffusion barrier between RPE cells and the choroid, a highly vascularized tissue. The photoreceptors and RPE cells are continually supplied in oxygen and nutrients through the choroid. The innermost layer of this tissue (the layer closest to Bruch's membrane), called the choriocapillaris, consists of numerous highly interlaced capillaries. Although several regions of the retina are supplied by blood

3. Visual acuity of 6/6 is the standard for good vision in the general population. For example, visual acuity of 6/12 is weaker vision that requires the individual to be at 6 metres in order to see what someone with good vision can see at 12 metres. This chart can also be expressed in feet, as is usually done in the American literature. Six metres equals 20 feet; 6/6 is therefore 20/20.

sources other than the choroid, the macula receives its nutrients only from the choriocapillaris layer. This tissular organization is one of the key elements of the pathophysiology of ARMD [Bressler et al., 2000].

4.2 DESCRIPTION OF THE FORMS OF AGE-RELATED MACULAR DEGENERATION (ARMD)

There are several clinical forms of age-related macular degeneration, ranging from the simple presence of drusen (yellowish, acellular debris) to atrophic plaques and more severe forms with neovascular membranes and their exudative and hemorrhagic complications. Since the cause of ARMD is not really known and its pathophysiology poorly understood, its definition encompasses all degenerative lesions of the macular region. These lesions appear on a previously normal eye after the age of 55 and cause a change in macular function and central vision [Bird et al., 1995].

ARMD has been divided into three histopathologic forms: an early form (also called age-related maculopathy (ARM) or pre-ARMD) and two advanced or progressive forms, called atrophic and neovascular forms [Bird et al., 1995].

In the scientific literature that was examined, many experts indicate that atrophic ARMD accounts for 80 to 90% of all new cases of ARMD (Figure 4). However, it is important to note that these authors thus include, in addition to the cases of atrophic ARMD (20 to 30%), the cases of ARM (60%). The neovascular form (also referred to as exudative or wet ARMD) reportedly accounts for 10 to 20% of the new cases of ARMD. However, according to the internationally accepted classification of the forms of ARMD (early form and advanced forms) [Fine et al., 2000; Bird et al., 1995], if the cases of ARM are excluded, the number of new cases of atrophic ARMD and that of new cases of neovascular ARMD are roughly the same, being 53% and 47%, respectively [Margherio et al., 2000].

FIGURE 3

Anatomy of the retina and the posterior part of the eye

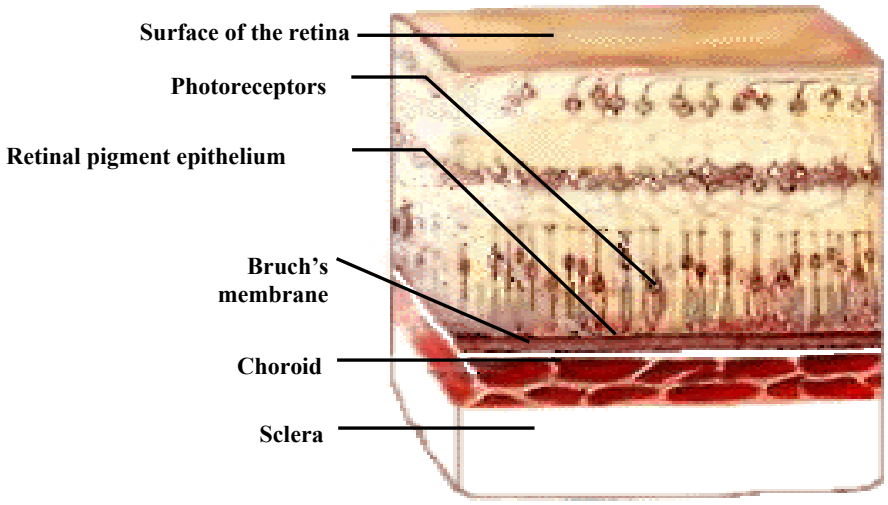

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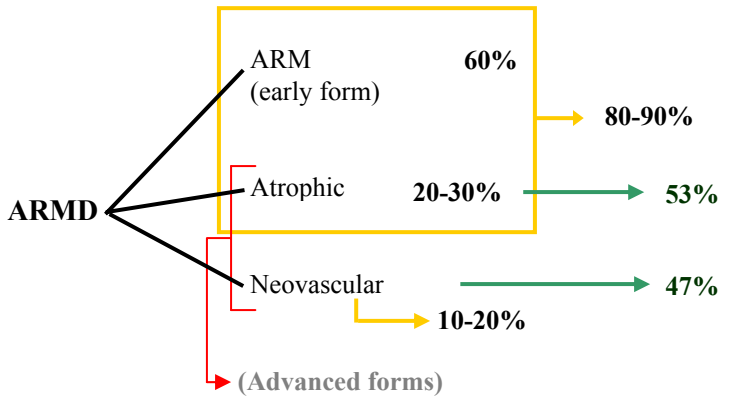
FIGURE 4

Classification of the different forms of ARMD



4.2.1 The early form

Age-related maculopathy (ARM) is an early form of ARMD. This stage of the disease is characterized by the presence of relatively small drusen, submacular pigment abnormalities and a few focal atrophic areas. At this stage of the disease, the loss of visual acuity is generally very small, and the symptoms are limited to visual difficulty or a need for brighter lighting. Ophthalmologic examinations performed in most people over the age of 50 reveal the presence of a least one druse (≤ 63 µm) in one or both eyes [Klein et al., 1997]. However, according to several studies, the advanced forms of ARMD could develop only in individuals with numerous large drusen (> 63 µm). [Mukesh et al., 2004; van Leeuwen et al., 2003b; Wang et al., 2003; AREDS Study Group, 2001; Fine et al., 2000; Klein et al., 1997].

4.2.2 The advanced or progressive forms

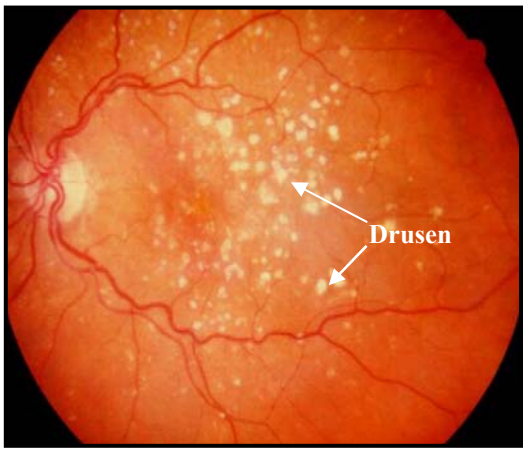
4.2.2.1 THE ATROPHIC FORM

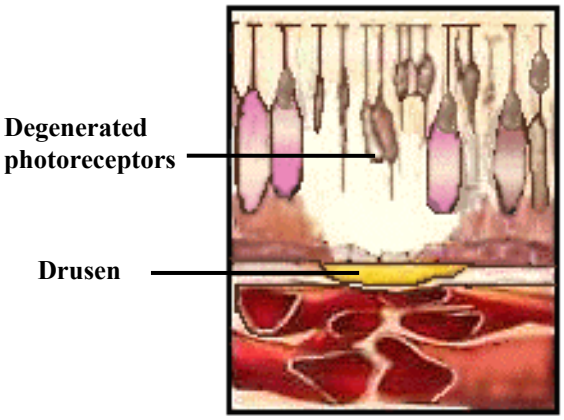
As acellular debris accumulates under the macula, the layers of photoreceptors and pigment epithelial cells rise and move away from the choriocapillaris. Atrophic ARMD is characterized by the gradual deterioration of photoreceptors, RPE cells and the choriocapillaris layer in the macular region (Figure 5). These pigmental and atrophic changes form small areas in the macula that tend to increase in size, leading to what is referred to as geographic atrophy, and to then coalesce to form a round central lesion known as areolar atrophy [Ambati et al., 2003; Fine et al., 2000].

The loss of several layers of photoreceptors results in scotomas (blind spots) in the visual field. Visual changes due to this type of macular degeneration occur slowly and gradually. The attendant vision loss is generally partial and transpires over a number of years (it takes 5 to 10 years before the point of legal blindness is reached). However, a few studies seem to indicate that patients with atrophic degeneration can maintain relatively good central vision (6/12 or better), but that they experience substantial functional limitations, such as unstable vision and limited vision at night or in low-lighting conditions [Fine et al., 2000; Steinmetz et al., 1993]. More severe vision loss can occur when complications affect the foveal region. In some cases, these signs may be precursors of the neovascular form of ARMD [Bressler and Gills, 2000]. Unfortunately, there is no treatment for atrophic ARMD.

FIGURE 5

The atrophic form of ARMD





A. Photograph an optic fundus exhibiting atrophic ARMD.

B. Drawing of a longitudinal section of a retina exhibiting atrophic ARMD.

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4.2.2.2 THE NEOVASCULAR FORM

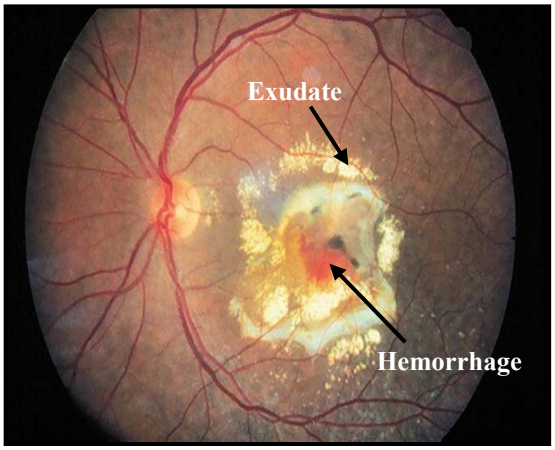
The neovascular form of the disease is much more pernicious and is responsible for about 90% of all severe ARMD-related vision loss. The disease is sudden in onset and can progress very quickly, causing irreversible damage to the macula, with a subsequent loss of central vision within a few weeks. In many cases, however, vision deteriorates more slowly, with progression to legal blindness (VA of 6/60 or less) taking up to two years. Very fortunately, in all cases, peripheral vision is preserved, which enables the patient to maintain a certain degree of autonomy [Lacour et al., 2002; Fine et al., 2000; MPS Group, 1996; MPS Group, 1991].

In this form of ARMD, the visual changes are caused by the abnormal growth of new blood vessels of choroidal origin in the subretinal space (Figure 6), a process better known as choroidal neovascularization (CNV). Its exact cause has yet to be elucidated. However, one interesting theory is that the continual accumulation of large drusen under the macula promotes the detachment of a layer of pigment epithelial cells and of a section of Bruch's membrane from the underlying choroidal tissue, thus preventing oxygen and nutrient transport to the photoreceptors [Bressler et al., 2000].

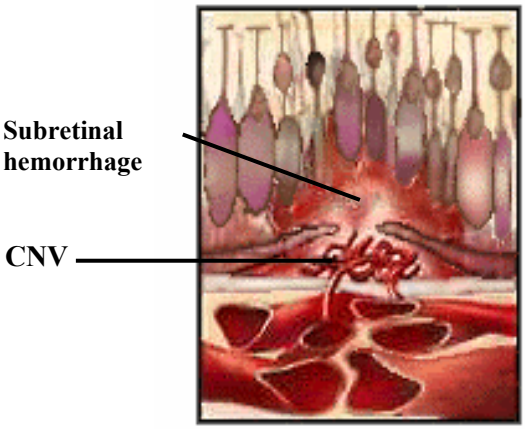
There are some indications that, unlike the pathologic process in the atrophic form, the decreased blood flow to the macula activates the formation of additional capillaries by the choriocapillaris by stimulating the secretion of angiogenic factors. These new vessels then pass through Bruch's membrane, which has already been weakened by the previous trauma, and invade the subretinal space in order to restore the energy supply to the retina. The endothelial wall of these new vessels is porous and allows blood and protein fluids to pass through easily, which causes lifting of the pigment epithelium and eventually hemorrhagic lesions and exudates [Arnold and Sarks, 2000; Bressler et al., 2000].

FIGURE 6

The neovascular form of ARMD



A. Photograph of an optic fundus exhibiting neovascular ARMD.



B. Longitudinal section of a retina exhibiting neovascular ARMD. Choroidal new vessels (CNV) have begun to invade the subretinal space

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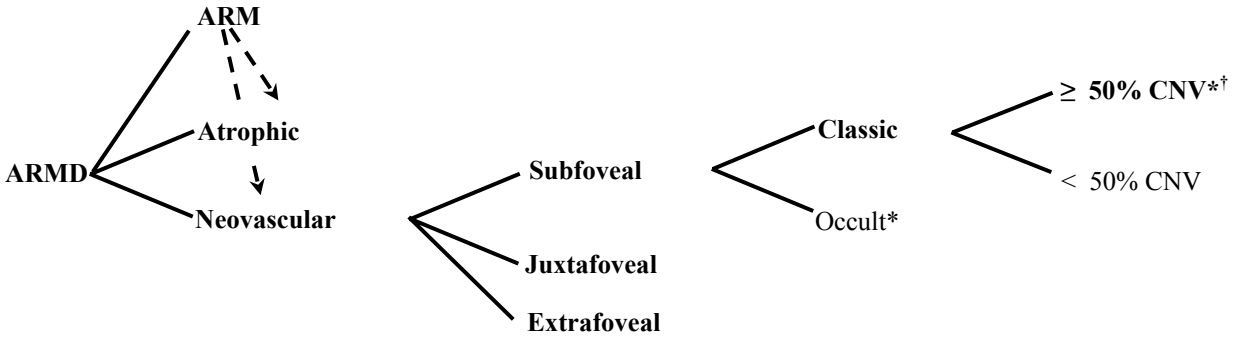
If the lesions are not treated, fibroblast growth will be greatly stimulated, with fibroblasts replacing the normal anatomic structures in the macula, including the photoreceptors. The course of the disease continues with the addition of new capillaries and the formation of a fibrous scar with atrophy of chorioretinal tissue and significant, irreversible visual loss [Ambati et al., 2003].

The lesions caused by the disease may be located outside the fovea (extrafoveal), at its periphery (juxtafoveal) or under the fovea (subfoveal or retrofoveal) (Figure 7). In addition, choroidal neovascular membranes can be divided into two types (classic and occult), depending on their appearance on fluorescein angiography. Classic membranes (also called visible) are characterized by a very clear demarcation and intense hyperfluorescence with leakage. Occult membranes have poorly demarcated boundaries and often appear as areas of fluorescence of undetermined source and with no precise shape. As a general rule, vision deteriorates much more quickly when the membranes are of the classic type [Arnold and Sarks, 2000].

FIGURE 7

Classification of the different forms of neovascular ARMD



* Indication for photodynamic therapy (see Section 5.2).
† CNV: choroidal neovascularization.

4.3 EPIDEMIOLOGICAL DATA

To date, there has been no epidemiological study of age-related macular degeneration in Québec. The ARMD incidence and prevalence data presented in this report were therefore extrapolated from the results of three rigorous population-based studies in Europe (Rotterdam Study) [Vingerling et al., 1995b], the United States (Beaver Dam Eye Study) [Klein et al., 1992] and Australia (Blue Mountains Eye Study) [Mitchell et al., 1995]. The results of these three studies are similar after adjustment for the distribution in the age groups studied. It is therefore highly likely that the prevalence and incidence of the disease in Québec are not much different from those observed in these countries.

These three studies provide estimates of the prevalence of progressive ARMD, which seems to be closely associated with the age of the study population. It is approximately 0.2% in people aged 55 to 64 and climbs to more than 13% in the over-85 age group [Smith et al., 2001]. The prevalence of ARMD in the over-55 population is 1.6% [Smith et al., 2001]. The prevalence of neovascular degeneration exhibits more or less the same profile, increasing from 0.17% (in people aged 55 to 64) to more than 5.8% in the over-85 population. If we apply the prevalence data by age group to the over-55 population in Québec (about 1,730,000) [Institut de la statistique du Québec, 2003], we can estimate that approximately 33,667 individuals have ARMD. In addition, according to the study by Margherio et al. [2000], slightly more than 47% of the population in the Western world with progressive ARMD have the neovascular form. It can therefore be extrapolated that 15,958 Quebecers over the age of 55 have this form of ARMD.

The incidence of ARMD is a bit more difficult to estimate, since the three research groups used different criteria to determine the stage of the disease. According to the Rotterdam Study, the 2-year cumulative incidence varies from 0.15% (65 to 74 years) to 1.75% (over 85 years), with a mean of 0.24% for the entire over-55 population [Klaver et al., 2001]. According to the authors of the Beaver Dam study, the 5-year cumulative incidence of the disease increases from 0.3% in the 55-to-64 age group to 5.4% in people over 75. The total incidence of the disease in people over the age of 55 is 0.9%. According to the same authors, the total incidence of neovascular ARMD in the target population (55 and over) is 0.4% [Klein et al., 1997]. According to the Blue Mountains study, the 5-year cumulative incidence of ARMD in the population is 1.1% and 1% for neovascular ARMD [Mitchell et al.,

2002a]. It should also be noted that other epidemiological studies have estimated the incidence of the disease by dividing the prevalence rates by the assumed average duration of the disease. These estimates yield an annual incidence of 1.2 to 6% in people over the age of 75. It is important to note that this methodology is questionable [Lacour et al., 2002; Vingerling et al., 1995c].

The incidence of ARMD is on the rise, and population aging is only one of the contributing factors to this increase [Desmettre et al., 2001; Fine et al., 2000]. The *Institut de la statistique du Québec* expects that the 55-and-over population will increase from 1,730,000 in 2001 to more than 3,170,000 in 2026, which will mean an increased demand for effective treatments for the disease. Some studies even estimate that the number of ARMD patients will probably triple within 25 years [Sharma, 2001].

Lastly, the disease is usually not bilateral in onset. When a patient has unilateral ARMD, the fellow eye is often affected within the four years following the initial diagnosis. The probability of the disease occurring in the fellow eye is 15% the first year. This figure increases cumulatively each year, to reach 60% after four years [Lacour et al., 2002; MPS Group, 1997].

4.4 CAUSES AND RISK FACTORS

The exact causes of ARMD have not yet been very clearly determined. However, case-control, cross-sectional and prospective cohort studies have revealed a number of risk factors [Fine et al., 2000; Klein et al., 1997; Mitchell et al., 1995; Vingerling et al., 1995b; EDCC Study Group, 1992]. Most of the studies examined found that, apart from age, the major risk factors are a family history of ARMD (genetic component) [Tuo et al., 2004; Klaver et al., 1998; Souied et al., 1998; Seddon et al., 1997; Klein et al., 1994] , smoking [Tomany et al., 2004b; Smith et al., 2001; Klein et al., 1998; Seddon et al., 1996; Christen et al., 1996], hypertension or atherosclerosis [van Leeuwen et al., 2003a; Bressler and Gills, 2000; Vingerling et al., 1995a] and a low intake or a low plasma level of lutein and zeaxanthin, two carotenoids obtained primarily from green vegetables [Seddon et al., 1994; EDCC Study Group, 1993]. Some studies have also shown that neovascular ARMD is more frequent in Caucasians [Friedman et al., 1999; Klein et al., 1995].

Several studies have found that ARMD is, at least partially, a hereditary disease. Epidemiological studies have shown that the rate of ARMD is higher in the first-degree relatives of an affected individual [Klaver et al., 1998; Seddon et al., 1997]. The importance of genetic factors has also been confirmed by studies involving homozygous twins, in whom a strong concordance of ARM and ARMD was found [Gottfredsdottir et al., 1999; Meyers et al., 1995; Klein et al., 1994]. It should, however, be borne in mind that ARMD is possibly a multifactorial, polygenic disease [Souied et al., 2001][4].

Smoking is one of the environmental factors most often associated with ARMD [Tomany et al., 2004b; Mitchell et al., 2002b; McCarty et al., 2001; Smith et al., 2001; Delcourt et al., 1998; Klein et al., 1998; Vingerling et al., 1996]. The relative risk of developing ARMD is five times higher for smokers, and this risk persists for 20 years after the individual stops smoking [Delcourt et al., 1998]. In addition, the disease develops 5 to 10 years earlier in

4. Linkage studies and molecular analyses have found nucleotide abnormalities in the gene sequence coding for proteins whose deffective function appears to be consistent with the appearance of the phenotype. These candidate genes might be responsible for the predisposition to ARMD [Tuo et al., 2004; Ambati et al., 2003]. The polymorphism found in the gene coding for apoprotein E (apoE) might play a role. Thus, allele ε2 is thought to be associated with a 50% increase in the risk of neovascular ARMD, allele ε4 with a 57% decrease in this risk [Souied et al., 1998]. Mutations in the retina-specific ATP-binding cassette transporter (ABCR) gene, which is responsible for Stargardt's disease, have also been associated with the occurrence of exudative ARMD [Souied et al., 2000; Allikmets, 2000; Allikmets et al., 1997]. Recently, the genes coding for the angiotensin-converting enzyme (ACE) and for the MSD (manganese superoxide dismutase) enzyme have also been implicated [Hamdi et al., 2002; Kimura et al., 2000]. It may be that just one of these genes is responsible for the predisposition to ARMD and that the others mainly influence the phenotype [Ambati et al., 2003; Hamdi and Kenney, 2003].

smokers and ex-smokers than in nonsmokers [Mitchell et al., 2002b]. This could be explained by the effects of smoking on antioxidant metabolism and on choroidal blood flow [Ambati et al., 2003]. The risk of atrophic ARMD is higher in male smokers than female smokers [Mitchell et al., 2002b]. However, it seems that the risk of progression to advanced ARMD is higher in female smokers (3.5 times higher) [Cote et al., 2002]. Furthermore, smoking is associated with an increased risk of recurrent neovascularization after laser photocoagulation [MPS Group, 1986]. In this case, nicotine stimulates neovascularization by causing endothelial cell proliferation and accelerating fibrovascular growth [Heeschen et al., 2001].

Lastly, other risk factors have been suggested, but the studies in question are sometimes contradictory or lack scientific rigour. Some of these potential risk factors are a low intake or a low plasma level of antioxidant vitamins (vitamins C and E) or of zinc [Smith et al., 1999; VandenLangenberg et al., 1998; Mares-Perlman et al., 1995; Seddon et al., 1994; West et al., 1994], the overconsumption of certain types of fats, such as monounsaturated and polyunsaturated fats, including linoleic acid [Cho et al., 2001; Seddon et al., 2001], overexposure to sunlight [Tomany et al., 2004a; Delcourt et al., 2001; Mitchell et al., 1998; Cruickshanks et al., 1993] and weakly pigmented irides (blue, green, etc.) [Klein et al., 1998; Holz et al., 1994; EDCC Study Group, 1992].

4.5 SYMPTOMS AND DIAGNOSIS

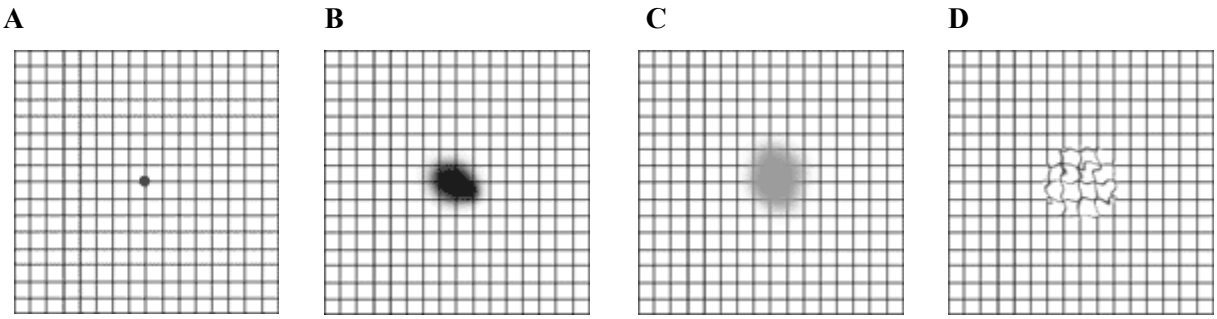
When there is abnormal growth of blood vessels of choroidal origin, the first symptoms mentioned by most patients are impaired colour vision and the appearance of areas of distortion in the visual field, of surfaces that seem abnormally wavy (metamorphopsia) or of dark spots in the central visual field. Patients sometimes notice these changes when looking at objects whose contours should be straight, such as tiles on a floor or the side of a building. As a general rule, affected individuals also note a relatively rapid decrease in visual acuity. Since this disease is usually not bilateral in onset, patients do not easily notice these changes when the unaffected eye is open [Guyer, 1997].

According to a number of organizations and authors, people can detect macular degeneration by performing a relatively simple test, the Amsler grid (Appendix A). There seems to be a professional consensus in the scientific literature and among the experts consulted that the Amsler grid is useful in detecting ARMD [Bressler, 2002; Mittra and Singerman, 2002; Sickenberg, 2001; Fine et al., 2000; Butler et al., 1997b; Canadian Task Force on the Periodic Health Examination, 1995]. The Amsler grid test is performed by holding the grid 35 cm from the eyes and fixing one's vision on the central dot with one eye at a time (Appendix A). As soon as disturbing symptoms appear (Figure 8), it is imperative that the patient see an ophthalmologist as quickly as possible.

The clinician can also use the Amsler grid to assess the loss of central vision [Guyer, 1997]. However, the disease is diagnosed with different tests, including examinations performed by means of a slit lamp, an ophthalmoscope and photographs of the optic fundus. Some of these examinations may reveal retinal bleeding, exudates and scarring. As soon as retinal changes are detected, the physician should recommend fluorescein or indocyanine green angiography and the relevant optic fundus photographs as soon as possible in order to confirm or rule out the disease and, if possible, to initiate treatments that can slow its progression [Guyer, 1997].

FIGURE 8

The Amsler grid test



A. Normal vision.

B to **D**. Vision of a person with ARMD. This figure depicts central lesions. However, all lesions are not central. Dark spots as well as deformations can therefore appear elsewhere on the grid.

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5 TREATMENTS FOR AGE-RELATED MACULAR DEGENERATION

Presently, there is no curative treatment for age-related macular degeneration (ARMD). The aim of the current therapies is instead to slow or stop the progression of the disease and to thus preserve the patient's residual vision. Photodynamic therapy (PDT) is a therapeutic modality for ARMD due to subfoveal choroidal neovascularization. It permits better preservation of the sensory retina and, consequently, of visual acuity. Other treatments include laser photocoagulation, transpupillary thermotherapy, surgical procedures (e.g., macular translocation and pigment epithelial cell transplantation), radiation therapy and therapy using interferon alfa-2a or other antiangiogenics. These treatments are currently in use or are presently being evaluated in clinical trials and will be discussed later.

5.1 PHOTODYNAMIC THERAPY

Photodynamic therapy involves irradiating, with low-intensity light, a tissue that has been subjected to a photosensitizer. Photosensitizers induce cytotoxic processes only when irradiated, and the damage is generally limited to a relatively precise area. This technique is already being used to treat various types of cancer, such as esophageal, bladder and lung cancer [AETMIS, 2004].

A number of photosensitizers are presently being investigated (Appendix B), but only verteporfin (Visudyne®) has been approved for the treatment of the neovascular form of ARMD.

5.1.1 Verteporfin

Verteporfin, which is marketed under the name of Visudyne®, was created by QLT Phototherapeutics Inc., of British Columbia. It is now marketed by Novartis Ophthalmics, a subdivision of Novartis. Visudyne has been approved for the treatment of the exudative form of ARMD with predominantly classic neovascularization in nearly 75 countries, and for the treatment of the pure occult form (Appendix C). Health Canada approved the use of this drug in May 2000 for the treatment of classic neovascularization. In April 2004, the indication was still in abeyance for the treatment of occult neovascularization. Visudyne is covered by the *Régie de l'assurance maladie du Québec* (RAMQ) as an exception drug.

The active ingredient in Visudyne is verteporfin, a benzoporphyrin derivative monoacid. Apart from an absorption spectrum with a peak at a wavelength of approximately 690 nm and the availability of a laser source matching this peak, this compound offers the advantage of rapid hepatic elimination within 24 hours of its administration, which limits the duration of visual or cutaneous photosensitivity [Desmettre et al., 2001; Scott and Goa, 2000]. Verteporfin is especially effective in ophthalmology, since it is light-activated by a monochromatically red diode laser that easily penetrates blood and fibrous tissues. It can therefore act on choroidal neovasculature [Soubrane, 2001].

Verteporfin is administered after liposomal encapsulation. The wall of the liposomes consists of a double layer of phospholipid that protects the photosensitizer from enzymatic breakdown mechanisms [Hooper and Guymer, 2003; Desmettre et al., 2001; Soubrane, 2001]. This vector also permits the formation of complexes with other lipophilic proteins, such as serum LDL (low-density lipoprotein) [Scott and Goa, 2000]. According to animal study data, proliferating cells, including neovascular endothelial cells and tumor cells, express large numbers of receptors for this lipoprotein [Kramer et al., 1996; Allison et al., 1994]. This LDL-liposome complex might

therefore facilitate the entry and accumulation of verteporfin in LDL receptor-rich choroidal neovascular vessels. The preferential binding to choroidal vascular endothelial cells is relatively specific, but the RPE cells express a certain number of these receptors as well [Scott and Goa, 2000; Husain et al., 1999; Miller et al., 1995].

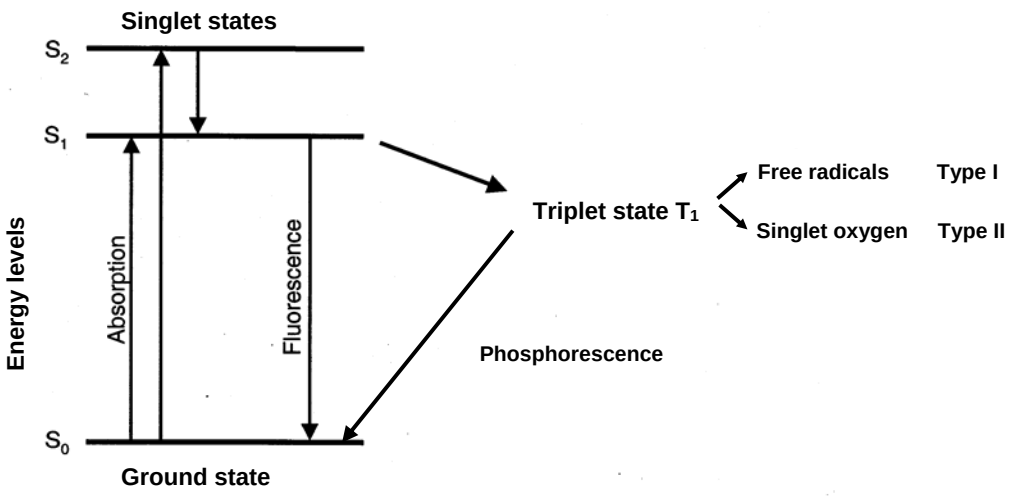
5.1.2 Mechanisms of action of photodynamic therapy

The mechanisms of action of PDT are based on the oxidation of organic tissue components. Activation of the photosensitizer by an appropriate light source causes a photochemical reaction better known as a photodynamic process. When the photosensitizer is activated by light, it absorbs a certain quantity of energy in the form of photons. The molecule thus becomes excited and goes through different excitation levels called *singlet states* (Figure 9). However, at this point, the photosensitizer has excess energy, which it will quickly lose. Thus, the higher singlet states (S_2, S_3, etc.) deactivate very quickly toward the lower-energy singlet state S_1. The latter, which is relatively more stable than the former, can lose its energy by releasing it in the form of heat into the surroundings, by emitting fluorescence or by passing to an intermediate state called the *triplet state*. The drop from the triplet state to the ground state is much slower than that from the singlet state. It is at the triplet state that the photosensitizer will have time to react with other molecules in the surrounding tissue [Hooper and Guymer, 2003; Rivellese and Baumal, 2000; Schmidt-Erfurth and Hasan, 2000].

Chemical processes can occur in the triplet state through two main pathways. In type I mechanisms, the photosensitizer reacts chemically with molecules via direct interaction. Redox reactions lead to the formation of radical species and, through complex processes generally involving oxygen (in the form of superoxide anions [O_2^-]), to the breakdown of adjacent molecules. Type II mechanisms require an energy transfer to oxygen that carries it to the singlet state ($^1O_2$), a highly oxidizing species. At the same time, the photosensitizer returns to its ground state and is ready to gather light energy again [Rivellese and Baumal, 2000].

FIGURE 9

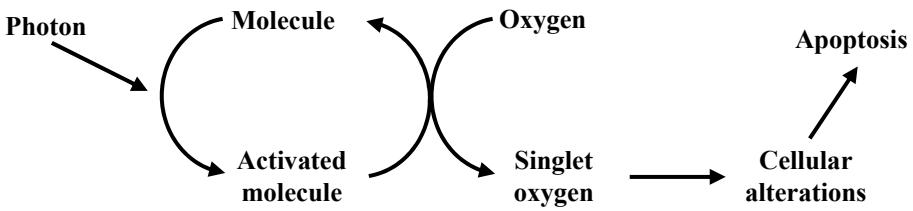
Diagram showing the energy levels of a molecule and the different pathways leading to the emission of fluorescence and to photosensitization processes



Source: Schmidt-Erfurth and Hasan, 2000.

FIGURE 10

Type II mechanisms are preponderant in the photodynamic process



Source: Desmettre et al., 2001.

The photodynamic process occurs mainly through type II mechanisms (Figure 10). Amino acids, enzymes, certain nucleic acid bases and, to a lesser extent, the lipid chains in membranes are very sensitive to the action of singlet oxygen. Since it does not diffuse into the surroundings, this highly reactive species damages tissues locally. The oxidative stress causes major cellular changes and eventually gives way to a mechanism of apoptosis (triggering of cell death) that acts both on the cell membranes and mitochondria. In the case of age-related macular degeneration, it is the endothelial cells of choroidal new vessels that are particularly affected. Local thromboses develop in these vessels, which can ultimately cause their destruction [Hooper and Guymer, 2003; Brown and Mellish, 2001; Shuler et al., 2001; Scott and Goa, 2000; Lin et al., 1994].

5.1.3 Treatment protocol

Photodynamic therapy is a two-step procedure. The first step consists in injecting the photosensitizer into a vein in the arm or hand. The quantity of photosensitizer injected depends on the body surface, which is calculated from the patient's height and weight, and it is injected at a concentration of 6 mg/m^2. The desired dose of Visudyne is first diluted in 5% dextrose in order to obtain a total volume of 30 mL of liquid, which is administered over a 10-minute period. The second step involves activating the photosensitizer. Fifteen minutes after the start of injection of the photosensitizer, irradiation of the retina is started with a monochromatic diode laser set at a wavelength of 689 nm (± 3 nm). The recommended fluence for treating choroidal new vessels is 50 J/cm^2, with an intensity of 600 mW/cm^2. A beam of light is therefore aimed at the retina, using an optic fiber or a slit lamp with the appropriate lenses [Miller et al., 1999]. Given that this type of laser does not produce any heat, there is generally no obvious effect on vision during the treatment, although, some patients may notice a transient decrease in visual acuity. After the treatment, the patient should avoid exposure to the sun and other intense light sources for two days (about 48 hours) [Miller et al., 1999]. Subsequently, the minimum frequency of follow-up visits is three months. PDT retreatments may prove necessary and extend over several years.

As mentioned earlier, the disease is generally not bilateral in onset. The affected eye (if it meets the treatment eligibility criteria) is treated with PDT, and the fellow eye is not treated. After the first treatment, there are regularly scheduled medical follow-up visits (about every three months), and fluorescein angiography is performed during each visit. If, during a given follow-up visit, it is found

that the disease seems to be progressing in the affected eye (leakage observed on fluorescein angiography), the patient will receive another PDT treatment. Depending on the course of the disease, the PDT retreatments may extend over a period of about three years. During this time, the disease may appear in the fellow eye, and, if it meets the PDT eligibility criteria, the treatment will be administered to both eyes at the same time. Briefly, then, a patient may have neovascular ARMD in one eye only or in both eyes at the same time. The disease may also appear in the fellow eye while the first eye is being treated or after the treatment has been completed. The PDT treatment profile will therefore vary from patient to patient.

5.2 THERAPEUTIC INDICATION

The indication for PDT with verteporfin for the treatment of age-related macular degeneration presently recognized by Health Canada is as follows: patients with subfoveal ARMD with more than 50% classic neovascularization. However, the manufacturer has submitted a request to broaden the indication to include patients with 100% occult subfoveal neovascular ARMD. This therapeutic indication (pure occult neovascular ARMD) has been recognized in the member countries of the European Union since August 2002 and in several other countries, and should be recognized in Canada in the near future.

6 EFFICACY

The examination of the clinical efficacy of PDT with verteporfin photosensitizer is based primarily on the results of two randomized, double-blind, multicentre clinical studies: the TAP (Treatment of Age-related Macular Degeneration with Photodynamic Therapy) study and the VIP (Visudyne in Photodynamic Therapy) study (Appendix D). The notions of visual acuity and angiographic changes will be discussed by study, whereas the notion of contrast sensitivity will be presented in a table with both studies grouped together.

6.1 PATIENTS WITH CLASSIC NEOVASCULARIZATION

The TAP study was conducted at 22 ophthalmology research centres in Europe and North America. It involved 609 patients, mostly with classic neovascularization and diminished visual acuity (1 to 5/10 on an ETDRS [Early Treatment Diabetic Retinopathy Study] logarithmic chart (Appendix E). The subjects were randomized to two groups, one receiving verteporfin by infusion, the other receiving placebo, in a ratio of 2:1 (402/207). Baseline visual acuity ranged from 6/12 (20/40) to 6/24 (20/80) in 50% of the participants.

The preliminary results, which were published 12 months into the study, showed that visual acuity, contrast sensitivity[5] and the angiographic appearance of the lesions were significantly better in the treatment group than in the control group (Tables 1 and 3). However, visual acuity gradually diminished in both groups: 54% of the placebo-treated eyes showed a decrease in visual acuity of at least three lines[6] (15 letters of visual acuity on an ETDRS chart or on the Bailey-Lovie test) compared to 39% of the eyes in the group treated with verteporfin. When a greater decrease[7] in visual acuity was taken into account, i.e., six lines, the difference persisted (15% of the eyes in the verteporfin-treated group; 24% of the eyes in the control group).

The subgroup analysis showed that PDT was more effective in the eyes with predominantly classic neovascularization than in those with occult neovascularization. Thus, only 33% of the eyes with more than 50% classic neovascularization (n = 242) lost at least three lines compared to 61% of the control group eyes. When classic neovascularization was considered separately (no occult neovascularization), visual acuity remained stable or improved in the treatment group (67% vs. 27% in the control group) [TAP Study Group, 1999].

The results of the examinations performed at 24 months (TAP Study II) confirmed those obtained at 12 months. All the results presented are significant. Approximately 85% of the patients recruited at the outset completed the second year of the study: 189 (47%) of the 402 eyes in the verteporfin-treated group lost at least three lines of visual acuity compared to 129 (62%) of the 207 control group eyes. There was substantial avoidance of severe visual acuity loss: 18% of the eyes in the verteporfin-treated group lost more than six lines ($\geq$ 30 letters) of visual acuity compared to 30% of the control group eyes. At the end of the second year, in the subjects with predominantly classic neovascularization, a considerably higher percentage of those in the control group than of verteporfin-treated patients had lost at least three lines of visual acuity (69% vs. 41%). When only the patients with classic lesions with no occult element are considered, this figure climbs to 71% for the control group compared to 30% for the verteporfin-treated group.

5. Contrast sensitivity (CS) can be defined as the ability to detect changes in lighting between two areas or to discriminate between an object and its background under varying degrees of lighting [Zanlonghi, 2001; Casson and Racette, 2000].

6. One line of visual acuity on an ETDRS chart equals five letters.

7. In this report, a moderate loss of visual acuity means a loss of three lines of vision. A severe loss of visual acuity is a loss of six lines of vision.

TABLE 1

Results of the TAP (Treatment of Age-related Macular Degeneration with Photodynamic Therapy) study

POPULATION AND SUBPOPULATION **Number of lines of visual acuity lost**	FOLLOW-UP VISITS (MONTH)	VERTEPORFIN, NUMBER OF EYES (%)	PLACEBO, NUMBER OF EYES (%)	*P*
Total patient population (n = 609)				
≥ 3	12	156 (39)	111 (54)	< 0.001
	24	189 (47)	129 (62)	< 0.001
≥ 6	12	59 (15)	49 (24)	0.006
	24	73 (18)	62 (30)	< 0.001
Patients with predominantly classic CNV (n = 242)				
≥ 3	12	52 (33)	50 (61)	< 0.001
	24	65 (41)	57 (69)	< 0.001
≥ 6	12	19 (12)	28 (34)	< 0.001
	24	24 (15)	30 (36)	< 0.001
▪ Patients with predominantly classic CNV with no occult CNV (n = 135)				
≥ 3	12	21 (23)	32 (73)	< 0.001
≥ 6	24	28 (30)	35 (71)	< 0.001
	12	9 (10)	18 (41)	< 0.001
▪ Patients with predominantly classic CNV with occult CNV (n = 111)				
≥ 6	12	10 (14)	10 (25)	0.17
	24	12 (17)	14 (36)	0.03

Note: The patients who lost fewer than three lines of visual acuity are not included in this table.
Sources: TAP and VIP Study Group, 2002; Bressler, 2001; TAP Study Group, 1999.

The evaluation of the decrease in visual acuity shows that, at one year, the mean loss in the verteporfin-treated group was 11.2 letters on an ETDRS chart versus 17.4 in the control group, and, at two years, 13.4 letters in the verteporfin-treated group versus 19.6 in the control group ($p < 0.001$) (Table 4b). The results of this study also show that contrast sensitivity remained relatively stable in the verteporfin-treated group, which only experienced a loss of 1.3 letters, with the control group experiencing a loss of 4.5 letters the first year and 5.2 the second (Table 3) [Bressler, 2001].

The 1-year results of an extension of a phase III trial have been published. They mainly show that visual acuity remained stable during the third year of therapy, with no additional adverse effects [Blumenkranz et al., 2002]. The patients in the verteporfin-treated group received an average of 1.3 treatments during this additional year, which is a significant decrease in the number of treatments. The patients were retreated an average of 3.4 times the first year and 2.2 times second, for a total of seven treatments in three years [Blumenkranz et al., 2002; Bressler, 2001a]. The control group patients were treated an average of 6.5 times during the first two years of the study. The subjects were retreated every three months if angiography showed fluorescein leakage [Bressler, 2001; TAP Study Group, 1999].

This randomized, controlled study showed that PDT with verteporfin is an effective treatment for slowing the progression of ARMD, especially in patients with more than 50% classic neovascularization. The greatest loss of visual acuity occurred within the first year

following the initial treatment and especially during the first three to six months. During the second year, visual loss was minimal. Such minimal loss of visual acuity and contrast sensitivity suggests that PDT selectively avoided substantial damage to the photoreceptors and the cells of the underlying retinal pigment epithelium [Bressler, 2001]. Overall, this study showed that PDT with verteporfin reduces the number of ARMD patients who become legally blind (less than 6/60) after two years (Table 4a). However, it is important to note that the visual acuity of the patients in this study continued to decrease (77% of those who received placebo vs. 70% of those treated with verteporfin) after 24 months of treatment [Bressler, 2001].

A number of studies examining substantially the same parameters, such as VIT (Verteporfin in Italy) and JAT (Japanese ARMD Trial), are currently in progress, and the preliminary results seem to confirm the efficacy data from the TAP study [JAT Study Group, 2003; Tano and JAT Study Group, 2002]. Other studies that have just been published, albeit nonrandomized and more methodologically flawed than the TAP and VIT studies, seem to confirm the efficacy of PDT in the treatment of predominantly classic neovascularization [Barnes et al., 2004; Sharma et al., 2004].

6.2 PATIENTS WITH OCCULT AND NO CLASSIC NEOVASCULARIZATION

The VIP study was conducted at 28 ophthalmology research centres in Europe and North America. This randomized, controlled study involved 339 patients mainly with occult and no classic neovascularization and with reduced visual acuity (1 to 5/10 on an ETDRS logarithmic chart). The study participants were randomized to verteporfin therapy or placebo therapy at a ratio of 2:1. The preliminary results, published after month 12 of the study, showed no significant beneficial effect in the verteporfin-treated patients: 51% of the treatment group eyes compared to 54% of the control group eyes had lost at least three lines of visual acuity [VIP Study Group, 2001].

However, after the 12th month, certain effects started to appear in the verteporfin-treated eyes (Table 2). The results of the month 24 examinations (VIP Study II) showed that 67% of the control group eyes (76/114) had lost at least three lines of visual acuity (15 letters of visual acuity on an ETDRS chart) compared to 54% of the experimental group eyes (121/225). For greater decreases in visual acuity ($\geq$ 6 lines or $\geq$ 30 letters), there was a substantial difference between the two groups (30% in the verteporfin-treated group vs. 47% in the placebo group) [VIP Study Group, 2001]. These results are statistically significant.

The subgroup analyses at two years revealed that PDT was effective in the patients with pure occult neovascularization. Thus, in the subgroup of patients with pure occult and no classic neovascularization (n = 258), the proportion of subjects who lost at least three lines of vision was 68% in the control group and 55% in the treatment group (p = 0.032). This subgroup consisted of only 258 eyes (339 eyes at the outset), since 24% (81 eyes) of the participants also had a certain proportion of classic neovascularization (< 50%). In addition, the decrease in visual acuity and contrast sensitivity was smaller in the verteporfin-treated group than in the control group. Thus, approximately 26% of the treated patients (compared to 40% of the controls) had a visual acuity of less than 6/60 (p = 0.006) (Table 4a). Similarly, 34% of the control group patients had lost at least nine letters of contrast sensitivity, while about 20% of the patients in the verteporfin-treated group experienced the same loss (p = 0.01). During the two study years, the patients received an average of five PDT treatments. They were retreated every three months when angiography showed fluorescein leakage [VIP Study Group, 2001].

The VIP study found that PDT with verteporfin significantly reduces moderate to severe visual acuity loss in patients with occult subfoveal neovascular lesions with no classic element. The subgroup analyses seem to suggest that this treatment is especially effective when the disease is in progression (manifested as the appearance of new blood vessels of choroidal origin, hemorrhage or exudates; an increase in the area of the lesion [at least 10%]; or a decrease in visual acuity [about one line or five letters]) in the 12 weeks preceding the medical examination. In addition, certain factors, such as lesion size and residual visual acuity, might affect the effectiveness of the treatment. Even if they had not been planned at the beginning of the study, additional analyses were performed on small subgroups of patients. Given the low statistical power and the ad hoc nature of these analyses, it is important to note that their results are much debated. The analyses will therefore have to be the subject of more-thorough studies before any firm conclusions can be drawn from them. These additional preliminary analyses do, however, suggest that PDT yields better results in the subgroup of patients with small lesions (fewer than four MPS [Macular Photocoagulation Study] disc areas or poor visual acuity (6/15 or less) (Table 2).

TABLE 2

Results of the VIP (Visudyne in Photodynamic Therapy) study

POPULATION AND SUBPOPULATIONS **Number of lines of visual acuity lost**	FOLLOW-UP VISITS (MONTH)	VERTEPORFIN, NUMBER OF EYES (%)	PLACEBO, NUMBER OF EYES (%)	*P*
Total patient population/eyes (n = 339)				
≥ 3	12	114 (51)	62 (54)	0.520
	24	121 (54)	76 (67)	0.023
≥ 6	24	67 (30)	54 (47)	< 0.001
Patients with pure occult CNV with no classic CNV (n = 258)				
≥ 3	12	85 (51)	51 (54)	0.515
	24	91 (55)	63 (68)	0.032
≥ 6	12	37 (22)	30 (33)	0.070
	24	48 (29)	43 (47)	0.004
Patients with pure occult CNV with small lesions or poor visual acuity (n = 189)				
≥ 3	24	60 (49)	48 (75)	< 0.001
≥ 6	24	26 (21)	31 (48)	< 0.001
Patients with pure occult CNV with large lesions and good visual acuity (n = 73)				
≥ 3	24	31 (72)	14 (52)	0.09*
≥ 6	24	22 (51)	11 (41)	0.40*

Sources: TAP and VIP Study Group, 2002; VIP Study Group, 2001.

* Although not significant, the benefits of the treatment were superior in the control group patients.
Note: The patients who lost fewer than three lines of visual acuity are not included in this table.

Several similar studies, such as the VIO (Visudyne in Occult) study, are presently under way, and their preliminary results seem to confirm the results presented in this report [Schachat and VIP Study Group, 2001].

The TAP and VIP studies found that photodynamic therapy reduced by about 9% and 14%, respectively, the rate of blindness after two years in ARMD patients who were eligible for this treatment [Bressler, 2001] (Table 4a). However, these studies evaluated the efficacy of PDT in patients with a visual acuity in the eye to be treated of 6/12 to 6/60. They did not find any beneficial effects in the patients whose visual acuity in the eye to be treated was less than 6/60 (legal blindness). In addition, these studies did not examine the aspects of the patients' quality of life or the functional capacities relating to these visual differences. Thus, no conclusions can be drawn about the benefits, in terms of the patients' quality of life, of preserving a few lines of vision. It should also be added that the TAP and VIP studies used very stringent patient selection protocols and very rigorous, preestablished treatment and follow-up procedures. A study conducted at the Royal Victorian Eye and Ear Hospital, in Australia, found that when the therapeutic indications and the patient follow-up and monitoring procedures were not the same as those in the TAP and VIP studies, the disease normally progressed to a loss of visual acuity and that PDT offered few visual benefits [Essex et al., 2003]. This study showed that to obtain results comparable to those of randomized, clinical trials in current medical practice, one must necessarily use the same patient selection, treatment and follow-up guidelines.

TABLE 3

Changes in contrast sensitivity in the patients who participated in the TAP and VIP studies

FOLLOW-UP VISIT (MONTHS)	CONTRAST SENSITIVITY (Number of letters lost)		
	Verteporfin	**Placebo**	***P***
TAP study: total study population (n = 609)			
12	1.3	4.5	< 0.001
24	1.3	5.2	< 0.001
VIP study: patients with pure occult CNV (n = 258)			
12	3.6	4.4	0.164
24	3.7	6.1	0.004

Sources: TAP and VIP Study Group, 2002; VIP Study Group, 2001; Bressler, 2001; TAP Study Group, 1999.

TABLE 4a

Outcomes in the TAP and VIP studies

Primary outcome: rate of legal blindness

	TAP STUDY		VIP STUDY	
	Treatment (% of patients)	Placebo (% of patients)	Treatment (% of patients)	Placebo (% of patients)
Rate of legal blindness (< 6/60)	41	55	26	40

TABLE 4b

Outcomes in the TAP and VIP studies

Secondary outcome: mean difference between visual acuity in the experimental group and that in the control group

	Loss of visual acuity (number of letters)			
	TAP STUDY		VIP STUDY	
	Treatment	Placebo	Treatment	Placebo
	13.4	19.6	19.1	25.1
Mean difference between treatment and placebo (number of letters)	6.2		6.0	

Sources: VIP Study Group, 2001; TAP Study Group, 1999.

6.3 PATIENTS WITH MINIMALLY CLASSIC NEOVASCULARIZATION

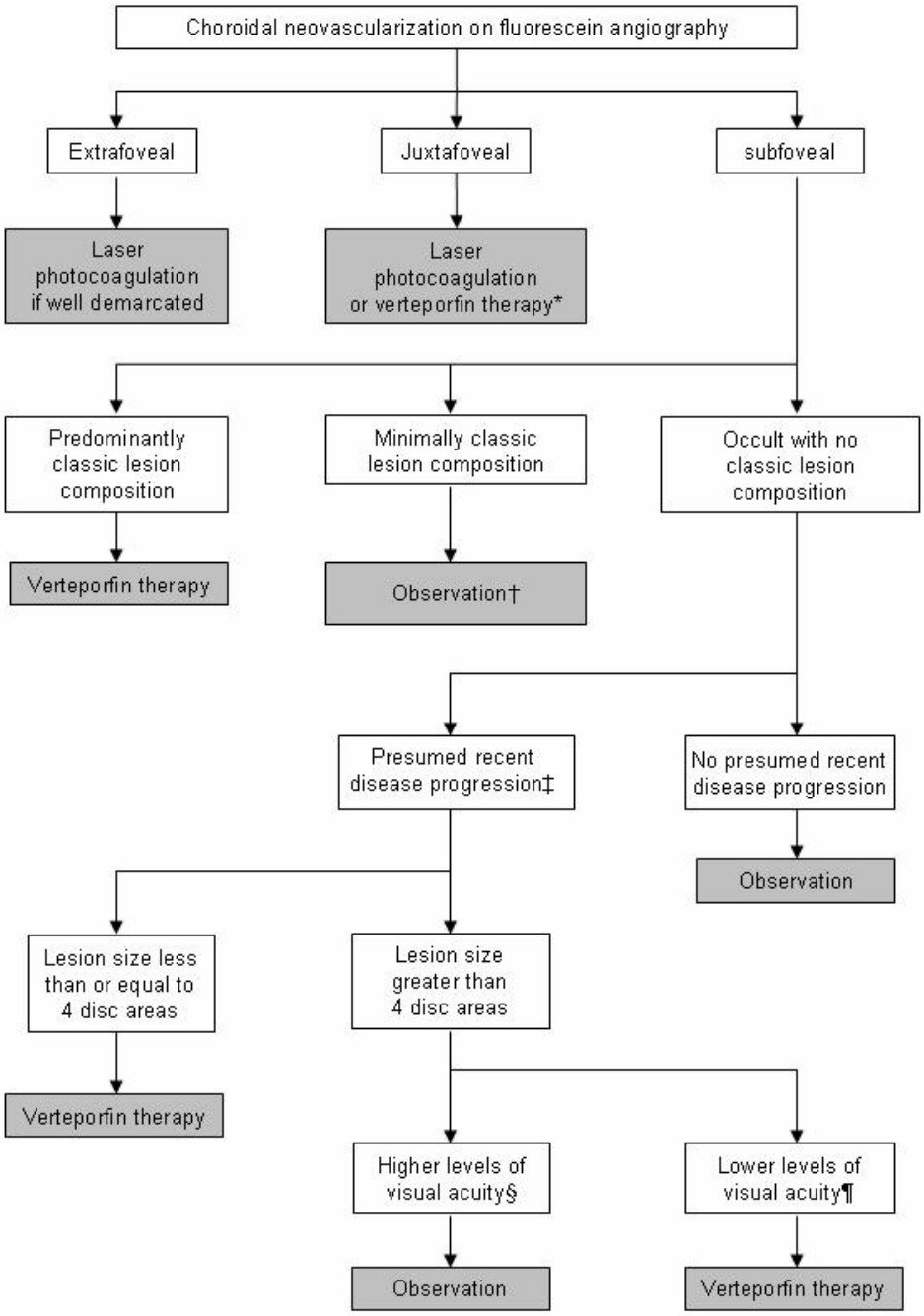
A subgroup of patients recruited for the TAP and VIP studies had minimally classic subfoveal lesions, i.e., the area of classic neovascularization occupied less than 50% but more than 0% of the entire lesion. The data gathered in these studies indicate that PDT has no beneficial effect on this type of lesion.

However, an analysis of a small subgroup of these participants seems to suggest that this therapy might be effective when the disease is in progression, when the proportion of classic neovascularization approaches 50%, when the size of the lesion is less than four MPS disc areas, and when the patient has poor visual acuity (< 6/15). When these conditions were met, 63% of the placebo patients and 47% of the PDT patients lost at least three lines. However, these data concern a small number of subjects. Other, more-exhaustive studies should be undertaken to confirm whether or not this treatment is effective in patients with ARMD with less than 50% classic neovascularization [VIP Study Group, 2001; Bressler, 2001].

In 2002, researchers who had collaborated in the TAP and VIP studies established guidelines for the utilization of PDT with verteporfin photosensitizer to treat ARMD patients. These guidelines were developed from scientific data and consensus of expert opinion [TAP and VIP Study Group, 2002] (Figure 11).

FIGURE 11

Algorithm for managing patients with symptomatic neovascular ARMD



Source: TAP and VIP Study Group, 2002.

* Verteporfin therapy should be considered for juxtafoveal lesions that are so close to the fovea that they cannot be treated by photocoagulation.

† Verteporfin therapy might be considered when the proportion of classic CNV is increasing and approaching 50% or when the lesion is relatively small and associated with poor visual acuity, and when the proportion of classic CNV is approximately 50%.

‡ Presence of blood associated with CNV, or growth of lesion within the 12 weeks preceding the medical consultation, or deterioration of visual acuity within the past 12 weeks.

§ VA > 6/15.

¶ VA ≤ 6/15.

7 ADVERSE EFFECTS AND SAFETY

7.1 PHOTODYNAMIC THERAPY

Photodynamic therapy with verteporfin photosensitizer has a good safety profile and is generally well tolerated. A number of adverse effects have, however, been observed. Transient visual disturbances (decreased vision or visual field alterations) are observed in 18% of cases. One to 4% of patients may experience severe vision loss (six or more lines of visual acuity) during the week following the treatment, but in most cases there is a partial recovery of eyesight. In 13.4% of the cases, patients also complained of various injection site reactions, in particular, pain, edema and inflammation. Lumbar pain occurring only during the infusion was reported in 2.2% of the cases. This pain always disappeared as soon as the injection was stopped. Lastly, 3% of the patients indicated that they experienced transient photosensitivity reactions. Fewer than 2% of the patients stopped their treatment because of adverse effects [Arnold et al., 2004; Azab et al., 2004; Bressler, 2001; American Academy of Ophthalmology, 2000b].

7.2 FLUORESCEIN ANGIOGRAPHY

The adverse reactions that occur after fluorescein angiography are usually minor. They are mainly nausea and vomiting. According to the studies examined, the incidence of adverse reactions is approximately 5% (range: 0.6 to 16%) in patients undergoing angiography for the first time [The Medical Letter, 2003; Seigel, 2002; McLauchlan et al., 2001; Lopez-Saez et al., 1998; Jennings and Mathews, 1994; Kwiterovich et al., 1991; Yannuzzi et al., 1986]. The frequency of adverse reactions to subsequent angiographies is, however, different. Thus, the percentage of reactions was 1.8% when the patients did not experience any adverse effects during their first angiography and 48% when they did [Kwiterovich et al., 1991].

- **Minor reactions**: Nausea (3%), vomiting (1.2%), extravasation of dye (causing complications: pain at the injection site, subcutaneous granuloma and cutaneous necrosis) (0.2%); transient yellow coloration of the conjunctivae, skin and urine.
- **Moderate reactions** (0.5 to 1.5% of cases): Itching, hives, excessive sneezing, vagal discomfort, hypotension, dyspnea and syncope.
- **Severe reactions** (0.05%): Allergic (asthma, angioedema, anaphylactic reaction), cardiac (cardiac arrest, myocardial infarction), and neurological (seizures, coma, stroke) reactions. The number of cases of fatal anaphylactic shock has been estimated at 1 in 220,000 angiographies [The Medical Letter, 2003; Seigel, 2002; McLauchlan et al., 2001; Johnson et al., 1998; Lopez-Saez et al., 1998; Jennings and Mathews, 1994; Kwiterovich et al., 1991; Yannuzzi et al., 1986; Marcus et al., 1984; Pacurariu, 1982].

8 PREVENTIVE APPROACH

The AREDS (Age-Related Eye Disease Study Research Group) study, which was unveiled in October 2001 by the National Eye Institute (NEI), examined the effect of daily dietary addition of antioxidant (vitamins C and E and beta-carotene) and zinc supplements in patients with ARMD (Table 5). This randomized, double-blind, multicentre study found that in those patients at risk for a progressive form of ARMD (patients with ARM with large drusen or with unilateral neovascular ARMD), the use of these supplements at the doses indicated in Table 5 reduced by 25% the risk of the disease occurring [AREDS Study Group, 2001].

TABLE 5

Recommended daily doses of supplements in the AREDS study

SUPPLEMENT	DOSE
Antioxidants	
Vitamin C	500 mg
Vitamin E	400 IU
Beta-carotene	15 mg
Zinc	
Zinc oxide	80 mg
Copper oxide	2 mg

Source: AREDS Study Group, 2001.

However, after five years in this study, no significant benefit could be found for the subjects with only numerous but relatively small drusen or a few intermediate-size drusen, good vision or weak progression of the disease. When these patients were excluded from the analysis, the risk of disease progression to an advanced form was 28% for the control group subjects, 23% for those who took antioxidants only, 22% for those who took zinc only, and 20% for those who took both antioxidants and zinc. For this outcome measure, the effects of the treatment in relation to placebo were statistically significant for zinc only (odds ratio: 0.71) and for zinc in combination with antioxidants (odds ratio: 0.66). The main outcome measure was, however, moderate loss of visual acuity. In this case, the risk of losing three lines of vision after five years was 29% for the control group, 26% for the antioxidant group, 25% for the zinc group and 23% for the zinc-plus-antioxidant group. Thus, only the zinc-antioxidant combination had a statistically significant protective effect (odds ratio: 0.73) compared to placebo [AREDS Study Group, 2001].

Many experts feel that there is no evidence at this time to support the use of the vitamin and mineral supplementation recommended in the AREDS study when no trace of the disease has been detected in at least one eye [The Medical Letter, 2003; Kuzniarz et al., 2002; Seigel, 2002]. The use of these supplements would therefore be pointless in such cases. Taking vitamins C and E, beta-carotene or zinc separately is also not recommended for the prevention of ARMD, since their prophylactic effect has been demonstrated only for the combination recommended in the AREDS study [2001]. A randomized, double-blind study has shown that taking 500 IU (international units) of vitamin E daily does not prevent the onset of ARMD or its progression to its advanced stages, unlike the use of a combination of vitamins C and E, beta-carotene and zinc [Taylor et al., 2002].

In addition, such supplements should not, under any circumstances, be taken without medical supervision, since they are not without risk. The supplement doses recommended in the AREDS study largely exceed the recommended dietary allowances (RDAs) established by the FNB (Food and Nutrition Board of the National Academy of Sciences —National Research Council) in collaboration with Health Canada [Food and Nutrition Board, 2000] (Appendix F). These sup-

plements can cause serious health problems in certain types of individuals [Ambati et al., 2003; The Medical Letter, 2003; Food and Nutrition Board, 2002], such as those with cancer [Watkins et al., 2000], heart disease [Yusuf et al., 2000], Alzheimer's disease [Rulon et al., 2000; Bush et al., 1994]or diabetes [Cunningham et al., 1994; Raz et al., 1989]. Furthermore, drug interactions can occur. For example, the high dose of zinc recommended in the AREDS study can cause considerable copper depletion and severe anemia [Food and Nutrition Board, 2000]. To overcome this problem, copper supplements have had to be added to the AREDS formula.

Many epidemiological studies have shown that a diet rich in fruits and vegetables with a high carotenoid content reduces the risk of cancer [Lee, 1999; Patterson et al., 1997; Mayne, 1996]. However, high doses of beta-carotene supplements can have the opposite effect by acting as prooxidants. Such supplementation fosters the neoplastic transformation of normal cells [Palozza et al., 2001; Lee, 1999; Palozza, 1998; Patterson et al., 1997]. Two large, randomized, double-blind studies (CARET and ATBC) found that high daily doses of beta-carotene increased the risk of lung cancer in smokers. The CARET (Beta-Carotene and Retinol Efficacy Trial) found that the use of beta-carotene and vitamin A supplements increased the incidence of lung cancer in smokers by 28% and the mortality rate by 17%. These antioxidants also increased the incidence of cardiovascular disease in these individuals [Omenn et al., 1996a; Omenn et al., 1996b]. The final results of the ATBC (Alpha-Tocopherol, Beta-Carotene Cancer) trial confirmed those of the CARET study. In particular, they showed that the incidence of lung cancer had increased by 16% in the smokers who participated in the study. This study also reported harmful interactions between beta-carotene and alcohol. For instance, the incidence of lung cancer increased significantly in those individuals who had more than one drink a day [Patrick, 2000; Albanes et al., 1996].

The antioxidant activity of vitamin E has been reported in several observational studies. This vitamin scavenges and breaks down free radicals and highly reactive oxygen species [Esterbauer et al., 1991; Burton and Ingold, 1989]. It might therefore play an important role in the prevention of many diseases. However, although some researchers recommend doses of vitamin E (alpha-tocopherol) between 200 and 400 IU, the daily dietary allowance recommended by the FNB and Health Canada is about 15 mg (22 IU) [Food and Nutrition Board, 2000]. A number of studies indicate that, contrary to popular belief, vitamin E supplements do not have just beneficial effects on health. In many cases, the observed effects are even contradictory (on cardiovascular disease, cancer) [Jialal et al., 2001; Yusuf et al., 2000; Lee, 1999; Brigelius-Flohe and Traber, 1999; Patterson et al., 1997; Stephens et al., 1996]. In certain conditions, when taken in large quantities, supplemental vitamin E (alpha-tocopherol) can act as a prooxidant and damage cells and tissues [Weinberg et al., 2001; Brown et al., 1997; Bowry et al., 1992]. Some people who take high doses of vitamin E supplements experience fatigue, nausea and diarrhea. Vitamin E can also cause bleeding problems, especially in people on anticoagulants [Food and Nutrition Board, 2000].

9 ALTERNATIVE TREATMENTS FOR NEOVASCULAR ARMD

9.1 TREATMENT WITH PROVEN EFFICACY: LASER PHOTOCOAGULATION

A few years ago, conventional laser photocoagulation (argon green laser and krypton red laser) was the only approved therapy for treating exudative macular degeneration. The lasers used in photocoagulation emit rays of sufficient energy to cause an intense thermal reaction that results in the occlusion, through coagulation, of new vessels. Because of heat dissipation, these types of lasers destroy, in addition to new vessels, choriocapillaries, retinal pigment epithelial cells and adjacent photoreceptors [Green, 1991; Smiddy et al., 1984].

The beneficial effects of this treatment have been demonstrated in several studies. A study conducted by the MPS (Macular Photocoagulation Study) research group found that this treatment could be administered to about 15% of the patients with neovascular ARMD (patients with classic extrafoveal or juxtafoveal neovascular ARMD) [MPS Group, 1991]. The conventional laser cannot be used in subfoveal neovascular ARMD because it would destroy the retina immediately adjacent to the target area and thus cause an immediate loss of central visual acuity [Arnold and Sarks, 2000].

The different clinical studies conducted by the MPS group found that photocoagulation significantly decreases the loss of visual acuity due to extrafoveal neovascular ARMD. After five years of follow-up, the investigators observed severe visual acuity loss (> 6 lines) in 48% of the treated eyes compared to 62% of the control group eyes [MPS Group, 1991]. In the case of juxtafoveal lesions, the differences between the two groups were not as great: 52% of the treated eyes versus 61% of the control group eyes had sustained severe visual loss [MPS Group, 1994]. But, the main factor limiting the benefits of this therapy is recurrent neovascularization. Thus, after five years of follow-up, only 26% of the eyes with juxtafoveal lesions and 46% of those with extrafoveal lesions did not show any signs of recurrent neovascularization. The latter was often subfoveal and prevented retreatment, since retreatment would have led to a permanent loss of vision [MPS Group, 1991; MPS Group, 1990]. Laser photocoagulation is, nonetheless, the only effective treatment for patients with extrafoveal lesions and certain types of juxtafoveal lesions [Arnold and Sarks, 2000; Coscas et al., 1991; MPS Group, 1991].

9.2 TREATMENTS PRESENTLY BEING EVALUATED

9.2.1 Transpupillary thermotherapy

Transpupillary thermotherapy (TTT) is a technique whereby ocular structures are irradiated through the pupil. However, unlike photocoagulation, transpupillary thermotherapy involves the use of an 810-nm, near-infrared monochromatic diode laser. The objective of TTT is to create and maintain tissular hyperthermia in order to arrest the neovascularization process without damaging the normal retina. To do this, the infrared laser is set at a low intensity and irradiates the retina for one minute, which causes a moderate intraocular temperature increase of about 4 to 9ºC compared to 40ºC for photocoagulation [Hooper and Guymer, 2003].

Pilot studies seem to indicate that this treatment might be effective in destroying predominantly occult, but also classic, subfoveal new vessels, with a low revascularization rate. [Algvere et al., 2003; Thach et al., 2003; Reichel et al., 1999]. High-metabolism cells, such as neovascular endothelial cells, seem more

sensitive to hyperthermia than others. On the other hand, normal cells are able to overexpress proteins that protect against thermal stress, such as heat-shock proteins (HSPs). Following treatment, a coagulation mechanism is therefore triggered in the choroidal vascular endothelium [Mainster and Reichel, 2000].

Although promising, transpupillary thermotherapy is still in the experimental stage, and there are no data on its long-term effects or its potential adverse effects [Algvere et al., 2003; Newsom et al., 2001; Desmettre et al., 2001; Mainster and Reichel, 2000; Ip et al., 1999]. The most appropriate clinical approach for the future evaluation of transpupillary thermotherapy is a randomized, multicentre study presently under way in the United States (ttt4CNV). It is being conducted by the National Eye Institute.

9.2.2 Radiotherapy

Many clinical studies, some randomized, some not, have examined the possibility of slowing the progression of visual loss due to neovascular degeneration, using different radiotherapy treatments. Some of these studies did not find any real benefit, while others report a certain degree of efficacy [Ciulla et al., 2002; Hart et al., 2002; Marcus et al., 2002; Kobayashi and Kobayashi, 2000; Char et al., 1999; RAD Study Group, 1999; Bergink et al., 1998]. One study that examined the adverse effects of radiotherapy for the treatment of ARMD found that ocular complications occurred in nearly one-third of the cases during a mean follow-up of 15 months. Some of these complications resulted in major functional sequelae [Mauget-Faysse et al., 2000]. It is important to note that the adverse effects are dose-dependent and vary according to the treatment protocol [Kirwan et al., 2003; Flaxel, 2002]. Given these contradictory findings, radiotherapy for the treatment of ARMD is still considered experimental.

9.2.3 Macular surgery

9.2.3.1 Surgical excision of neovascular membranes

This procedure consists in making an incision in the retina and removing the subretinal new vessels and the surrounding vitreous body [Thomas et al., 1994]. However no study has demonstrated the effectiveness of this modality in suppressing neovascularization due to ARMD, and it carries a high risk of ocular complications, such as cataract formation, retinal detachment and macular hemorrhage [Roodhooft, 2000; Arnold and Sarks, 2000]. The most appropriate clinical approach for the future evaluation of surgical excision is the Submacular Surgery Trial (SST), a large, randomized, double-blind study that is being coordinated by the National Eye Institute in the United States. The final results of the study should be published in 2004 [National Eye Institute, 2003]. However, preliminary analyses indicate that the excision of subfoveal new vessels that appear after laser photocoagulation does not yield better results than photocoagulation alone [SST Group, 2000a; SST Group, 2000b].

9.2.3.2 Retinal macular translocation

Macular translocation consists in artificially causing a partial or total detachment of the retina by injecting fluid under the sensory retina, with the pigment epithelium remaining in place. Subsequently, two techniques can be used. The sclera can be shortened through its anteroposterior diameter by a sutured fold (Eckardt macular rotation or de Juan's limited scleral fold), or a 360-degree retinotomy can be performed to shift the central retina laterally [Hooper and Guymer, 2003; Bressler, 2001; de Juan, 2001; Kubota et al., 2001; Toth and Freedman, 2001]. In both cases, the retina that previously lined the entire wall of the

globe is displaced and becomes redundant. Thus, by shifting, the new vessels, together with the pigment epithelium, will stay in place, while the macular area in the sensory retina will be displaced. It is then easy to laser-photocoagulate these new vessels, which are now at a distance from the new macula, and to try to preserve the patient's central vision [Soubrane et al., 2001; Roodhooft, 2000].

Although studies seem to have observed that this procedure conferred certain short-term benefits to patients with exudative ARMD [Abdel-Meguid et al., 2003; Chang et al., 2003], its long-term efficacy has yet to be demonstrated, and it cannot be compared with other therapies, since the trials involved a very small number of patients [American Academy of Ophthalmology, 2000a].

9.2.3.3 EPITHELIAL CELL TRANSPLANTATION

Transplanting cells from the retinal pigment epithelium (RPE) or the iridial pigment epithelium (IPE) after surgical excision of choroidal neovascular membranes is another possible approach. These transplants permit photoreceptor preservation in animals. Because of the advanced stage of the disease in most humans who undergo surgery, the results of the preliminary studies were not very satisfactory from a functional standpoint, since the photoreceptors and pigment epithelium had already been destroyed [Soubrane et al., 2001]. Allografts of retinal pigment epithelial cells have also been attempted, but without success because the cells were rejected within a few months [Algvere et al., 1999; Algvere et al., 1997]. The transplantation of autologous IPE cells is a more promising approach [Crafoord et al., 2001].

A study involving subjects with early-stage ARMD [Thumann et al., 2000] found that IPE cells can easily substitute for RPE cells from a functional standpoint and that the risk of complications is fairly low compared to other macular surgical procedures. Furthermore, the rates of recurrent neovascularization were lower in the patients who underwent this surgical procedure than in those who underwent the other treatments Thumann et al., 2000]. However, larger studies will need to be conducted before it can be concluded that this technique is effective and safe [Holz et al., 2003].

9.2.4 Antiangiogenic therapies

Researchers hope that antiangiogenic agents might reduce or avoid the use of lasers to treat ARMD and to treat vessels that are difficult to visualize angiographically. These agents might also be used as a prophylactic treatment. Large studies for finding a safe and effective antiangiogenic agent are therefore under way.

9.2.4.1 INTERFERON ALPHA-2A

Studies have shown that interferon alpha-2a can inhibit the *in vitro* proliferation of vascular endothelial cells and their migration. In humans, this agent is effective in treating hemangiomas and Kaposi's sarcoma [Arnold and Sarks, 2000]. However, a large, randomized, double-blind study involving more than 480 patients with neovascular ARMD did not find this treatment to be effective [PTMD Study Group, 1997]. Furthermore, it is expensive and can cause serious adverse effects, such as profound fatigue and central and peripheral nervous system disturbances [Arnold and Sarks, 2000; Roodhooft, 2000].

9.2.4.2 THALIDOMIDE

Thalidomide is a synthetic derivative of glutamic acid. It was marketed in Europe in 1957 as a sedative and had to be withdrawn a few years later because of its potent teratogenic effect. Thalidomide caused limb malformations by suppressing blood vessel growth during fetal development. This antiangiogenic inhibits corneal neovascularization induced by vascular endothelial growth factor (VEGF) in rodents [Kaven et al., 2001]. However, human studies have failed to demonstrate its efficacy in treating choroidal neovascularization due to ARMD [Maguire et al., 2001; Roodhooft, 2000].

9.2.4.3 MOLECULAR APPROACHES

All the stages of angiogenesis are potential therapeutic targets [Soubrane and Bressler, 2001]. Thus, action targeting growth factors, practically all of which are expressed in classic new vessels (bFGF [basic fibroblast growth factor], FGF1, FGF2 and VEGF), might inhibit endothelial cell proliferation. The only current experiment along these lines involves the intravitreal or subtenonian injection of anti-VEGF antibodies or VEGF-specific oligonucleotides. The published preliminary results seem promising [Eyetech Study Group, 2003; Eyetech Study Group, 2002; Heier et al., 2002]. It should be noted that VEGF stimulates endothelial cell proliferation.

The various components of the extracellular matrix, components that are indispensable for endothelial cell migration, could also be targetted. Human neovascular membranes express several metalloproteases, including MMP2 within these membranes and MMP9 on their external aspect. Presently, inhibitors of these metalloproteases are being synthesized, which might permit selective inhibition of endothelial cell migration [Berglin et al., 2003; Lambert et al., 2002; Leu et al., 2002; Kvanta et al., 2000]. Similarly, integrins $\alpha V\beta 3$ and $\alpha V\beta 5$ are indispensable for cellular adhesion. These transmembrane receptors are expressed in the membranes of new vessels due to ARMD. The use of inhibitors of these integrins might prevent endothelial cell migration [Soubrane et al., 2001; Roodhooft, 2000]. Researchers are presently attempting to develop compounds better suited for human use.

Corticosteroids can inhibit endothelial cell proliferation in experimental models. These subtenonianly administered compounds are undergoing preliminary evaluations in humans. Triamcinolone is a synthetic glucocorticoid that modulates extracellular matrix turnover and decreases endothelial cell migration and proliferation. It also reduces VEGF synthesis [Liu and Regillo, 2004; Hooper and Guymer, 2003]. This compound is presently being investigated in studies, some randomized, some not [Gillies et al., 2003; Jonas et al., 2003; Spaide et al., 2003; Ranson et al., 2002]. Anecortave acetate is a steroid that exerts its angiostatic effect by preventing the breakdown of extracellular matrix by direct inhibition of plasminogen activator and metalloproteases. Like triamcinolone, it acts both on endothelial cell migration and proliferation [Liu and Regillo, 2004; Hooper and Guymer, 2003; Soubrane et al., 2003]. Two randomized studies assessing the efficacy of subtenonianly injected anecortave acetate in treating predominantly classic subfoveal neovascularization are currently in progress [D'Amico et al., 2003a; D'Amico et al., 2003b].

Lastly, angiostatin, a potent angiogenesis inhibitor, could prove extremely useful. However, studies have only involved animal models [Soubrane et al., 2001].

Regardless of the strategy used to treat neovascular ARMD, the therapeutic efficacy is often transient. Choroidal neovascularization is actually a complication of ARMD, and all the current treatments have no effect on the initial changes caused by the disease. Recurrent neovascularization is therefore frequent.

10 ECONOMIC ANALYSIS

10.1 METHOD

We constructed a decision tree for predicting the costs and effects of photodynamic therapy in individuals with ARMD. A Markov-type model was constructed using Excel (Microsoft Corp., 2000). The population chosen for this model was all Quebecers aged 55 and older in 2001, or 1,730,000 people [Institut de la statistique du Québec, 2003]. To be eligible for photodynamic therapy (PDT), a person must have subfoveal ARMD with more than 50% classic neovascularization or pure occult neovascularization. The decision tree concerns a cohort of incident cases and a cohort of prevalent cases in the Québec population. This method enables us to predict the costs and effects of PDT treatment in a situation where the population is treated systematically and where there is a catch-up program, i.e., where all people with ARMD who are eligible for PDT (cohort of prevalent cases) are treated. The budget impact analyses (Section 10.8.2) take both the incident cases and prevalent cases into account.

The model was designed to apply ARMD incidence data to the 55-and-over population. An ARMD patient is classified according to the type of ARMD that he/she has. If the patient is eligible for PDT treatment, two options are compared: photodynamic therapy or no treatment. The *no-treatment* option was preferred to the treatment by photocoagulation option, since about 92% of the patients eligible for PDT would not have been eligible for photocoagulation [Miller et al., 1999].

With the photodynamic-therapy option, the patient receives treatment over a period of three years and is followed for one year after the end of treatment. During this time, it is possible that the disease will appear in the fellow eye. Thus, a Quebecer over the age of 55 may have unilateral or bilateral neovascular ARMD. As mentioned earlier, a patient may, therefore, at the outset, have bilateral ARMD, but the disease may also appear in the fellow eye while the first eye is being treated, or ARMD may occur in the second eye after the first eye has finished being treated. If the fellow eye is eligible for PDT as well, the patient will be treated and followed for an additional year, for a total period of up to four years. Given all the treatment application scenarios, we devised a model with a time horizon of eight years. With the *no-treatment* option, a PDT-eligible patient does not receive any treatment in either eye.

We chose to follow patients with unilateral ARMD for four years to check if the disease appears in the fellow eye. The scientific literature on this subject gives us the number of new cases for the fellow eye for the four years following the onset of the disease in the first eye, i.e., the number of years during which the probability of ARMD occurring in the fellow eye is the highest [Lacour et al., 2002; MPS Group, 1997]. We also assume that the condition of the first affected eye stabilizes after four years. In other words, an ARMD eye will not sustain any change in visual acuity after these four years of treatment.

In this model, the number of treatments is based on the practice in Québec and on the results of randomized studies. Thus, a patient who has access to PDT receives an average of 3.4 treatments the first year, 2.1 treatments the second year, a single treatment the third year and none the fourth year. There is a medical follow-up visit every three months during the first two years, every six months the third year, and once a year thereafter.

As mentioned earlier in this section, the model was designed for predicting the costs and effects of PDT in patients with two types of ARMD: 1) predominantly classic subfoveal

neovascular ARMD and 2) pure occult subfoveal neovascular ARMD. The effects and costs associated with treating these two groups of patients were first calculated together, then separately. Given that the efficacy of the treatment differs between these two populations and that pure occult ARMD is not yet an approved therapeutic indication, we wanted to be able to predict the cost-utility ratios for all cases involving only predominantly classic neovascular ARMD and for PDT-treatable cases of ARMD (i.e., with predominantly classic or pure occult neovascularization).

The Markov-type model is especially suited for this type of evaluation. A Markov model is useful when the risk of occurrence of the disease is continuous in time and when the clinical outcomes can occur several times [Sonnenberg and Beck, 1993]. A Markov model assumes that a patient is always in a well-defined state of health. The clinical outcomes are the passage from one state to another.

The states chosen for this model are the *loss* of three lines of vision or the *non-loss* of three lines a vision. A patient can go from one state to another. However, even if randomized studies found that visual acuity increased after treatment in about 5% of the patients [Bressler, 2001], this state was not an assumption, since such improvement in visual acuity should not lead to changes in patient management costs.

10.2 DATA SOURCES

A review of the scientific literature identified the main ARMD incidence and prevalence data relating to PDT treatment. The economic data are mainly from the *Institut Nazareth et Louis-Braille*. The data on the equipment needed for PDT treatment (laser and camera for angiography) were obtained from the different companies that sell these products (Opal Photoactivator™, Visudyne®), and companies that sell digital cameras. The data on the population and the demographic trends in Québec are from Statistics Canada and the *Institut de la statistique du Québec*. Lastly, two retinologists were consulted for the purpose of confirming the data that were to be used.

10.3 EPIDEMIOLOGICAL DATA

The epidemiological data needed for the model are the incidence data for individuals with more than 50% classic or 100% occult subfoveal neovascular ARMD. The incidence data are used to determine the number of Quebecers who have the disease in one eye, but also to determine the number of patients in whom it will occur in the fellow eye.

The 2-year cumulative incidence data for ARMD for each age group are used as the starting point (Table 6).

If we apply the ARMD incidence data to all Quebecers over the age of 55, we find 4,152 new cases for a single cohort over a period of two years. These people may have atrophic or neovascular ARMD. However, only those with neovascular ARMD can be treated with PDT, or about 47% [Margherio et al., 2000] of the above-mentioned individuals (1,951 of these 4,152 patients).

Neovascular ARMD can be extrafoveal, juxtafoveal or subfoveal. In this study, we are interested in the subgroup of patients with subfoveal lesions. Approximately 83% of patients with neovascular ARMD are in this subgroup [Margherio et al., 2000], which works out to 1,619 of these 1,951 patients.

Subfoveal neovascular membranes can be of the classic or occult type. PDT treatment is intended for patients whose lesions include more than 50% classic new vessels. It should be noted that 65% of patients with subfoveal neovascular ARMD have classic neovascularization, or 1,053 of these 1,619 patients. Lastly, 66% of these lesions contain more than 50% classic membranes, or 695 of these 1,053 patients. Photodynamic therapy can also be administered to patients with pure occult neovascularization. This subgroup accounts

for 35% [Margherio et al., 2000] of the cases of subfoveal neovascular ARMD, or 567 patients. According to these calculations, there would be an indication for PDT treatment for 1,261 patients with ARMD in at least one eye for a single cohort in Québec over a period of two years.

Furthermore, the probability of the disease occurring in the fellow eye (regardless of the form of ARMD) is about 15% per year for the entire ARMD population. This probability is cumulative each year. In other words, a group of patients with ARMD in one eye has a 15% risk of developing ARMD in the fellow eye the first year following the onset of the disease. If they do not develop ARMD in the fellow eye the first year, they will have a 30% risk of developing it in the healthy eye the second year following onset of the disease. Thus, in four years, a group of people with unilateral ARMD will have a 60% risk of developing the disease in the fellow eye [Lacour et al., 2002; MPS Group, 1997].

10.4 EFFICACY OF PHOTODYNAMIC THERAPY AS MEASURED IN TERMS OF QUALITY OF LIFE

The efficacy of PDT is first calculated in terms of the loss or non-loss of three lines of vision on an ETDRS chart. The loss of three lines of vision has different repercussions, depending on the initial visual acuity. It can be considered that for a person with poor visual acuity, losing three lines of vision would be more problematic than if his/her initial visual acuity were good. The utility of PDT therefore greatly depends on the visual acuity in the better-seeing eye.

The decision to measure the efficacy of photodynamic therapy in terms of quality-adjusted life-years (QALYs) has to do with the fact that the clinical outcome depends on the initial visual acuity, not only on the loss or non-loss of three lines of vision. It will be recalled that, in our model, the patient may onlylose lines of vision or maintain the same visual acuity.

The utility of PDT associated with a loss of vision due to age-related macular degeneration can be calculated by different methods. Brown et al. [2000a; 2000b] assessed the utility of PDT using two different methods: time trade-off and standard gamble. Although there seems to be no consensus as to which method should be used, the time trade-off method yields the most comparable results to those obtained by direct evaluation [Bleichrodt and Johannesson, 1997].

To derive the utility of PDT in our model, we utilized the time trade-off method. By means of interviews, Sharma et al. [2001; 2000] extracted sociodemographic data on the ARMD population. They then asked these patients how many more years they thought they would live and how many years of life they would be willing to sacrifice to have perfect vision again.

The utility that a given patient derives from the treatment is equal to [1 - (the proportion of his/her life expectancy that he/she would be willing to swap for perfect vision)]. For example, for a patient who thinks he is going to live for another 20 years and who is willing to sacrifice two years of his life to get perfect vision, the utility would be 0.9[8]. He would therefore be willing to sacrifice 10% of his life expectancy to get perfect vision.

Since our analysis is based on a dichotomous outcome (loss or non-loss of three lines of vision), we indicate, in Table 7, the utility associated with PDT according to the visual acuity for each of these outcomes.

8. The calculation for this utility is 1 (which corresponds to maximum quality of life) - (2/20), or the number of years of life the patient is willing to sacrifice to get perfect vision divided by the number of years that he/she has to live. The utility is 0.9 = 1 - (2/20).

TABLE 6

2-year cumulative incidence of ARMD in the population by age group

AGE GROUP	2-YEAR CUMULATIVE INCIDENCE OF ARMD IN THE POPULATION (%)	ANNUAL INCIDENCE OF ARMD IN THE POPULATION (%)*
55-64	0.10†	0.050
65-74	0.15	0.075
75-84	0.61	0.305
85 and over	1.75	0.875
Total (55 and over)	0.24	0.120

Sources: Klaver et al., 2001; Mitchell et al., 2002; Klein et al., 1997.

* For the purposes of this analysis, the annual incidence is the 2-year cumulative incidence divided by 2.
† In the study by Klaver et al. [2001], the 2-year cumulative incidence for the 55-to-64 age group was 0.00% (this study did not include any subjects in this age group). In our analysis, we therefore estimated a 2-year incidence rate from the Beaver Dam and Blue Mountains studies, in which the cumulative incidence was calculated over five years.

TABLE 7

Utility associated with the loss or non-loss of three lines of vision by visual acuity

VISUAL ACUITY IN THE BETTER-SEEING EYE	UTILITY ASSOCIATED WITH THE LOSS OF THREE LINES OF VISION	UTILITY ASSOCIATED WITH THE NON-LOSS OF THREE LINES OF VISION
6/12	0.57	0.81
6/60	0.40	0.52

Source: Sharma et al., 2001.

10.5 ECONOMIC DATA

The economic data include different types of costs, specifically, the costs directly associated with the treatment and the costs associated with managing an ARMD patient.

The costs associated with the treatment include the cost of a visit to an ophthalmologist and a retinologist, the cost of angiography, the cost of photodynamic therapy as such, and the cost of managing people with poor vision. The costs associated with the *no-treatment* option include the cost of the first visit to an ophthalmologist and a retinologist, the cost of angiography and the cost of managing people with poor vision. The clinical management scenarios that were used to calculate the total cost are presented in Table 8.

10.5.1 Cost of the first visit and follow-up visits

- First visit to an ophthalmologist: $33.
- First visit to a retinologist: $31.
- Follow-up visit to the retinologist (plus the reading of an angiogram): $60.

TABLE 8

Treatment modalities for patients with predominantly classic or pure occult ARMD (1st eye only) for the first four years

	TREATMENT OPTION	*NO-TREATMENT* OPTION
Diagnosis	1 visit to an ophthalmologist 1 visit to a retinologist 1 angiogram	1 visit to an ophthalmologist 1 visit to a retinologist 1 angiogram
Treatment	3.4 treatments* the 1st year 2.1 treatments the 2nd year 1 treatment the 3rd year	3.4 visits to a retinologist, including an angiogram the 1st year 2.1 visits to a retinologist, including an angiogram the 2nd year 1 visit to a retinologist, including an angiogram the 3rd year
Follow-up	4 follow-up visits† the 1st year 4 follow-up visits the 2nd year 2 follow-up visits the 3rd year 1 follow-up visit the 4th year	4 follow-up visits the 1st year 4 follow-up visits the 2nd year 2 follow-up visits the 3rd year 1 follow-up visit the 4th year

* Each treatment includes a visit to a retinologist, an angiogram and photodynamic therapy.
† The follow-up visit can be done at the same time as the treatment visit.

10.5.2 Unit cost of an angiogram

The unit cost of an angiogram is based on a mean cost that includes the amounts paid to or for a technician (accredited or nonaccredited medical photographer), a nurse, a digital camera, a vial of fluorescein and a butterfly for injecting the fluorescein, and the cost of developing the photographic film. One must also include the purchase of emergency equipment (defibrillator, intubation equipment, oxygen, resuscitation drugs) in the event of a severe reaction during the test. The unit cost includes the amortization of the digital camera, which, alone, can cost between $60,000 and $180,000. However for a given number of angiograms performed, the difference between the different costs of a digital camera will cause very little variation in the unit cost of a single angiogram. Variation in the number of angiograms performed will therefore have a greater impact on the magnitude of the unit cost. Lastly, one should add the cost of renting space where photodynamic therapy is provided (about 14 m^2) and the cost of managing the case. In short, the per-test cost variations will depend mainly on the number of examinations. The estimate of the mean unit cost of an angiogram is based on the mean unit cost at a private clinic and at a hospital.

- Mean unit cost of an angiogram: $429

10.5.3 Unit cost of photodynamic therapy

The cost of photodynamic therapy per se includes the cost of the laser and of the verteporfin (Visudyne®). The unit cost of PDT also includes the cost of amortizing the laser, although this cost is small, given the large number of treatments that can be expected. The laser is amortized over a period of 10 years, and this cost accounts for only one hundredth of the unit cost of photodynamic therapy. These costs apply to each PDT treatment performed.

- Cost of a vial of verteporfin (Visudyne): $1,750.
- The unit cost of amortizing the laser, renting space and paying the nursing staff or technicians: $79.
- Retinologist's fees: $150.

10.5.4 Cost of patient management

The cost of managing people with poor vision largely depends on the level of visual disability. A patient with ARMD in one eye will probably not require rehabilitation, as long as he/she can compensate with the other eye. A patient with bilateral ARMD whose vision is deteriorating may be placed in a centre for semiautonomous or nonautonomous persons, be hospitalized or receive care at home. Appendix G summarizes the levels of visual acuity considered in this report and their relationship with the degree of disability.

The services received by patients with neovascular ARMD are generally provided by visual impairment rehabilitation workers. The latter can provide support for the activities of daily living, teach Braille or provide computer rehabilitation. Other services are offered as well, such as psychology, counselling and mobility assistance services. The patient management costs are presented according to three levels of visual acuity and reflect a change in autonomy in relation to the patient's initial visual acuity. In addition, it should be noted that, regardless of the patient's visual acuity, these costs vary widely.

The data used in the analysis are from the *Institut Nazareth et Louis-Braille*. The mean figures presented in this report therefore follow a uniform distribution in the model. They are the costs for one year. Given that they are mean values, the mean cost for the first year is the same as the cost for the fourth year of patient management. However, a patient can go from a low-management situation to a medium- or even high-management situation. It should also be noted that, in Québec, there are no programs for systematically managing all ARMD patients. Since we do not know what proportion of individuals with ARMD are not being managed by the system, the scenario chosen is rather pessimistic in terms of costs, since it includes the systematic management of all legally blind individuals with ARMD (Appendix G). It will be noted that the range has been established solely for the purposes of the sensitivity analyses.

10.5.5 Annual unit cost of patient management

- Low: $2,500 (range: $1,250 to $3,750).
- Moderate: $3,500 (range: $1,750 to $5,250).
- High: $40,000 (range: $20,000 to $60,000).

10.6 PLAN OF ANALYSIS

The estimate of the anticipated costs and effects of each strategy was obtained by adding the products of the probabilities and respective cost and effect values. The mean cost-utility ratios were used to assess the *no-treatment* option in relation to the *treatment* option. The incremental cost-utility ratio [(cost of the *treatment* option minus the cost of the *no-treatment* option) / (effects in the *treatment* option minus the effects in the *no-treatment option*)] was used for the incremental analysis of the efficiency of photodynamic therapy. These ratios were first calculated for the population of patients with predominantly classic neovascular ARMD, then calculated again for all PDT-treatable patients (i.e., those with predominantly classic neovascular ARMD and those with pure occult neovascular ARMD).

The results were presented according to a societal perspective. The utility values were derived from a familial perspective (i.e., the perspective of each individual with ARMD), and the costs were derived from a health-care system perspective. We did not take into account the dollar cost of travel and waiting time for the examinations, treatments and other care from a familial perspective, since these costs are reflected, in part, in the utility derived from the treatment for each individual, but we did take into account the life expectancy of affected individuals.

Given the time horizon in our analysis (eight years), we discounted the costs and effects using a basic discount rate of 3%.

10.7 SENSITIVITY ANALYSES

For comparative purposes with other studies, we first performed a univariate analysis to examine the effect of different discount rates on the results. The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) recommends that results be presented without discounting (0%) and with discounting (3% [reference model] and 5%). We then simulated the effects on the incremental cost-utility ratio of earlier diagnosis in ARMD patients.

The extreme values for 58 input variables are presented in Appendix H. To calculate these extreme values, we divided or multiplied by 1.5 the rates for the epidemiological parameters, as well as the number of treatments and follow-up visits in the reference model and the patient management costs.

To take into consideration the relative importance of the various input parameters on the results, a Monte Carlo-type dynamic sensitivity analysis was performed using the Crystal Ball 2000 software program (a product of Decisioneering Inc.). This analysis yielded 95% confidence intervals for the costs, efficacy and cost-utility ratio. This type of simulation executes the model numerous times (1,000 times in our analysis), by simultaneously modifying the values for the 58 variables on the basis of a predefined probability distribution.

This approach provides a distribution of samples and, therefore, descriptive values (mean, median, maximum, minimum and probability distribution) that are used to analyze the results. The variables, their intervals and their predefined distributions are presented in Appendix H.

10.8 RESULTS

This model shows that the efficacy of the treatment in terms of the *non-loss* of vision is mainly (85%) situated in the first two years following the start of treatment. The model also shows that the treatment of predominantly classic subfoveal ARMD with photodynamic therapy yields better results when the patient's initial visual acuity is relatively good. Given that our model examines the treatment of both eyes, it yields more optimistic results in terms of the *non-loss* of vision than a model that only examines the treatment of the fellow eye.

The model shows that the effects on quality of life take on importance over time. It will be noted that the randomized studies of photodynamic therapy have shown that this treatment has sustained efficacy over time [VIP Study Group, 2001; TAP Study Group, 1999]. Once vision loss is slowed, the effects in terms of quality of life automatically persist over time.

The treatment itself is rather expensive, with verteporfin accounting for the major portion of the cost. However, the cost of managing a patient after visual loss has occurred is higher than the cost of the treatment as such. Thus, a growing increase in the number of legally blind patients who require a greater level of management would result in a heavier burden to society. This is particularly clear in the *no-treatment* option, in which there are higher patient management costs associated with a greater loss of vision. One major advantage of the treatment is, therefore, the management costs avoided.

In brief, the incremental cost-utility ratio per QALY for a patient with predominantly classic subfoveal ARMD who has been treated by PDT is $33,880 per QALY (3% discount rate) over an 8-year time horizon (Table 9). For a 2-year time horizon, the incremental cost-utility ratio is $102,332 for each QALY associated with photodynamic therapy compared to no treatment. This difference is due mainly to two factors: the treatment of both eyes is not completed, which leads to a lower level of benefits in terms of efficacy, and essentially zero patient management, which reduces the financial benefits of photodynamic therapy.

If patients with pure occult ARMD are added to this group, the cost-utility ratio increases to $43,253 per QALY (3% discount rate) over an

8-year time horizon (Table 9). For a 2-year time horizon, the cost-utility ratio increases to $95,625 per QALY. The difference between the cost-utility ratios (when one takes into account only patients with predominantly classic neovascular ARMD or when patients with pure occult ARMD are included with this group of patients) is due mainly to the fact that the benefits of PDT for patients with pure occult neovascularization are not as great the first year [VIP Study Group, 2001]. In other words, the benefits of PDT in terms of the *non-loss* of vision appear sooner in the subgroup with predominantly classic neovascular ARMD.

It is important to bear in mind that the time horizon in our model is only eight years (maximum duration of treatment for both eyes), whereas patient management costs continue well beyond that point.

10.8.1 Results of economic analyses performed in other studies

A number of other studies have performed economic analyses of photodynamic therapy for the treatment of ARMD. However, these studies used methods different from the one that we used in our study, which makes comparisons quite difficult. This very delicate exercise is intended only to give a general idea of the results obtained. But these analyses cannot, under any circumstances, be used to make precise comparisons with the results presented in this report.

The study carried out by the National Institute for Clinical Excellence (NICE) [2003], which is based primarily on the data presented in the study by Meads et al. [1997], gives a cost-utility ratio of $365,945, which was discounted at a rate of 3%, over a 2-year period, compared to $102,332 in our study over the same length of time. The study by Sharma et al. [2001] gives a cost-utility ratio of $67,109 and $134,177, respectively, for patients with a visual acuity of 6/12 and 6/60 in the better-seeing eye at the start of treatment. The results of Sharma's study concern an 11-year period and are discounted at a rate of 3%

The main difference between Sharma's study and ours is mainly the fact that Sharma does not include the substantial cost of the avoided patient management. As for the NICE study, the analysis is based on a decision tree that assumes that patients receive one to eight treatments in two years. The costs associated with the treatments are therefore very high, while few benefits are achieved during the first two years. Furthermore, these two studies only take into account the treatment of one eye, not of both eyes.

The study performed by Smith et al. in 2002 concerned the treatment of only one eye and extended over a period of five years. The cost-utility ratio per QALY was $53,374 to $104,336, depending on the initial visual acuity in the better-seeing eye. The study did not take into account the cost of managing ARMD patients, which can explain, in part, the higher cost-utility ratio. However, the study does conclude that early intervention can yield acceptable cost-utility ratios [Smith et al., 2002]. The importance of early detection, which improves the cost-utility ratios, is therefore emphasized.

Lastly, the study conducted by Lees et al. in 2002 reports an incremental cost- utility ratio of $20,360 to $30,593 per year of vision gained, which is a different indicator from the one we used in our analysis. Although these authors did not use the same indicator, the ratios they obtained are comparable to those we obtained in our analysis. The main reason for this is that this study takes into account the avoided management costs. The study concludes that photodynamic therapy with verteporfin photosensitizer is a good, cost-effective option for treating predominantly classic neovascular ARMD [Lees et al., 2002]. However, it is important to note that the results of the studies by Smith [2002] and Lees [2002] have only been presented at conferences and have yet to be published in a scientific journal.

TABLE 9

Cost-utility ratio for the PDT-treatment option over eight years at a discount rate of 3% for a cohort of new cases of predominantly classic or pure occult neovascular ARMD

	COST	EFFICACY/QALY*	INCREMENTAL COST-UTILITY RATIO †
No treatment – 8 years Predominantly classic	$494,112	44	$33,880
Treatment with PDT – 8 years Predominantly classic	$664,085	49	
No treatment – 8 years Predominantly classic and pure occult	$826,138	85	$43,253
Treatment with PDT – 8 years Predominantly classic and pure occult	$1,136,654	92	

* QALY: Quality-adjusted life-year. † Incremental cost-utility ratio = (cost of the *treatment* option - cost of the *no-treatment* option) - (*treatment* option QALY – *no-treatment* option QALY).

10.8.2 Budget impact

We can deduce the direct budget impact of photodynamic therapy if it were to be offered to all Quebecers who qualify for it. We chose to calculate this budget impact for two different scenarios.

In the first scenario, the budget impact analyses estimate the cost for the cohort of prevalent cases in Québec. Here, the budget impact is the catch-up cost for ARMD patients and includes those cases that are already being managed. In the second scenario, the budget impact analysis estimates the cost of a given steady-state year. In other words, it takes several cohorts into account but only calculates the cost of an average year. The cost is therefore for a specific year, a cross-section in time, for the cohorts of incident cases in the years to come.

This first budget impact is the amount spent for Quebecers who presently have predominantly classic or pure occult subfoveal neovascular ARMD and concerns the scenario where the entire ARMD population is presently being treated, but where the incident cases are not take into account. Based on the figures arrived at in Section 4.3, the cohort consists of 15,958 affected individuals. The cohort of prevalent cases receives the first treatment during year 1. The time horizon for this budget impact is eight years, or the point at which the entire cohort of prevalent cases in the population would have completed their treatment. This scenario is the one with the greatest budget impact, since it includes all the prevalent cases, which are greater in number than the incident cases.

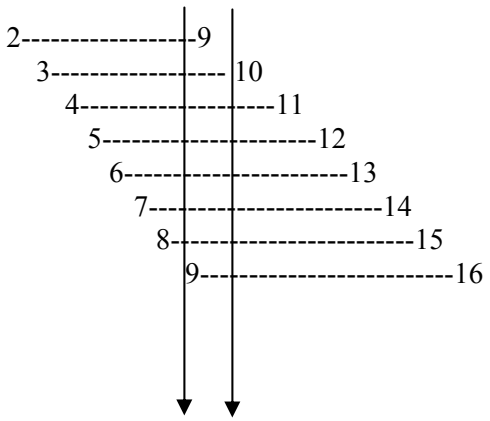
The budget impact is given with a 95% confidence interval (CI). We simulated the model 100 times by varying the following parameters: patient management costs, the incidence of the disease, the number of treatments and follow-up visits, and efficacy in terms of the loss or non-loss of three lines of vision. In this scenario, in which we use a discount rate of 3%, it would cost an average of $60.9 million per year, or $487 million for the entire cohort for the next eight years (95% CI: $314 million to $710 million) to treat all the patients who presently have ARMD and who are eligible for photodynamic therapy. On the other hand, the avoided patient management costs in the *no-treatment* option would be $43.6 million a year, or $348.6 million for the entire cohort of prevalent cases over an 8-year period (95% CI: $150 million to $685 million). The mean net cost of photodynamic therapy for the next eight years would be $17.3 million, or $148 million for the entire cohort.

The second budget impact analysis estimates the cost for a single year when several cohorts of incident cases are considered. Figure 12 clearly shows this situation:

The budget impact of an average year of treatment is $1.14 million (95% CI: $0.6 million to $2.5 million). This same average year with the *no-treatment* option would cost $0.8 million (95% CI: $0.3 million to $2 million). The net budget impact is $0.3 million.

FIGURE 12

Budget impact in steady-state conditions



The most important benefit of PDT is that it slows the progression of the disease, thereby stabilizing the patient's visual acuity. Without this treatment, the patient will lose his/her central vision and will be at high risk of no longer being able to perform many of his/her activities of daily living. In most cases, these patients will have to be managed by society, this process ranging from the provision of ordinary reading aids to complete management in a residence for nonautonomous persons.

As mentioned earlier, it is extremely important to bear in mind that the cost of patient management depends greatly on the level of visual impairment. At the present time, 45% of patients with unilateral ARMD have a mean visual acuity of less than 6/60 when they visit a retinologist, that is, when they are legally blind in one eye [Margherio et al., 2000]. Given that these patients are followed for this eye, the chances of early detection of the disease in the fellow eye are better, which makes it possible to preserve good visual acuity in at least one eye. When the patient has good vision in at least one eye, management is uncomplicated and may simply involve the use of a magnifying glass or a cane, or consist of a few hours of rehabilitation. However, patients who are not followed for the fellow eye will probably be legally blind upon their first visit to a retinologist. In such cases, the management is complicated and the cost is high.

Given that photodynamic therapy reduces the likelihood of patient management, thanks to close monitoring of the fellow eye, it helps reduce the related costs. Furthermore, early ARMD screening should prevent severe bilateral vision loss and therefore avoid the substantial cost of managing legally blind patients or those with severe vision loss.

10.9 SENSITIVITY ANALYSES

10.9.1 Univariate analysis

At first, the univariate analysis concerns the sensitivity of the results to variation in the discount rate. The incremental cost-utility ratio per QALY for a patient with predominantly classic subfoveal neovascular ARMD treated with PDT is $30,054 if there is no discounting, $33,880 with a discount rate of 3%, and $36,344 with a discount rate of 5%. If patients with pure occult neovascular ARMD are included, we obtain an incremental cost-utility ratio per QALY of $32,331 if there is no discounting, $43,253 with a discount rate of 3%, and $54,879 with a discount rate of 5%. Therefore, our results are not very sensitive to variations in the discount rate.

We also wanted to examine the effect of earlier diagnosis on the incremental cost-utility ratio in terms of QALYs. Since most of the benefits are expressed in terms of quality of life, we wanted to simulate the impact of an earlier diagnosis leading to better visual acuity during the patient's first visit to a retinologist. Assuming that 10% of the ARMD population has better initial visual acuity in an early-screening setting, the incremental cost-utility

ratio decreases from $33,880 per QALY to $20,701 per QALY. If patients with pure occult neovascularization are included, the incremental cost-utility ratio per QALY drops from $43,253 to $22,813. To simulate an increase in initial visual acuity in 10% of the patients, one must increase the proportion of the population with better visual acuity and decrease the proportion of the population with lower initial visual acuity.

There are two reasons for this improvement in the ratios. First, PDT is more effective when the initial visual acuity is better. Second, with better initial visual acuity, the likelihood of severe cases (legal blindness) is greatly diminished, which translates into lower patient management costs, especially in patients with pure occult ARMD, in whom the benefits in terms of the non-loss of vision appear later. The likelihood of managing mild cases is increased, but this cost would be much lower.

10.9.2 Multivariate analysis

Appendix I shows the results of the multidimensional simulation of the 58 parameters (presented in Appendix H) for the incremental cost-utility ratio with a 95% confidence interval. Each point on the graph represents the result of one simulation. The vertical axis represents the incremental cost and the horizontal axis, efficacy in terms of quality-adjusted life-years gained.

Most of the results are situated in the upper right quadrant, the quadrant where photodynamic therapy improves the quality of life but is more expensive than the *no-treatment* option. However, it should be borne in mind that the cost of patient management is underestimated in our analysis, since the analysis time line is only eight years, whereas the management costs continue well beyond the number of years required for treatment. The cost-utility ratio quartiles are shown in Table 10.

The result in the reference scenario in terms of the incremental cost-utility ratio is comparable to the median obtained in the dynamic Monte Carlo analysis. In other words, our analysis seems very robust with regard to the probability of the events occurring.

TABLE 10

Descriptive statistics from the multivariate analysis

QUARTILE	INCREMENTAL COST-UTILITY RATIO (PREDOMINANTLY CLASSIC NEOVASCULAR ARMD ONLY)
25%	$14,153/QALY
50%	$32,631/QALY
75%	$57,034/QALY
95%	$60,857/QALY
QUARTILE	**INCREMENTAL COST-UTILITY RATIO (CLASSIC AND OCCULT NEOVASCULARIZATION)**
25%	$15,421/QALY
50%	$44,085/QALY
75%	$57,793/QALY
95%	$79,578/QALY

11 DISCUSSION

The efficacy of photodynamic therapy with verteporfin photosensitizer in patients with predominantly classic subfoveal ARMD was demonstrated in the two rigorous, randomized studies (TAP and VIP) that serve as the basis of our analysis. In this section, we shall discuss the results obtained by other assessment agencies and the economic and organizational aspects of this therapeutic modality in Québec.

11.1 RESULTS OBTAINED BY OTHER TECHNOLOGY ASSESSMENT AGENCIES

In September 2000, the SMM (Norwegian Centre for Health Technology Assessment) published an assessment report on the efficacy of PDT in the treatment of ARMD. The report concludes that this technology is more effective for treating patients with subfoveal neovascular ARMD [SMM, 2000]. It should be noted that, when this report was published, the data from the first year of the TAP study had just been published. In August 2001, the Australian assessment agency, the Medical Services Advisory Committee (MSAC), recommended in its assessment report that, in Australia, public funds only cover the treatment of patients with predominantly classic neovascular ARMD [MSAC, 2001]. In September 2001, the *Agence nationale d'accréditation et d'évaluation en santé* (ANAES) came to the same conclusion [ANAES, 2001]. It should, however, be noted that when these assessment reports were being drafted, the findings of the VIP study were not yet available. Furthermore, these reports do not contain any economic analyses.

In September 2003, the British agency, the National Institute for Clinical Excellence (NICE), published an assessment report on PDT as a treatment for ARMD. The authors of this report did not, however, assess the efficacy of PDT in patients with pure occult neovascularization. There are two parts to the report: an assessment of the efficacy of this therapeutic modality and an economic analysis. As regards the efficacy of PDT, NICE concludes that it is effective in slowing the progression of ARMD in two categories of patients: those with 100% classic neovascular lesions with no occult neovascularization[9] and those with more than 50% classic neovascular lesions. However, their economic analysis indicates that this treatment has a good cost-effectiveness ratio only for classic neovascular lesions with no occult component. For these reasons, NICE recommends that PDT be used only for this form of ARMD [NICE, 2003]. However, its economic study did not take into account the cost of managing patients with poor vision.

11.2 SIGNIFICANCE OF THE RESULTS OF THE ECONOMIC ANALYSIS

The economic analysis yields a favourable result. Based on the grid used by Laupacis et al. [1992], this treatment is at the borderline of recommendation category B: strong evidence in favour of adopting this new technology (Appendix J).

This analysis does have some weaknesses, in particular, the obligation for the patient who commences treatment to continue with it to the very end, except in the case of death. A patient may therefore not voluntarily discontinue the treatment once he/she has been diagnosed. This weakness is attenuated by the fact that studies show that only 1.7% of patients stop treatment because of adverse effects [TAP Study Group, 1999].

9. The authors of the NICE report use the term *ARMD with 100% classic neovascularization with no occult neovascularization*, whereas the authors of the TAP and VIP studies use the term *ARMD with predominantly classic neovascularization with no occult neovascularization* [Bressler, 2001; VIP Study Group, 2001].

Furthermore, since the patient is closely followed from the onset of ARMD in the first eye, if the disease appears in the fellow eye, the visual acuity prognosis should be better than when the disease was detected in the first eye. However, for first-time patients with bilateral ARMD, this is no guarantee of better visual acuity in the fellow eye. The model does not take into account patients who seek medical attention when they have bilateral ARMD the first year.

Another weakness of the study was that the decision to retreat was based on the interpretation of the angiogram, specifically, by the ability to accurately identify the type of ARMD. Thus far, no study has determined the reliability and reproducibility of this interpretation between different retinologists. In addition, the merits of including or excluding from the model additional treatments when the patient's visual acuity has been stabilized or is diminishing despite PDT have not been established, since there is not enough evidence.

Lastly, the patient management data also vary according to the amount of time that has passed since the first diagnosis of ARMD. New patients require many more services during the first year following diagnosis than patients who have had the disease for several years. The difference can therefore be considerable if all of these cases are taken into account. Furthermore, a large percentage of ARMD patients suffer from depression due to their vision loss. These costs cannot be estimated directly in the economic analysis, but they should be taken into account. The depression calculation is, however, taken into consideration in terms of the loss of utility, since depression is included in the time trade-off model.

11.3 CAPACITY OF THE HEALTH-CARE SYSTEM AND ACCESS TO PHOTODYNAMIC THERAPY

In 2002, in Québec, about 33 retinologists were able to administer photodynamic therapy to ARMD patients, but only 15 of them did so. Québec's main urban centres (Montréal, Québec City and Sherbrooke) are home to most of these retinologists and most of the necessary facilities. It should also be noted that, based on information provided by a representative of the manufacturer of verteporfin, some ophthalmologists—fewer than five, all of whom are in regional practice—administer PDT as well.

Each retinologist performed about 40 to 50 PDT treatments a month, which works out to about 7,400 treatments a year for all the retinologists concerned. This number of treatments does not, however, correspond to the number of patients treated, since, as it will be recalled, a given patient receives an average of three treatments the first year following diagnosis and several others during the subsequent years. The number of treatments administered in Québec was well below the number of ARMD patients eligible for PDT (see Section 10.3)

Based on information obtained from the company Coherent-AMT in 2002, there were 15 lasers (Opal Photoactivator™) in different parts of Québec. Technically, treatment time with the device is about 20 minutes. Even if the instrument can be used nearly continuously for an almost unlimited amount of time, it is obvious that a retinologist would find it difficult to devote all of his/her time just to patients with ARMD. However, with a certain amount of calibration, the instrument could potentially be moved from one physical location to another. It would therefore be possible for several other specialists to share an instrument, which could increase the number of treatments performed.

In 2003, one university hospital reduced its Visudyne® budget by about 60%[10]. Only complex cases are treated there, while the less complex cases are referred to private clinics. It is very important to note that, despite the savings realized by the hospitals concerned, these measures lead to additional costs to the pa-

10. Based on information provided by the MSSS (personal communication, June 8, 2004).

tients, since the physicians who perform this procedure at private clinics usually bill them for the cost of the medications and anesthetics. The patients must also make a copayment to obtain the drug at a pharmacy, which can amount to $200 to $839 a year, depending on the category of insured. It should be borne in mind that this treatment may be dispensed every three months for several years. It could therefore financially overburden some patients. On the other hand, to meet the needs of ARMD patients, some retinologists have decided to practice in the private sector so as to be able to treat them as quickly as possible.

To illustrate the care organization-related problems that could prevent patients from being treated within a reasonable amount of time, we conducted, in the summer of 2002, an exploratory study using semistructured interviews with seven retinologists in different settings: university hospitals, general and specialized hospitals, and private clinics. In addition, we contacted ophthalmologists (or receptionists, depending on the physicians' availability at the time of the interview) at public and private ophthalmology clinics. These clinics are located in several of Québec's administrative regions. The following is a summary of the information obtained during these interviews.

According to the interviewees, in general, a patient who notices symptoms that might suggest a degenerative eye disease first consults an ophthalmologist. Since an ophthalmologist does not necessarily have all the expertise required to determine the exact form of ARMD, he/she will often refer the patient to a physician specializing in the retina. In most cases, only retinologists are able to perform the treatment. Afterwards, the retinologist must determine the exact form of ARMD using fluorescein angiography. If this examination shows that the patient is eligible for PDT treatment, the retinologist should perform the treatment within a week. A period of one week between the angiogram and PDT ensures optimal therapeutic efficacy [Bressler, 2001; TAP Study Group, 1999]. During our interviews, a number of individuals reported a problem with access to angiography. They indicated that the problem is due mainly to a lack of medical imaging personnel, nurses and technicians qualified to perform the procedure. In addition, ARMD patients are not the only ones who need to undergo angiography.

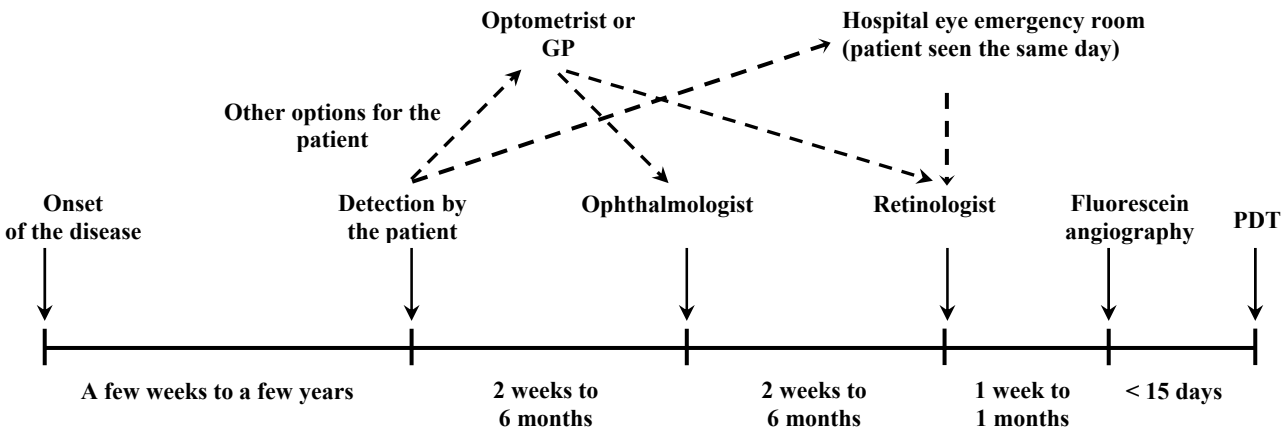
This points to a certain lag between when a patient notices the problem and when he/she is treated, which could result in the treatment being less effective, in a loss of vision and, as a result, in substantial costs. Again, based on the information obtained during the semistructured interviews, we reconstructed the typical itinerary of an ARMD patient (Figure 13).

The first time period is between the onset of the disease and its detection by the patient. According to the practitioners who were interviewed, the amount of time in question varies the most. Given that the disease is usually unilateral in onset, the patient can compensate with the fellow eye and does not necessarily notice any symptoms until this eye is affected as well. The rate of progression of the disease is highly variable as well.

The second time period is between when the patient notices the symptoms and the first appointment with an ophthalmologist. Variability in the waiting time could, to a large extent, be explained by the severity of the symptoms experienced or described by the patient and the region in which the ophthalmologist practices. Naturally, when a patient presents with symptoms such as acute pain, hemorrhage or a discharge, an ophthalmologist will see him/her very quickly. However, a patient with ARMD will seldom have such symptoms. Some patients may also go through another intermediary, an optometrist or a general practitioner, which would now lengthen their itinerary.

FIGURE 13

Typical itinerary of a patient with ARMD (information obtained during the 2002 interviews)



The time period between the appointment with an ophthalmologist and that with a retinologist varies as well and depends on a number of factors. The retinologist's symptom severity perception is the main factor contributing to this variability. Thus, the average wait for a first visit with a retinologist is one week to about two months when the ophthalmologist determines that the patient probably has neovascular ARMD. However, at some hospitals, when fluorescein angiography has not first been performed by an ophthalmologist, the patient may wait for up to six months for his/her appointment. It is important to note that ophthalmologists do not systematically order an angiogram. Furthermore, some retinologists try to synchronize the patient's angiogram and appointment because of a lack of access to angiography or because the patient lives in a remote area. This can increase waiting times. Several retinologists also told us that if a patient presents to the emergency room of a hospital with a well-structured ophthalmology department, he/she will be seen the same day and treated, if eligible, very quickly. Lastly, the wait can also vary according to the region where the retinologist practices.

The last time period that could be improved is between the visit to the retinologist and the fluorescein angiogram. As a general rule, a patient can undergo angiography within two weeks after his/her visit to the specialist. However, because of the aforementioned lack of personnel, the patient may have to wait for up to a month for this examination. Lastly, photodynamic therapy is usually performed within 15 days after the angiogram.

Thus, based on the information obtained, the period of time between when a patient notices a visual abnormality and when he/she receives a first PDT treatment can be quite long. Despite the inherent limitations of the method we used, it is worth noting that a survey conducted in 2002 by the Fraser Institute among general practitioners and specialists tends to confirm the waiting times mentioned in our interviews. The survey found that, in Québec, the average waiting time to see a medical eye specialist was 11 weeks and that the average wait for ophthalmologic treatment was 27 weeks (6½ months) [Esmail and Walker, 2002]. It should, however, be pointed out that the survey did not specifically concern ARMD. One should also consider the fact that

ARMD patients generally have to see two medical eye specialists (an ophthalmologist and a retinologist) before receiving treatment.

To optimally implement this technology will therefore require major changes to the organization of health-care services. There will need to be better coordination between ophthalmology, retinology and optometry services, and between such services and hospitals.

11.4 INCREASE IN THE DISEASE IN THE POPULATION

The health services needs of ARMD patients will intensify considerably in the coming years, since the number of affected individuals is steadily on the rise. Several factors are contributing to the increase in the disease in the population: the increase in the over-55 population, the increase in the incidence of non-age-related ARMD, and the increase in life expectancy.

It is estimated that the over-55 population will increase from 1,730,000 in 2002 to 3,170,000 in 2006 [Institut de la statistique du Québec, 2003]. Furthermore, in 2002, in Québec, life expectancy at birth was 76.33 years for men and 81.90 years for women. Life expectancy at 65 is 16.45 years for men and 20.35 years for women [Institut de la statistique du Québec, 2002]. Life expectancy in Québec is steadily increasing. An ARMD patient may therefore have the disease for many years. It should also be noted that the incidence of the disease is increasing even after the age distribution effect is controlled for. This could be explained by several factors, including pollution, sun exposure and smoking. If all these factors are combined, it is estimated that there will be three times as many ARMD patients in 25 years.

The cost of managing ARMD patients who have lost their central vision is very high. In addition, since there is no systematic process for managing such patients, it is difficult to accurately determine the number of patients concerned or the costs.

11.5 EARLY DETECTION

As mentioned above, the most important time period is generally between the onset of the disease and its detection by the patient, in particular, when only one eye is affected. However, since ARMD has the potential to progress rapidly, its early detection could considerably reduce the risk of severe, irreversible vision loss and the costs associated with visual rehabilitation. Some studies tend to show this [Bonastre et al., 2003].

Based on our economic analysis, early screening could reduce the incremental cost-utility ratio from $33,880 per QALY to $22,701 per QALY (patients with classic neovascular ARMD) and from $43,253 to $20,813 (classic and occult neovascular ARMD), which is a substantial decrease. The main reason for this decrease in the cost-utility ratio is that early detection of the disease results in patients receiving a first treatment when they have better initial visual acuity and that, as has been shown, photodynamic therapy is more effective when the patient's visual acuity is good [Bressler, 2001].

It is important to add that our analysis only examines the costs associated with the rehabilitation and management of patients at centres for semiautonomous or nonautonomous persons but does not include the costs associated with the other symptoms that visual loss leads to. Thus, impaired vision may substantially reduce mobility and, as a result, increase the risk of fall-related injuries. Ivers et al. [1998] found that individuals with neovascular ARMD have a 70% greater risk of falling at least twice in 12 months. As well, visual impairments significantly reduce an individual's ability to perform his/her daily activities, which creates anxiety, emotional distress and depression [Casten et al., 2004; Williams et al., 1998].

Several factors could help promote earlier detection of ARMD in the population. Increasing patient awareness of the first symptoms of the disease, encouraging regular self-

examination using a valid test, and better detection of ARMD by primary care health professionals could be some of the basic components of better detection.

11.5.1 Increasing patient awareness

Although no study has specifically examined this subject, most researchers who investigate ARMD and all the comments obtained during the semistructured interviews concur: most adults know little about macular degeneration and do not know that there are effective treatments for it. A survey conducted by Wang et al. [1998] found that one-third of Americans over the age of 50 who present for a periodic ophthalmologic examination that reveals an ophthalmologic problem were not aware that they had an eye disease.

The elderly frequently forget to report their visual loss symptoms to health-care professionals, as they generally attribute them to normal aging or the development of a cataract [Butler et al., 1997a]. According to a number of authors and the experts we met, it is therefore important to sensitize patients to the first signs and symptoms of macular degeneration so that they can report any visual problem as early as possible and at a stage where the disease can still be treated effectively.

Health professionals (optometrists, general practitioners and ophthalmologists) could therefore play a more important role in disseminating information on ARMD. They should ensure that patients report any sudden loss of vision.

11.5.2 Self-examination using the Amsler grid

While many eye diseases are characterized by potentially annoying symptoms that can prompt the patient to seek medical attention, neovascular ARMD is often asymptomatic in its early stages. According to many authors and professional organizations, people can detect a macular problem on their own by performing a daily self-examination using the Amsler grid, as this test is simple, inexpensive and quick [Bressler, 2002; Mittra and Singerman, 2002; Sickenberg, 2001; Butler et al., 1997b].

We therefore performed an exhaustive search of the scientific literature using the keywords *grid* and *Amsler*. It identified 110 scientific articles, including eight on the grid's validity in screening for certain maculopathies (Appendix K). However, none of these articles demonstrated the validity of this test in the context of early ARMD detection. Consequently, we cannot, for the time being, recommend its use for population ARMD screening.

11.5.3 ARMD detection by primary care health professionals

Given that the first symptoms of visual loss are usually reported to general practitioners and optometrists[11] [Mittra and Singerman, 2002], they should be able to correctly identify patients with maculopathy and those at high risk for ARMD. This is apparently not the case at this time. An American study indicates that general practitioners have problems correctly diagnosing maculopathies [Mittra and Singerman, 2002]. To ensure better patient routing, measures should be taken to increase the training in ophthalmology of general practitioners. A number of studies found that when primary care physicians were trained to recognize the symptoms of diabetic retinopathy, the rate of detection and referral to ophthalmologists among patients at high risk for visual loss due to this disease was better [Awh et al., 1991]. Positive results could be obtained if the same were done for the signs and symptoms of age-related macular degeneration [Bressler, 2002].

As for optometrists, it appears that most of them do have the necessary training and instruments for detecting macular problems [Ordre des optométristes du Québec, 2002]. In October 2003, Québec's National Assembly granted optometrists greater power to inter-

11. This information was obtained during the semistructured interviews as well.

vene therapeutically[12]. These measures should increase access to oculovisual health services for all Quebecers by allowing eye specialists and superspecialists to focus on activities that are more in line with their interventional capacity [Ordre des optométristes du Québec, 2002]. However, the potential for earlier maculopathy detection by optometrists suggests the possibility of earlier treatment, but to achieve this, there would need to be better coordination between optometry and ophthalmology services, for example, by establishing structured referral paths between optometrists and medical eye specialists.

Furthermore, it might be useful to closely examine the experience of certain Canadian provinces in the field of ocular health care and service organization. The case of Nova Scotia provides an interesting example. In that province, the optometrist works in close collaboration with the family physician, sending him/her all the results of his/her oculovisual examinations. The physician can therefore manage cases more efficiently, since he/she is aware of the entire course of a given visual disease. Furthermore, when a family physician suspects an eye problem in a patient, he/she first refers the patient to an optometrist. The optometrist can eventually refer the patient, if his/her condition so warrants, to the appropriate medical eye specialist or treat the patient directly, if the situation so permits [Ordre des optométristes du Québec, 2002; Ordre des optométristes du Québec, 2001].

12. Prescribing and administering drugs and care for the purposes of treating certain disease states: conjunctivitis, inflammation of the eyelids, corneal disorders and the removal of foreign objects from the surface of the eye.

12 CONCLUSION

The chief objective of this report was to assess the efficacy of photodynamic therapy as a treatment for neovascular ARMD and to describe the practice of this treatment in Québec, particularly with regard to the related costs, accessibility and care organization.

We can draw certain conclusions from the in-depth analysis of studies of the efficacy and safety of various treatment modalities for ARMD and from the analysis of the Québec model of the organization of the care pertaining to this disease.

12.1 EFFICACY OF PHOTODYNAMIC THERAPY

- The evidence gathered on photodynamic therapy with verteporfin photosensitizer (TAP and VIP studies) indicates that this technology effectively slows predominantly classic and pure occult subfoveal neovascular ARMD in patients with a visual acuity of at least 6/60.
- For patients with minimally classic neovascular ARMD (between 0 and 50% classic neovascularization), we cannot, from the existing studies, draw any conclusions as to the efficacy of PDT.
- Photodynamic therapy should be performed only by retinologists or ophthalmologists who are thoroughly familiar with this technology.
- Although other types of treatment modalities are presently being evaluated, only photodynamic therapy has been approved for the treatment of predominantly classic and pure occult **subfoveal** neovascular ARMD. In addition, it will take several more years of studies before a conclusion can be drawn with regard to the efficacy of the other types of treatment modalities.
- The dietary supplements recommended by the AREDS study may be effective in preventing the onset or progression of the disease in patients at risk for an advanced form of ARMD (patients with ARM with large drusen or with unilateral neovascular ARMD). However, patients should not, under any circumstances, take such supplements without first consulting a physician, since major adverse effects can occur in certain types of individuals.

12.2 ECONOMIC ANALYSIS

- The results of the economic analysis are favourable with regard to the use of photodynamic therapy in cases of predominantly classic or pure occult exudative neovascular ARMD. The incremental cost-utility ratio per QALY for patients with classic neovascularization is $33,880. If patients with pure occult neovascularization are included, the incremental cost-utility ratio per QALY increases to $43,253. The net annual budget impact is approximately $17.3 million in the scenario where all prevalent and incident cases are included. If only the incident cases are included, the net budget impact for an average year would be $0.3 million.

- Given the potentially rapid progression of neovascular ARMD, its early detection could substantially reduce the risk of severe, irreversible visual loss and thus avoid major expenses to the public system by reducing the costs associated with rehabilitation (from $33,880 per QALY to $20,071 per QALY for patients with predominantly classic neovascular ARMD) and with the treatment of other problems (depression, falls, etc.) resulting from a loss of vision. If we also include patients with pure occult neovascularization in our analysis, early detection would result in a greater reduction in the cost-utility ratio per QALY, i.e., from $43,253 to $22,813.

12.3 ACCESS TO OPHTALMOLOGY SERVICES

- Several factors could help promote earlier detection of ARMD in the population. Increasing public awareness of the first symptoms of the disease, encouraging regular self-examination using a valid test, and better detection of ARMD by primary care health professionals might be some of the basic components of better screening. Furthermore, changes to the organization of ocular health services aimed at better coordination between optometry, ophthalmology and retinology services would be desirable. It should be noted that, even if there is a consensus among health professionals regarding the usefulness of the Amsler grid in detecting the first symptoms of age-related macular degeneration, the Agency cannot recommend the use of this test, since its validity has not been demonstrated in the context of early ARMD detection by patients.

- Presently, in Québec, ARMD patients do not always have access to photodynamic therapy within a reasonable amount of time. Problems gaining access to eye specialists (ophthalmologists and retinologists) and to fluorescein angiography contribute to increasing patient waiting time for a first treatment with photodynamic therapy.

- Furthermore, in 2003, for budgetary reasons, some of the hospital clientele that were receiving this treatment were transferred to the private sector. The main consequence is that patients have to assume a substantial portion of the cost of the drugs, which can further limit access to this therapy.

In short, the efficacy of photodynamic therapy has been demonstrated, and its budget impact, as estimated for a Québec cohort, is acceptable if the improvement in quality of life is taken into account. However, the problems accessing this technology will need to be dealt with.

13 RECOMMENDATIONS

Our analysis of the current situation therefore leads us to make certain recommendations.

Photodynamic therapy: an effective technology

1. *Photodynamic therapy should be considered a technology that can effectively slow the progression of certain forms of macular degeneration.*

Photodynamic therapy is a technology that can slow the progression of subfoveal neovascular ARMD with predominantly classic neovascularization or pure occult neovascularization in patients whose visual acuity is at least 6/60. However, it should be noted that, to achieve this type of outcome in current medical practice, one must necessarily use the same therapeutic indications, patient follow-up and monitoring procedures as those used in the TAP and VIP studies and, consequently, improve access to this treatment.

To optimally implement this technology will therefore require major changes to the organization of health-care services. There will need to be better coordination between ophthalmology, retinology and optometry services and between such services and hospitals.

A public health problem

2. *Policymakers in Québec's health-care system should recognize ARMD as a major public health problem.*

The prevalence and incidence of ARMD and its seriousness in terms of blindness and disability, the efficacy of the therapeutic modalities for slowing its progression, and the results of this economic analysis argue in favour of this recommendation.

The concept of preventable blindness

3. *In Québec, initiatives for the population-based management of ARMD should be part of a more global effort to manage preventable blindness.*

ARMD and this report aside, it would be useful to mention that various groups are already asking or will soon ask policymakers in Québec's health-care system to initiate measures to improve the care provided to patients with various chronic eye diseases. Initiatives aimed at improving diabetic retinopathy screening are presently being started in Québec [Boucher, 2001], and evaluations aimed at establishing better glaucoma screening modalities are continuing [Harasymowycz and Kamdeu Fansi, 2003]. AETMIS has contributed in both cases to the advancement of these projects. To us, the concept of managing preventable blindness seems to be an attractive option for avoiding operating in a compartmentalized fashion and, as a result, splitting efforts. This concept is inspired, in particular, by the World Health Organization's Vision 2020—Right to Sight Initiative [2000; 1997], which is aimed at alleviating the social burden of preventable blindness in developing and industrialized countries. In industrialized countries, age-related eye diseases, such as ARMD, glaucoma and diabetic retinopathy, are considered leading causes of preventable blindness, although refraction errors and trauma could also be taken into consideration [Congdon et al., 2003; Lee et al., 2003].

Mobilizing many parties

4. *The planning and implementation, in the wake of this report, of the next few steps in the broader context of managing preventable blindness could be facilitated by creating a task force charged with proposing a concrete plan to the Ministère de la Santé et des Services sociaux (MSSS).*

The task force could consist of representatives of the *Association des opthalmologistes du Québec*, the *Fédération des médecins omnipraticiens du Québec*, the *Collège des médecins du Québec*, the *Ordre des optométristes du Québec*, the *Régie de l'assurance maladie du Québec*, the *Association des hôpitaux du Québec*, the MSSS and AETMIS, and the two leading researchers in the above-mentioned glaucoma and diabetic retinopathy screening projects. The task force should also examine the possibility of including one or more patient representatives.

In the specific context of ARMD, the task force should pay special attention to the increasing demand for ARMD-related care. Specifically, solutions will need to be found to increase access to retinologists and angiography to ensure adequate management of the growing number of individuals who will be seeking medical attention. In addition, the task force should closely examine the training needs of primary care health professionals (general practitioners and optometrists) so that they can better recognize the first signs and symptoms of ARMD. Given the recent broadening of optometrists' field of activity, it would probably be advisable to facilitate the process of referring patients to retinologists when optometrists discover maculopathy in their patients. The task force should also consider raising public awareness of ARMD, but only after services have been reorganized in order to meet the demand.

Avenues of research

5. *The Agency recommends that the Vision Network/FRSQ consider the possibility of giving priority to the carrying out of studies, in the near future, evaluating the validity of the Amsler grid in the context of ARMD screening.*

The Amsler grid could prove very useful in the early ARMD detection and could lead to a decrease in the cost of managing visually impaired patients. However, the validity of this test has not been demonstrated in the specific context of ARMD, including its detection by patient self-examination, which many authors recommend.

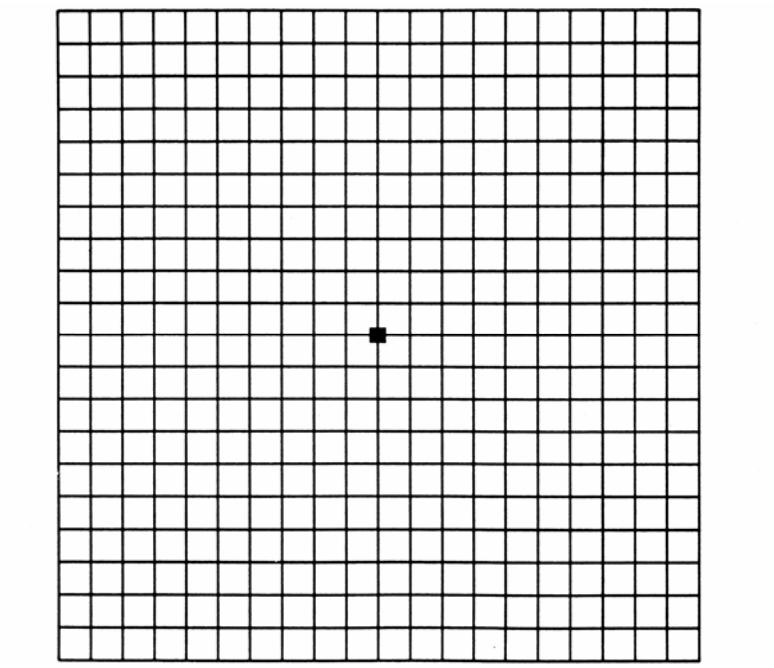
6. *The Agency also recommends that the Vision Network/FRSQ undertake more-thorough studies to determine, with the necessary rigour, the needs relating to the organization of services pertaining to ARMD and preventable blindness in Québec.*

For the purposes of this assessment, only one exploratory study has been conducted. More-precise data on access to services and on service organization between primary care professionals (general practitioners and optometrists) and specialized services would be needed. One would also have to take into account the trend toward privatizing part of the cost of verteporfin, which will certainly have an impact on the management and organization of the care relating to photodynamic therapy.

APPENDIX A

THE AMSLER GRID

The Amsler grid is used to detect retinal abnormalities in the central visual field (20 degrees). This test consists of a grid with a central fixation point. Each square measures 5 mm and occupies an angle of 1 degree in the visual field at an observation distance of 30 cm.



Instructions

1. Hold the grid at your normal reading distance (about 30 to 40 cm). If you use reading glasses, wear them.

2. Cover your right eye with a card.

3. Look at the dot in the centre of the grid with your left eye.

4. Ask yourself the following questions: Are the lines straight? Are all the squares the same size? Do you see the four corners? Are there any empty, distorted or blurred areas or wavy lines?

5. Repeat the test with the other eye.

When the eye being examined focuses on the central dot, the image of the grid is limited to the macula. Therefore, a "Yes" answer to any of the above questions indicates a macular disorder. The patient should thus see an eye specialist at once.

APPENDIX B

CURRENT PHOTOSENSITIZERS

AGENT	TRADE NAME	IRRADIATION PARAMETERS	CLINICAL STATUS	ADVANTAGES	DRAWBACKS
Verteporfin	**Visudyne®** Novartis Ophthalmics	690 nm, 150 J/cm^2	3 years of known data from phase III clinical studies. Approved for the treatment of classic neovascular ARMD in 52 countries.	Efficacy demonstrated for classic and pure occult choroidal neovascularization (CNV). Rapid elimination by the body (24 hours).	Numerous dropouts
SnET2	**Purlytin™** Miravant-Pharmacia & Upjohn	664 nm, 36-126 J/cm^2	2 years of known data from a phase III clinical study. 2-year, randomized, double-blind, multicentre study. Promising results.	Fewer treatments necessary than with verteporfin.	Long clearance time: 4 weeks
Lutetium texaphyrin	**Lutex/ Optrin®** Pharmacyclics-Alcon	732 nm, 75-125 J/cm^2	Presently being tested in a phase Ib/II clinical trial.	**Can be used as a diagnostic tool because of its fluorescence spectrum.** Soluble, hence rapid infusion time. Rapid clearance time.	No study has actually demonstrated its efficacy.
ATX-S10	Allergan and Hamamatsu Photonics	670 nm, 7.4 J/cm^2	Presently at the preclinical trial stage.	Optimal wavelength, as with SnET2. Rapid elimination, as with verteporfin. Amphiphilic (both hydrophilic and lipophilic or hydrophobic), hence rapid infusion time. Long-lasting occlusion effects, in monkeys.	Clinical trials involving humans have not begun.
Mono-L-aspartyl chlorine e6	**Npe6** Meiji Seika Kaisha	664 nm, 2.3-7.5 J/cm^2	Presently at the preclinical trial stage.	Can be used as a diagnostic tool. Soluble, hence rapid infusion time.	Clinical trials involving humans have not begun.

Sources: Hunt and Margaron, 2003; Shuler et al., 2001.

APPENDIX C

COUNTRIES IN WHICH VISUDYNE® HAS BEEN APPROVED

As at 2004, Visudyne® had been approved as a treatment in 72 countries. These countries are listed below according to the conditions of approval [QLT inc., 2004].

1. Exudative age-related macular degeneration (ARMD) with predominantly classic subfoveal neovascularization

Costa Rica	Honduras	Romania	South Africa
Cyprus*	Hungary	Saudi Arabia	Taiwan
El Salvador	Indonesia	Singapore	Tunisia
Estonia	Malaysia		

* Member of the European Union

2. Exudative age-related macular degeneration (ARMD) with predominantly classic subfoveal neovascularization, or pathologic myopia (with subfoveal neovascularization)

Latvia*	Czech Republic*	Slovenia*	Ukraine
Lithuania*	Russia	Trinidad	Vietnam
Malta*	Slovakia*	Turkey	

* Member of the European Union

3. ARMD and pathologic myopia with predominantly classic subfoveal neovascularization, or presumed ocular histoplasmosis

Canada
United States

4. ARMD and pathologic myopia with predominantly classic subfoveal neovascularization, or choroidal neovascularization resulting from other maculopathies

Brazil	Panama
India	Philippines

5. **Exudative age-related macular degeneration (ARMD) with predominantly classic or pure occult subfoveal neovascularization, or pathologic myopia with subfoveal neovascularization**

Germany*	Denmark*	Iceland	The Netherlands*
Argentina	Spain*	Ireland*	Poland*
Austria*	Finland*	Italy*	United Kingdom*
Belgium*	France*	Luxembourg*	Sweden*
Bulgaria	Greece*	Norway	Switzerland
Chile			

* Member of the European Union.

6. **Exudative age-related macular degeneration (ARMD) with predominantly classic or pure occult subfoveal neovascularization, pathologic myopia with subfoveal neovascularization, or presumed ocular histoplasmosis**

Korea

7. **Exudative age-related macular degeneration (ARMD) with predominantly classic or pure occult subfoveal neovascularization, or choroidal neovascularization resulting from other maculopathies**

Australia	Guatemala	New Zealand	Syria
Bolivia	Hong Kong	Paraguay	Thailand
Columbia	Israel	Peru	Uruguay
Ecuador	Lebanon	Sri Lanka	Venezuela

8. **Exudative age-related macular degeneration (ARMD) with subfoveal choroidal neovascularization**

Japan

9. **Exudative age-related macular degeneration (ARMD) with subfoveal choroidal neovascularization, or choroidal neovascularization resulting from other maculopathies**

Mexico

APPENDIX D

D.1 INCLUSION CRITERIA IN THE TAP AND VIP STUDIES

	TAP	VIP
Lesion size and location	▪ Angiographic evidence of subfoveal neo-vascularization due to ARMD ▪ < 5400 μm in diameter	▪ Angiographic evidence of subfoveal neovascularization due to ARMD ▪ < 5400 μm in diameter
Pathological states accepted	▪ Hemorrhage, angiographic hypofluorescence or a pigment epithelium tear occupying less than 50% of the entire lesion	▪ The area of choroidal neovascularization occupies at least 50% of the entire lesion
Type of lesion	▪ Classic or classic and occult	▪ 100% occult or evidence of classic neovascularization if visual acuity (VA) letter score greater than 70
Visual acuity	▪ 73 to 34 letters (20/40 to 20/200)	▪ 100% occult: 50 letters (20/100 or better) ▪ Classic: 70 letters
Recent disease progression	▪ Not specified	▪ If pure occult lesion, then presumed to have recent disease progression (visual or anatomic) within the last 3 months or evidence of hemorrhage
Age	▪ 50 and over	▪ Not specified

D.2 EXCLUSION CRITERIA IN BOTH STUDIES

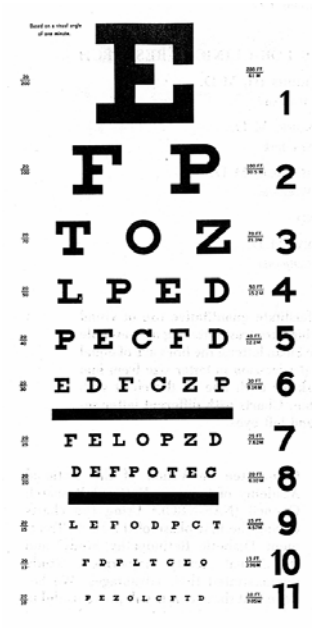
- Tear of the macular pigment epithelium during the prerecruitment visit.
- Ocular disease that effects or that could affect vision and compromise the validity of the data gathered during the studies: pseudovitelliform macular dystrophy, central serous chorioretinitis, isolated drusenoid pigment epithelium detachment.
- Disabling hepatic, renal or neurological diseases.
- Class III or IV cardiovascular diseases (according to New York Heart Association criteria).
- Porphyria, allergy to porphyrin derivatives, hypersensitivity to sunlight or to intense artificial light.
- Cancer treatment.
- Inability to perform fluorescein angiography, for example, because of poor venous access.
- Participation in another ophthalmic clinical trial or the use of any other investigational drug within the 12 months before the start of the current trial.
- Eye surgery within the three months preceding the study treatment.
- Any problem other than ARMD (pathologic myopia) constituting an additional exclusion criteria in the VIP study.

APPENDIX E

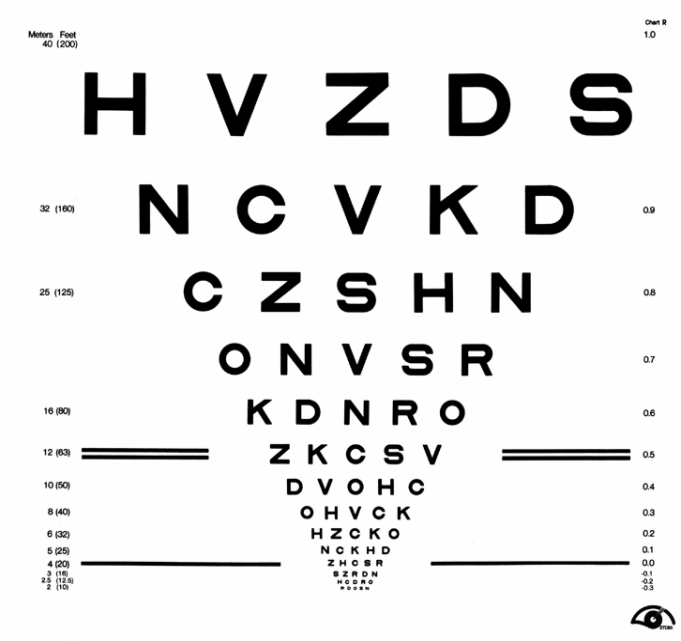
E.1 VISUAL ACUITY AND VISUAL ACUITY TESTS

Visual acuity (VA) can be defined as the minimum angle (or size) that a letter or form projected at a given distance from the eye must have for two separate black points, lines or spaces that make up the letter or form to be discriminated by the retinal photoreceptors.

Optotypes used to determine visual acuity



A. Snellen chart



B. EDTRS chart (R card)

Reproduced with permission of the National Eye Institute.

Visual acuity can be determined with the use of optotypes, whose type of notation differs according to the test. Angular notation (minimum arc), or the minimum angle of resolution (MAR), is the angle at which the separation between two points is seen and located in space. Snellen notation uses a mathematical conversion of the angular notation as a function of the distance from which the chart is viewed. The Bailey-Lovie and ETDRS charts use a logarithmic notation in which the logarithm of the minimum angle of resolution (logMAR) is calculated.

Note: A gain or loss of lines means an improvement or a deterioration in visual acuity represented by the number of lines that can be discerned correctly. For example, a person with a visual acuity of 6/15 (Snellen chart) can read line 6. If the individual loses three lines of vision, he/she can now only discern the letters of line 3 correctly and therefore now has a corrected visual acuity of 6/21. The same procedure can be performed with the ETDRS chart, but the loss or gain in vision will be measured in letters. Generally, three lines of visual acuity corresponds to 15 letters.

E.2 CHARTS FOR DETERMINING VISUAL ACUITY

TYPE OF CHART	PRINCIPLE	COMMENTS
Snellen chart	▪ Uses capital letters of decreasing size. ▪ Angular acuity is indicated by the value of the angle at which details in the optotype can be distinguished. ▪ This chart consists of lines ranging from 6/3, 6/4, 6/5, 6/6...to 6/60 and 6/120. ▪ Since this chart is not linear, the loss or gain of a line after a given intervention does not necessarily constitute the same difference at every point on the chart.	▪ The following equation is used as the method of calculation: V = d/D, where "d" is the test distance and "D" is the distance at which a healthy individual with an angular notation of 1 can read a given optotype. It depends on the test distance (4, 5 or 6 m), but the ratio d/D does not vary.
Bailey-Lovie logarithmic chart	▪ The size of the optotypes varies from row to row according to a logarithmic progression. ▪ The geometric progression factor equals 1.2589, or 0.1 log unit. ▪ The chart contains 14 lines with 5 letters each, with the letter size increasing as one goes further down the chart.	▪ On one side of this chart is the Snellen notation, on the other, visual acuity given as the logarithm of the MAR to the base 10 log of the visual angle subtended by the optotype equivalent to the Landolt ring.
ETDRS logarithmic chart	▪ Consists of three scales: R, I and II. ▪ "R" is used to measure refraction, "I" to test the right eye and "II" to test the left eye. ▪ Each chart is read at a distance of 4 m (1 m for individuals with poor vision).	▪ A progression of 15 letters (3 lines) on the ETDRS charts corresponds to a doubling of the visual angle.

APPENDIX F

DIETARY REFERENCE INTAKES (DRIs)

F.1 WHAT ARE DIETARY REFERENCE INTAKES?

DRIs are a set of scientifically based nutrient reference values for healthy populations. Governments and nongovernment organizations will use these values to develop policies and programs [Food and Nutrition Board, 2002; Food and Nutrition Board, 2000]. They serve as a scientific basis for numerous decisions that have an impact on the health and safety of Canadians. DRIs include four reference values:

Estimated Average Requirement (EAR)
The median usual intake value that is estimated to meet the requirement of half the healthy individuals in a life-stage and gender group. At this level of intake, the other half of the individuals in the specified group would not have their needs met. The EAR is used to calculate the RDA.

Recommended Dietary Allowance (RDA)
The average daily dietary intake level that is sufficient to meet the nutrient requirement of nearly all healthy individuals in a particular life-stage and gender group. If the distribution of requirements in the group is assumed to be normal, then the RDA is the value that exceeds the needs of 97 to 98% of the members of the group. It is therefore used as a goal for usual intake of individuals. If the distribution of requirements in the group is assumed to be normal, then the RDA can be calculated from the EAR and the standard deviation of requirements (SD_{REQ}) as follows:

$$RDA = EAR + 2\ SD_{REQ}$$

Adequate Intake (AI)
If sufficient scientific evidence is not available to establish an estimated average requirement and set a recommended dietary allowance, an AI is derived for the nutrient instead. The adequate intake is a recommended average daily nutrient intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group or groups of apparently healthy people who are assumed to be maintaining an adequate nutritional state.

For example, for infants, the AI is usually based on the daily mean nutrient intake supplied by human milk for healthy, full-term infants who are exclusively fed human milk. For adults, the AI may be based on data from one type of experiment or on estimated dietary intakes in apparently healthy population groups, or result from a review of data from different approaches. The AI is expected to meet or exceed the needs of most individuals in a specific group. The AI can be used as the goal for an individual's intake when there is no recommended dietary allowance for a given nutrient.

Tolerable Upper Intake Level (UL)
The highest level of continuing daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals in a given life-stage group. As intake increases above the UL, the potential risk of adverse effects increases. The term "tolerable" intake was chosen to avoid implying a possible beneficial effect. Instead, the term is intended to specify a level of intake with a high probability of being tolerated biologically. The UL is not intended to be a recommended level of intake.

Unless specifically identified in the nutrient reports (e.g., for folate in the prevention of neural tube defects), there is no currently established benefit to healthy individuals of ingesting nutrients in amounts exceeding the recommended dietary intake or adequate intake.

F.2 DIETARY REFERENCE INTAKE VALUES FOR VITAMINES A (BETA-CAROTENE), C AND E, AND FOR ZINC

NUTRIENT	ROLE	AGE GROUPS (YEARS)	RDA/AI*	UL	DIETARY SOURCES	ADVERSE EFFECTS OF OVERCONSUMPTION	SPECIAL CONSIDERATIONS
Vitamin A Includes provitamin A carotenoids, which are precursors of retinol (beta-carotene). Note: The values are in retinol activity equivalents (RAEs) : 1 RAE = 1 **µ**g of retinol, 12 **µ**g of β-carotene, 24 **µ**g of α-carotene, or 24 **µ**g of β-cryptoxanthin	▪ Required for normal vision ▪ Gene expression ▪ Reproduction ▪ Embryonic development ▪ Immune system	Children 0-6 months 7-12 months 1-3 4-8 Men 9-13 14-18 19- > 70 Women 9-13 14-18 19- > 70	**(µg/day)** 400* 500* **300** **400** **600** **900** **900** **600** **700** **700**	**(µg/day)** 600 600 600 600 1,700 2,800 3,000 1,700 2,800 3,000	Liver Dairy products Fish	▪ Teratogenic effects ▪ Hepatic toxicity	▪ People who consume large amounts of alcohol or who have a preexisting liver disease, hyperlipidemia or severe protein malnutrition are likely to experience adverse effects if they consume excessive amounts of vitamin A. ▪ Beta-carotene supplements are recommended as a source ofvitamin A for people at risk for vitamin A deficiency.
Vitamin C Other names: *ascorbic acid*, *dehydroascorbic acid* (*DHA*).	▪ Cofactor in reactions requiring reduced copper or ferric metalloenzymes ▪ Antioxidant	Children 0-6 months 7-12 months 1-3 4-8 Men 9-13 14-18 19- > 70 Women 9-13 14-18 19- > 70	**(mg/day)** 40* 50* **15** **25** **45** **75** **90** **45** **65** **75**	**(mg/day)** ND ND 400 650 1,200 1,800 2,000 1,200 1,800 2,000	Lemons Strawberries Tomatoes Tomato juice Potatoes Cabbage Brussels sprouts Cauliflower Broccoli Spinach	▪ Gastrointestinal disorders ▪ Kidney stones ▪ Excessive iron absorption	▪ Smokers need 35 mg more of vitamin C per day than nonsmokers. ▪ Nonsmokers exposed to cigarette smoke should ensure that they get their RDA of vitamin C.

Note: This table is adapted from DRI reports. Recommended dietary allowances (RDAs) are boldfaced. Adequate intakes (AIs) are followed by an asterisk.
ND: Not determined.

F.2 (Cont'd)

NUTRIENT	ROLE	AGE GROUPS (YEARS)	RDA/AI*	UL	DIETARY SOURCES	ADVERSE EFFECTS OF OVERCONSUMPTION	SPECIAL CONSIDERATIONS
Vitamin E Other name: *α-tocopherol* Note: α-tocopherol includes RRR-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the *2R*-stereoisomeric forms (*RRR*-, *RSR*-, *RRS*- and *RSS*-α-tocopherol) that are found in fortified foods and supplements.	▪ Vitamin E is a nonspecific antioxidant with an inhibitory effect. ▪ The metabolic function has not yet been determined.	Children 0-6 months 7-12 months 1-3 4-8 Men 9-13 14-18 19- > 70 Women 9-13 14-18 19- > 70	**(mg/day)** 4* 5* **6** **7** **11** **15** **15** **11** **15** **15**	**(mg/day)** ND ND 200 300 600 800 1,000 600 800 1,000	Vegetable oils Unprocessed cereal grains Nuts Fruits Vegetables Meat (small quantities)	▪ There is no evidence that vitamins in food cause any adverse effects. ▪ One of the potential adverse effects of supplemental vitamin E is hemorrhagic toxicity. ▪ The tolerable upper intake level of vitamin E applies to all forms of α-tocopherol in supplements, fortified foods or a combination of the two.	▪ Patients on anticoagulation therapy should consult a physician before taking vitamin E supplements.
Zinc	A component of numerous enzymes and proteins involved in gene regulation.	Children 0-6 months 7-12 months 1-3 4-8 Men 9-13 14-18 19- > 70 Women 9-13 14-18 19- > 70	**(mg/day)** 2* **3** **3** **5** **8** **11** **11** **8** **9** **8**	**(mg/day)** 4 5 7 12 23 34 40 23 34 34	Fortified cereals Red meat Certain types of seafood	▪ Reduces iron absorption.	▪ Zinc absorption is poorer in vegetarians than nonvegetarians. ▪ It is therefore advisable for vegetarians to consume twice as much zinc as the RDA.

Sources: Food and Nutrition Board, 2002; Food and Nutrition Board, 2000.

Note: The table is adapted from DRI reports. Recommended dietary allowances (RDAs) are boldfaced. Adequate intakes (AIs) are followed by an asterisk. ND: Not determined.

APPENDIX G

G.1 CONCEPT OF VISUAL IMPAIRMENT

According to the World Health Organization (WHO) International Classification of Diseases (ICD-9) [1977], the levels of visual acuity (VA)-related visual impairment are defined as follows:

- No visual acuity-related visual impairment: better-eye VA between 6/3 and 6/7.5 (VA > 6/9).
- Mild visual impairment: better-eye VA between 6/9 and 6/18 (6/9 > VA > 6/18).
- Moderate visual impairment: better-eye VA between 6/18 and 6/60 (6/18 > VA > 6/60).
- Severe visual impairment: better-eye VA between 6/60 and 6/120 (6/60 ≥ VA > 6/120).
- Profound visual impairment: better-eye VA between 6/120 and 1/60 (6/120 ≥ VA > 1/60).
- Near-blindness: better-eye VA between 1/60 and no light perception (1/60 ≥ VA > no light perception).
- Total blindness: complete absence of light perception.

Note: The *Régie de l'assurance maladie du Québec* (RAMQ) used this classification as a basis for defining the eligibility requirements for visual impairment rehabilitation programs. The condition specifically concerning visual acuity is that it must be less than 6/21 in the better eye after refraction. Based on these definitions (WHO or RAMQ), individuals with a visual acuity of less than 6/21 in one eye but with visual acuity greater than or equal to 6/18 in the fellow eye do not have low vision and are not eligible for these programs.

G.2 COST OF PATIENT MANAGEMENT BY DEGREE OF VISUAL IMPAIRMENT

VA 1st EYE	THERAPEUTIC OUTCOME, 1st EYE	VA, 2nd EYE	THERAPEUTIC OUTCOME, 2nd EYE	COST OF MANAGEMENT IN TERMS OF ADAPTATION AND REHABILITATION
6/12	No change 6/12	Makes no difference	Makes no difference	No cost, regardless of the therapeutic outcome for the 2nd eye
6/12	Deterioration 6/24 (loss of 3 lines)	6/12	No change 6/12	No cost, regardless of the therapeutic outcome for the 1st eye
6/12	Deterioration 6/24	6/12	Deterioration 6/24	Management because of moderate visual impairment (low cost)
6/12	Deterioration 6/24	6/60	Makes no difference	Management because of moderate visual impairment (low cost)
6/60	Makes no difference	Not affected	Makes no difference	No cost
6/60	Makes no difference	6/12	No change 6/12	No cost
6/60	Makes no difference	6/12	Deterioration 6/24	Management because of moderate visual impairment (low cost)
6/60	No change 6/60	6/60	Makes no difference	Management because of severe visual impairment (moderate cost)
6/60	Deterioration 6/120 (loss of 3 lines)	6/60	No change 6/60	Management because of severe visual impairment (moderate cost)
6/60	Deterioration 6/120	6/60	Deterioration 6/120	Management because of profound visual impairment (high cost)

Annual cost of managing a patient:

- Low: $2,500 (range: $1,250 to $3,750)
- Moderate: $3,500 (range: $1,750 to $5,250)
- High: $40,000 (range: $20,000 to $60,000)

Source: Data provided by the *Institut Nazareth et Louis-Braille*.

APPENDIX H

INPUT VARIABLES IN THE SENSITIVITY ANALYSIS

INPUT VARIABLES	HIGH-VALUE SCENARIO	BASELINE VALUE	LOW-VALUE SCENARIO	PROBABILITY DISTRIBUTION
Prevalence and incidence of ARMD	**1.5 x baseline value**		**0.75 x baseline value**	**Triangular**
Prevalence of ARMD in the 55-to-64 age group		0.0021		
Prevalence of ARMD in the 65-to-74 age group		0.0085		
Prevalence of ARMD in the 75-to-84 age group		0.0459		
Prevalence of ARMD in the 85-and-over age group[13]		0.1305		
Incidence of ARMD in the 55-to-64 age group[14]		0.001		
Incidence of ARMD in the 65-to-74 age group		0.0015		
Incidence of ARMD in the 75-to-84 age group		0.0061		
Incidence of ARMD in the 85-and-over age group[15]		0.0175		
Number of treatments and follow-up visits over four years[16]	**1.5 x baseline value**		**0.75 x baseline value**	**Triangular**
Number of treatments: 1st year		3.4		
Number of treatments: 2nd year		2.1		
Number of treatments: 3rd year		1		
Number of treatments: 4th year		0		
Number of follow-up visits: 1st year		4		
Number of follow-up visits: 2nd year		4		
Number of follow-up visits: 3rd year		2		
Number of follow-up visits: 4th year		1		
Cost of managing a patient with a visual acuity of 20/80, 20/200 and above 20/400[17]	**2 x baseline value**		**0.5 x baseline value**	**Triangular**
Low management		$2,500		
Moderate management		$3,500		
Intense management		$40,000		
Unit cost to the health-care system of an angiogram and a treatment with photodynamic therapy with verteporfin	**1.5 x baseline value**		**0.75 x baseline value**	**Log-normal**
Cost of an angiogram[18]		$429		
Cost of a treatment with PDT[19]		$1,979		

13. Smith et al., 2001.
14. Klein et al., 1997.
15. Klaver et al., 2001.
16. Current practice in Québec (personal communication with Drs. Chen, Turcotte and Boucher, ophtalmologists).
17. Personal communication, *Institut Nazareth et Louis-Braille*.
18. Based on the cost figures provided by a private clinic and a hospital clinic.
19. Cost figures for the laser and verteporfin provided by the manufacturers.

APPENDIX H (Cont'd)

INPUT VARIABLES	HIGH-VALUE SCENARIO	BASELINE VALUE	LOW-VALUE SCENARIO	PROBABILITY DISTRIBUTION
Probability of losing or not losing three lines of vision by visual acuity (6/12 or 6/60) during the first two years and by treatment option (*treatment* or *no-treatment*)[20]	**1.25 x baseline value (up to a maximum of 100%)**		**0.75 x baseline value**	**Normal**
Classic neovascularization: *treatment* option				
VA 6/12: probability of losing 3 lines of vision the 1st year		0.453		
VA 6/60: probability of losing 3 lines of vision the 1st year		0.322		
VA 6/12: probability of not losing 3 lines of vision the 1st year		0.547		
VA 6/60: probability of not losing 3 lines of vision the 1st year		0.678		
VA 6/12: probability of losing 3 lines of vision the 2nd year		0.562		
VA 6/60: probability of losing 3 lines of vision the 2nd year		0.377		
VA 6/12: probability of not losing 3 lines of vision the 2nd year		0.438		
VA 6/60: probability of not losing 3 lines of vision the 2nd year		0.623		
Occult neovascularization: *treatment* option				
VA 6/12: probability of losing 3 lines of vision the 1st year		0.510		
VA 6/60: probability of losing 3 lines of vision the 1st year		0.510		
VA 6/12: probability of not losing 3 lines of vision the 1st year		0.490		
VA 6/60: probability of not losing 3 lines of vision the 1st year		0.490		
VA 6/12: probability of losing 3 lines of vision the 2nd year		0.670		
VA 6/60: probability of losing 3 lines of vision the 2nd year		0.420		
VA 6/12: probability of not losing 3 lines of vision the 2nd year		0.330		
VA 6/60: probability of not losing 3 lines of vision the 2nd year		0.580		
***No-treatment* option**				
VA 6/12: probability of losing 3 lines of vision the 1st year		0.574		

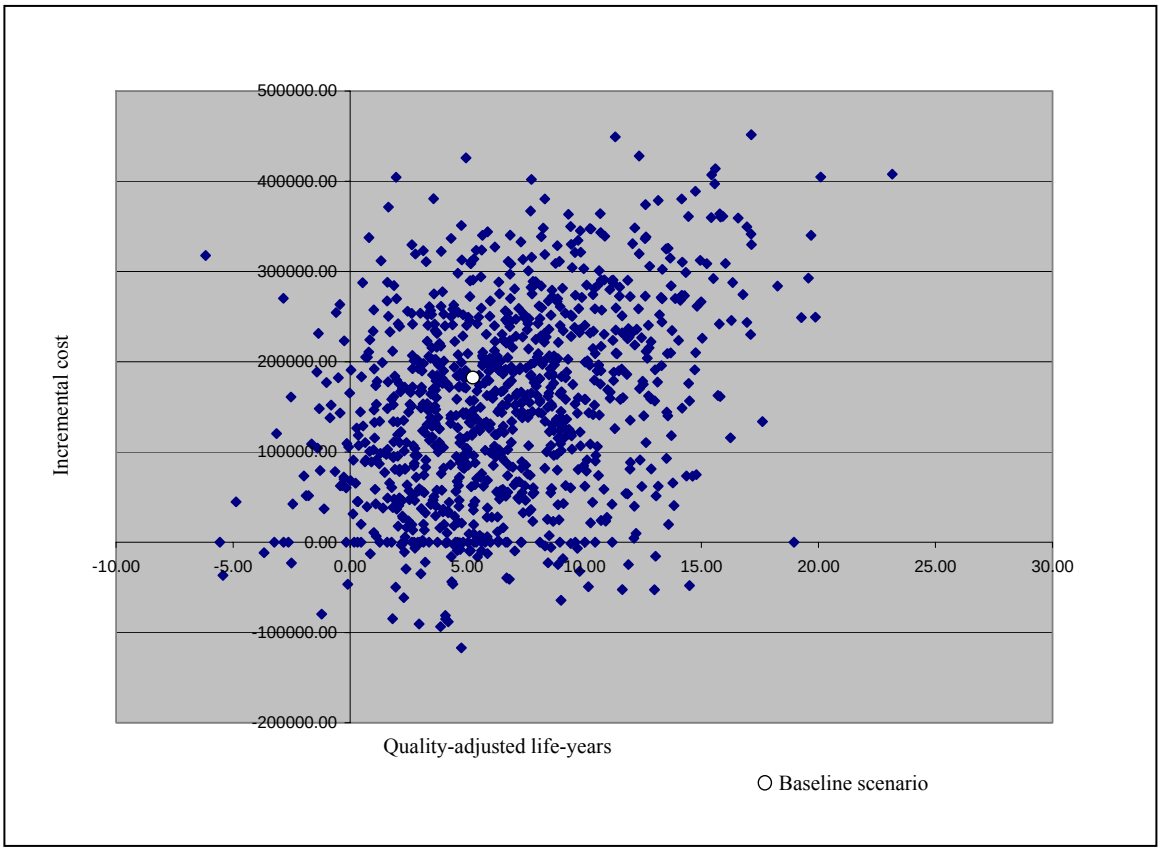
20. VIP Study Group, 2001a; TAP Study Group, 1999.

INPUT VARIABLES	HIGH-VALUE SCENARIO	BASELINE VALUE	LOW-VALUE SCENARIO	PROBABILITY DISTRIBUTION
***No-treatment* option (Cont'd)**				
VA 6/60: probability of losing 3 lines of vision the 1st year		0.500		
VA 6/12: probability of not losing 3 lines of vision the 1st year		0.426		
VA 6/60: probability of not losing 3 lines of vision the 1st year		0.500		
VA 6/12: probability of losing 3 lines of vision the 2nd year		0.653		
VA 6/60: probability of losing 3 lines of vision the 2nd year		0.594		
VA 6/12: probability of not losing 3 lines of vision the 2nd year		0.347		
VA 6/60: probability of not losing 3 lines of vision the 2nd year		0.406		
Probability of having a VA of 6/12 or 6/60 in the first eye and fellow eye[21]	**1.25 x baseline value**		**0.75 x baseline value**	**Triangular**
Probability of having a VA of 6/12 in the first eye, with or without treatment		0.55		
Probability of having a VA of 6/60 in the first eye, with or without treatment		0.45		
Probability of having a VA of 6/12 in the fellow eye, with treatment		0.70		
Probability of having a VA of 6/60 in the fellow eye, with treatment		0.30		
Probability of having a VA of 6/12 in the fellow eye, without treatment		0.55		
Probability of having a VA of 6/60 in the fellow eye, without treatment		0.45		
Change in utility due to a loss or the non-loss of 3 lines of vision by visual acuity (6/12 or de 6/60)[22]	**1.25 x baseline value**		**0.75 x baseline value**	**Uniform (plateau)**
Utility associated with the following outcome: loss of 3 lines of vision when the initial visual acuity is 6/12-6/24		0.57		
Utility associated with the following outcome: non-loss of 3 lines of vision when the initial visual acuity is 6/12-6/24		0.81		
Utility associated with the following outcome: loss of 3 lines of vision when the initial visual acuity is 6/48-6/60		0.40		
Utility associated with the following outcome: non-loss of 3 lines of vision when the initial visual acuity is 6/48-6/60		0.52		

21. Margherio et al., 2000.
22. Sharma et al., 2000.

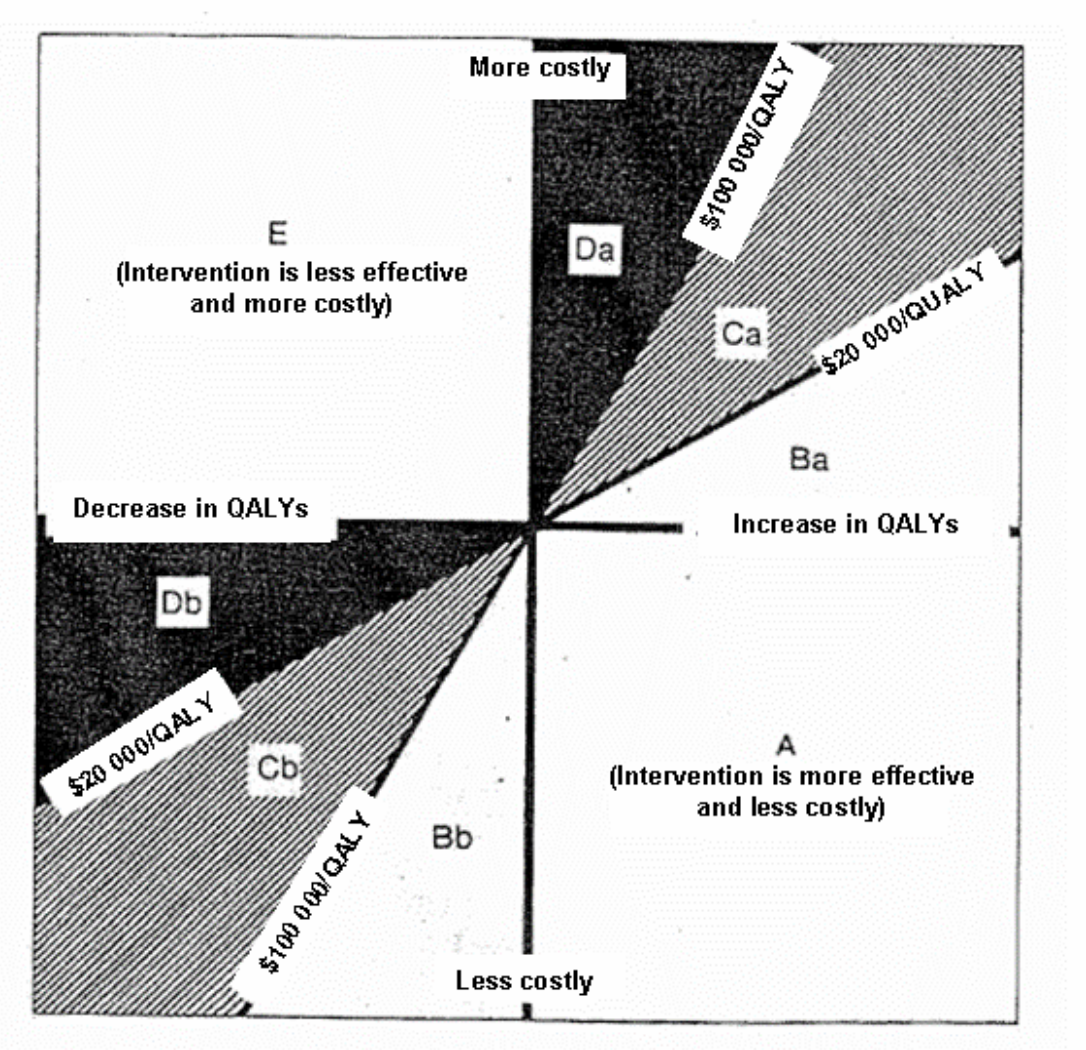
APPENDIX I

MONTE CARLO SENSITIVITY ANALYSIS



APPENDIX J

CATEGORIES OF RECOMMENDATIONS PROPOSED BY LAUPACIS ET AL. FOR ADOPTING AND USING NEW TECHNOLOGIES



VALIDITY OF THE AMSLER GRID IN DETECTING MACULOPATHIES

AUTHOR(S) (YEAR)	NUMBER OF EYES*	TYPE(S) OF AMSLER GRIDS STUDIED	STANDARD TEST(S)	VALIDITY	COMMENTS
Achard et al. (1995)	**Total number of eyes 16** ▪ Maculopathies ARMD 8 Idiopathic central serous chorioretinopathy 3 Presumed ocular histoplasmosis 2 Macular hole 2 Venous thrombosis 1 ▪ Normal vision 0	Black Amsler grid on white background White Amsler grid on black background (standard) Red Amsler grid on black background Threshold Amsler grid	Campimetric examination at 1 metre (screen made of black sheeting)	The **sensitivity** is not indicated in this study, but according to the authors, it is poor. Estimated **sensitivity**†: ▪ White grid: **80%** Abnormalities: 12/15 eyes ▪ Black grid: **80%** Abnormalities: 12/15 eyes ▪ Red grid: **80%** Abnormalities: 12/15 eyes ▪ Threshold grid: **93%** Abnormalities: 14/15 eyes The **specificity** was not determined in this study and cannot be estimated (since none of the patients were normally sighted).	**Objectives:** To evaluate the limitations, particularly those relating to the completion phenomenon, of Amsler grid tests in patients with central scotomas caused by macular disorders. To compare the extent and location of abnormalities detected with the Amsler grid and those detected with a standard test. **Analysis:** No validity data (sensitivity and specificity) are provided in this study. The authors conclude that the sensitivity of the Amsler grid is poor in relation to the standard test because of the difference in size and location of the scotomas. For the purposes of our report, this difference does not have the same importance, since we want to know what the grid's validity is in detecting macular abnormalities, regardless of their size and location. The authors also conclude that the completion phenomenon could be partly responsible for the fact that some patients do not perceive any abnormalities on the Amsler grid, despite having a macular disorder. Eight patients had ARMD, but the authors do not mention which type. The fact that the best sensitivity was observed with the threshold grid could be explained by the fact that the standard grid is a suprathreshold test.

*Some authors do not clearly explain if this figure is the number of eyes or the number of patients included in the study. An indication is given where the number of eyes is specifically mentioned. When no information is provided, the figures provided in the table are the quantitative unit given in the study in question.

†In some studies, a sensitivity value was not calculated after the patients were tested with the different Amsler grids. The estimated sensitivity was therefore deduced from the number of patients who perceived abnormalities on the Amsler grid out of the number of patients with ocular diseases.

APPENDIX K (Cont'd)

AUTHOR(S) (YEAR)	NUMBER OF EYES*	TYPE(S) OF AMSLER GRIDS STUDIED	STANDARD TEST(S)	VALIDITY	COMMENTS
Achiron et al. (1995)	**Total number of eyes: 28** ▪ Macular degeneration 20 ▪ Macular diabetic edema 6 ▪ Optic atrophy 2	Standard Amsler grid IHCMG (illuminated high-contrast macular grid) Amsler grid	Automated perimetric examination (Humphrey Field Analyzer)	The **sensitivity** is not indicated in the study. The estimated **sensitivity** is **80.5%** for ARMD patients with the conventional Amsler grid and **100%** with the IHCMG grid. The **specificity** was not determined.	**Objective:** To determine if the IHCMG modified Amsler grid is more effective than the standard grid. To compare the extent and location of abnormalities detected with the Amsler grid and those detected with a standard test. **Analysis:** No validity data are provided in this study. The authors do not provide any information on the type of ARMD in these patients. The goal of this study differs from that of AETMIS, given that the authors wanted to show that the size, location and number of scotomas were different between the standard test and the standard Amsler grid. However, the IHCMG Amsler grid has the same sensitivity as the perimetric examination.
Chen and Frenkel (1975)	**Total number of eyes: 348** ▪ Neuro-ophthalmic diseases 61 Homonymous hemianopia Bitemporal hemianopia Altitudinal hemianopia Hysterical fields Enlarged blind spots Central scotomas ▪ Glaucoma 212 Normal vision 75 Group of eyes with neuro-ophthalmic lesions 2 Group of glaucomatous eyes 73	Standard Amsler grid (white on black background) Standard Amsler grid with diagonal lines Modified Amsler grid for detecting neuro-ophthalmic diseases	Goldmann perimetric examination	**Neuro-ophthalmic diseases** Sensitivity 100% Specificity 100% **Glaucoma** Sensitivity 97% Specificity 93.4%	**Objective:** To assess the validity of various versions of the Amsler grid. **Analysis:** This study does not concern age-related macular degeneration, but some of the patients did have macular disorders. The specificity and sensitivity data are presented for all the grids, without distinction.

*Some authors do not clearly explain if this figure is the number of eyes or the number of patients included in the study. An indication is given where the number of eyes is specifically mentioned. When no information is provided, the figures provided in the table are the quantitative unit given in the study in question.

AUTHOR(S) (YEAR)	NUMBER OF EYES*	TYPE(S) OF AMSLER GRIDS STUDIED	STANDARD TEST(S)	VALIDITY	COMMENTS
Ariyasu et al. (1996)	**Total: 460** ▪ Refraction errors 134 ▪ Corneal diseases 28 ▪ Cataracts 49 ▪ Uveitis 5 ▪ ARMD or age-related maculopathy (ARM) 13 ▪ Retinopathies 53 ▪ Glaucoma 23 ▪ Optic neuropathies 5 ▪ Strabismus 12 ▪ Amblyopia 5 ▪ Other 77 ▪ Normal vision 56	Standard Amsler grid	Complete eye examination Optic fundus examination by indirect ophthalmoscopy	The grid's **sensitivity,** all ocular diseases combined, including and excluding refraction errors, was **19%** and **20%**, respectively. The grid's **specificity**, all ocular diseases combined, including and excluding refraction errors, was **88%** and **92%**, respectively.	**Objective:** To evaluate 4 visual function tests (Amsler grid, contrast sensitivity test, and near and distant visual acuity) to detect visual disturbances or vision-threatening eye conditions in new patients at a general ophthalmology clinic in order to determine if these tests could be used as diagnostic tools by physicians. **Analysis:** All the patients underwent Amsler grid testing, regardless of the disease involved, although it was designed to detect ocular disorders affecting the central 20 degrees of the retina. It should therefore not be used for other types of oculopathy. Only 20/600 eyes were ARMD eyes. Also, the author does not mention the type of ARMD in these eyes. **The sensitivity rate given in this study is not very useful, since it concerns all the eye problems in question.**

*Some authors do not clearly explain if this figure is the number of eyes or the number of patients included in the study. An indication is given where the number of eyes is specifically mentioned. When no information is provided, the figures provided in the table are the quantitative unit given in the study in question.

APPENDIX K (Cont'd)

AUTHOR(S) (YEAR)	NUMBER OF EYES*	TYPE(S) OF AMSLER GRIDS STUDIED	STANDARD TEST(S)	VALIDITY	COMMENTS
Cheng and Vingrys (1993)	**Total : 30** ▪ Pre-ARM 11 ▪ ARM 11 ▪ Normal vision 8	Amsler grids (white on black background) with two levels of contrast: ▪ 90% (standard) ▪ 18% (low contrast [LC])	Automated perimetric examination (Humphrey Field Analyzer)	The **sensitivity** is not indicated in this study. The estimated **sensitivity** is **66%** for the LC grid in patients with ARM (7 patients out of 11 detected abnormalities) and **33%** in patients with pre-ARM. The **specificity** was not evaluated. The estimated **specificity** is **100%** (none of the 8 normally sighted patients detected any abnormalities).	**Objective:** To determine the best visual tests for detecting the early symptoms of ARM. **Analysis:** No validity data were really obtained in this study. The authors do not indicate what type of ARM the patients had. The LC grid reportedly prevents the suprathreshold effect of the standard grid (90%) and has the same sensitivity as the threshold grid, but the LC grid is apparently more complicated to use at home. According to the authors, the LC grid is the most sensitive of the 3 tests (low- and high-contrast grids, perimetry).
Fine et al. (1986)	**Total: 130** ▪ Maculopathies ARMD 68 Ocular histoplasmosis 23 Pathologic myopia 5 Pathologic neovascularization 3 Grönblad-Strandberg syndrome 3 ▪ Other 1 ▪ Normal vision 0	Standard Amsler grid	Optic fundus examination Fluorescein angiography	The **sensitivity** is not indicated in this study. The estimated **sensitivity** of the standard grid is **97.8%** (48 patients out of 49 detected abnormalities) (see "Comments"). The **specificity** was not evaluated and cannot be estimated (no normally sighted patients).	**Objective:** To determine the reliability of the Amsler grid in helping patients detect the presence of submacular fluid. To determine the reliability of the Amsler grid when used at home. **Analysis:** Only 49 of the 103 study participants underwent Amsler grid testing. No validity data (sensitivity and specificity) are provided in this study. Which diseases the patients who underwent Amsler grid testing are not specifically mentioned. However, all of them had macular neovascularization.

*Some authors do not clearly explain if this figure is the number of eyes or the number of patients included in the study. An indication is given where the number of eyes is specifically mentioned. When no information is provided, the figures provided in the table are the quantitative unit given in the study in question.

AUTHOR(S) (YEAR)	NUMBER OF EYES*	TYPE(S) OF AMSLER GRIDS STUDIED	STANDARD TEST(S)	VALIDITY	COMMENTS
Schuchard (1993)	**Total number of eyes: 120** ▪ Maculopathies ARM 41 Other maculopathies 8 Macular edema 8 ▪ Retinopathies 27 ▪ Optic neuropathies 11 ▪ Other 15 ▪ Normal vision 10	Standard Amsler grid Threshold Amsler grid Testing with both grids was performed with a scanning laser ophthalmoscope (SLO) and the TA-300 system.	Hybrid perimetric examination (static and kinetic elements combined) with an SLO	The **sensitivity** varies from **79** to **82%** when all the types of abnormalities that can be detected by the grid are considered. The **sensitivity** varies from **60** to **65%** when only the empty spaces and blurred spaces in the grid are considered, with the exception of distortions. The **specificity** is **100%**. The threshold Amsler grid is more sensitive than the standard Amsler grid.	**Objectives:** To assess the validity of the Amsler grid and how perception through a scotoma and fixation characteristics can contribute to a false interpretation of Amsler grid test results. To determine if the Amsler grid can be used to make an accurate diagnosis. To compare the extent and location of abnormalities detected by the Amsler grid with those of abnormalities detected with a standard test. **Analysis:** Although all the patients had retinopathy, no validity measures are given for any of the 4 disease groups. The author does not provide any information on the type of maculopathy the patients had. The objective of this study was not the same AETMIS's objective. The author wanted to show that clinicians cannot use the Amsler grid to accurately diagnose an ocular disease and that scotomas perceived by a patient and the actual size and the location of these scotomas differ enormously between the Amsler grid test and standard tests.

*Some authors do not clearly explain if this figure is the number of eyes or the number of patients included in the study. An indication is given where the number of eyes is specifically mentioned. When no information is provided, the figures provided in the table are the quantitative unit given in the study in question.

APPENDIX K (Cont'd)

AUTHOR(S) (YEAR)	NUMBER OF EYES*	TYPE(S) OF AMSLER GRIDS STUDIED	STANDARD TEST(S)	VALIDITY	COMMENTS
Wall and May (1987)	**Total: 15** ▪ Macular disorders Atrophic MD 4 Trauma-induced chorioretinal scarring 2 Ocular histoplasmosis 2 Idiopathic neovascular membrane 1 ▪ Solar retinopathy 2 ▪ Diabetic retinopathy 2 ▪ Sulindac-induced retinopathy 1 ▪ Sarcoidosis 1 ▪ Normal vision 0	Standard Amsler grid Bright red Amsler grid (new set published by Hamblin) Red Amsler grid (fine, red lines that are less intense) Threshold Amsler grid	Static and kinetic campimetric examination performed at 2 metres Optic fundus photography Fluorescein angiography (8/10 patients)	The **sensitivity** is not indicated in this study. The estimated **sensitivity** for the threshold grid is **80%** (12/15 patients detected abnormalities). The **specificity** was not evaluated and cannot be estimated (no normally sighted patients).	**Objective:** To demonstrate that the threshold Amsler grid is more effective. **Analysis**: No validity data (sensitivity and specificity) are provided. This was a strictly **qualitative** study. Only two patients reportedly had ARMD, but the authors do not state which type. According to the authors, the most sensitive Amsler grid is the threshold grid followed by the grid with fine, red lines and, lastly, the standard grid and the grid with bright red lines, which have the same sensitivity.

Note: Only scientific articles taking maculopathies into account were selected for an in-depth analysis.
*****Some authors do not clearly explain if this figure is the number of eyes or the number of patients included in the study. An indication is given where the number of eyes is specifically mentioned. When no information is provided, the figures provided in the table are the quantitative unit given in the study in question.
†In some studies, a sensitivity value was not calculated after the patients were tested with the different Amsler grids. The estimated sensitivity was therefore deduced from the number of patients who perceived abnormalities on the Amsler grid out of the number of patients with ocular diseases.

Estimated sensitivity = TP/TP + FN.

It is important to note that the estimated sensitivity is not necessarily the same as the sensitivity indicated by the authors of the studies in question, since they did not necessarily use the term *sensitivity* to mean the same thing as we do.

CONCLUSIONS

The **sensitivity** varies from 19 to 100% (60-100%)

Considerations

- The type of eye disease considered.
- The type of abnormalities detected with the Amsler grid.
- The type of Amsler grid used.
- The objective of the study (comparison of the size and location of visual abnormalities detected with the Amsler grid with the size and location of those detected with a standard test).
- The small number of eyes per study.

The **estimated sensitivity** varies from 66% (ARM) to 97.8%.

The **specificity** varies from 88 to 100%.

Considerations

- The type of eye disease considered.
- Few studies have determined the specificity.
- Small number of normally sighted subjects per study.
- Small number of eyes per study.

Note: Several of the studies selected determined the grid's validity in detecting several other eye diseases (corneal diseases, other retinopathies, glaucoma, etc.) in addition to ARMD. According to these studies, the grid's sensitivity varies from 60 to 100%, the specificity from 88 to 100% [Ariyasu et al., 1996; Achard et al., 1995; Achiron et al., 1995; Schuchard, 1993; Cheng and Vingrys, 1993; Wall and May, 1987; Fine et al., 1986; Chen and Frenkel, 1975]. However, is important to consider the factors that can limit the significance of the results of these studies, such as the type of eye disease considered, the small number of eyes and the small number of normally sighted subjects per study, the type of Amsler grid used, and the type of abnormalities detected with the test, since these factors could distort the sensitivity values provided. In addition, the objective of these studies was often to compare the size and location of the visual abnormalities observed with the Amsler grid with the size and location of those detected with a standard test. Also, in several studies, the authors did not calculate the grid's sensitivity. In other words, the data were available, but the sensitivity was not calculated. Given these observations, we estimated the grid's sensitivity in several studies. The estimated sensitivity varies from 80 (ARMD) to 97.8%. It should, however, be noted that for age-related maculopathy, the estimated sensitivity is approximately 66%.

REFERENCES

Abdel-Meguid A, Lappas A, Hartmann K, Auer F, Schrage N, Thumann G, Kirchhof B. One year follow-up of macular translocation with 360 degree retinotomy in patients with age-related macular degeneration. Br J Ophthalmol 2003;87(5):615-21.

Achard OA, Safran AB, Duret FC, Ragama E. Role of the completion phenomenon in the evaluation of Amsler grid results. Am J Ophthalmol 1995;120(3):322-9.

Achiron LR, Witkin NS, McCarey B, Primo S. The illuminated high contrast macular grid: a pilot study. J Am Optom Assoc 1995;66(11):693-7.

Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). Assessment of photodynamic therapy using porfimer sodium for esophageal, bladder and lung cancers. Montréal: AETMIS, 2004.

Agence nationale d'accréditation et d'évaluation en santé (ANAES). Traitement de la dégénérescence maculaire liée à l'âge. Paris: ANAES, 2001.

Albanes D, Heinonen OP, Taylor PR, Virtamo J, Edwards BK, Rautalahti M, et al. Alpha-tocopherol and beta-carotene supplements and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: effects of base-line characteristics and study compliance. J Natl Cancer Inst 1996;88(21):1560-70.

Algvere PV, Libert C, Lindgarde G, Seregard S. Transpupillary thermotherapy of predominantly occult choroidal neovascularization in age-related macular degeneration with 12 months follow-up. Acta Ophthalmol Scand 2003;81(2):110-7.

Algvere PV, Gouras P, Dafgard Kopp E. Long-term outcome of RPE allografts in non-immunosuppressed patients with ARMD. Eur J Ophthalmol 1999;9(3):217-30.

Algvere PV, Berglin L, Gouras P, Sheng Y, Kopp ED. Transplantation of RPE in age-related macular degeneration: observations in disciform lesions and dry RPE atrophy. Graefes Arch Clin Exp Ophthalmol 1997;235(3):149-58.

Allikmets R. Further evidence for an association of ABCR alleles with age-related macular degeneration. The International ABCR Screening Consortium. Am J Hum Genet 2000; 67(2):487-91.

Allikmets R, Shroyer NF, Singh N, Seddon JM, Lewis RA, Bernstein PS, et al. Mutation of the Stargardt disease gene (ABCR) in age-related macular degeneration. Science 1997; 277(5333):1805-7.

Allison BA, Pritchard PH, Levy JG. Evidence for low-density lipoprotein receptor-mediated uptake of benzoporphyrin derivative. Br J Cancer 1994;69(5):833-9.

Ambati J, Ambati BK, Yoo SH, Ianchulev S, Adamis AP. Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. Surv Ophthalmol 2003;48(3):257-93.

American Academy of Ophthalmology. Ophthalmic procedure preliminary assessment: macular translocation. Ophthalmology 2000a;107(5):1015-8.

American Academy of Ophthalmology. Photodynamic therapy with verteporfin for age-related macular degeneration. Ophthalmology 2000b;107(12):2314-7.

AREDS Study Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 2001;119(10):1417-36.

Ariyasu RG, Lee PP, Linton KP, LaBree LD, Azen SP, Siu AL. Sensitivity, specificity, and predictive values of screening tests for eye conditions in a clinic-based population. Ophthalmology 1996;103(11):1751-60.

Arnold JJ, Blinder KJ, Bressler NM, Bressler SB, Burdan A, Haynes L, et al. Acute severe visual acuity decrease after photodynamic therapy with verteporfin: case reports from randomized clinical trials-TAP and VIP report no. 3. Am J Ophthalmol 2004;137(4):683-96.

Arnold JJ, Sarks SH. Extracts from "clinical evidence": age-related macular degeneration. BMJ 2000;321(7263):741-4.

Awh CC, Cupples HP, Javitt JC. Improved detection and referral of patients with diabetic retinopathy by primary care physicians. Effectiveness of education. Arch Intern Med 1991;151(7):1405-8.

Azab M, Benchaboune M, Blinder KJ, Bressler NM, Bressler SB, Gragoudas ES, et al. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: meta-analysis of 2-year safety results in three randomized clinical trials: Treatment of age-related macular degeneration with photodynamic therapy and verteporfin in photodynamic therapy study report no. 4. Retina 2004;24(1):1-12.

Barnes RM, Gee L, Taylor S, Briggs MC, Harding SP. Outcomes in verteporfin photodynamic therapy for choroidal neovascularisation—'beyond the TAP study'. Eye 2004 [Electronic publication].

Bergink GJ, Hoyng CB, van der Maazen RW, Vingerling JR, van Daal WA, Deutman AF. A randomized controlled clinical trial on the efficacy of radiation therapy in the control of subfoveal choroidal neovascularization in age-related macular degeneration: radiation versus observation. Graefes Arch Clin Exp Ophthalmol 1998;236(5):321-5.

Berglin L, Sarman S, van der Plœg I, Steen B, Ming Y, Itohara S, et al. Reduced choroidal neovascular membrane formation in matrix metalloproteinase-2-deficient mice. Invest Ophthalmol Vis Sci 2003;44(1):403-8.

Bird AC, Bressler NM, Bressler SB, Chisholm IH, Coscas G, Davis MD, et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. Surv Ophthalmol 1995;39(5):367-74.

Bleichrodt H, Johannesson M. Standard gamble, time trade-off and rating scale: experimental results on the ranking properties of QALYs. J Health Econ 1997;16(2):155-75.

Blumenkranz MS, Bressler NM, Bressler SB, Donati G, Fish GE, Haynes LA, et al. Verteporfin therapy for subfoveal choroidal neovascularization in age-related macular degeneration: three-year results of an open-label extension of 2 randomized clinical trials—TAP Report no. 5. Arch Ophthalmol 2002;120(10):1307-14.

Bonastre J, Le Pen C, Soubrane G, Quentel G. The burden of age-related macular degeneration: results of a cohort study in two French referral centres. Pharmacœconomics 2003;21(3): 181-90.

Boucher MC. Rapport d'évaluation de la technologie de caméra non mydriatique et de son application dans un contexte de télésanté pour le dépistage de masse de la rétinopathie diabétique. Université de Montréal: 2001;123 p.

Bowry VW, Ingold KU, Stocker R. Vitamin E in human low-density lipoprotein. When and how this antioxidant becomes a pro-oxidant. Biochem J 1992;288(Pt 2):341-4.

Bressler N. Visual acuity stable during third year of Visudyne (Verteporfin) therapy for macular degeneration. The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. Fort Lauderdale, USA: May 2001a.

Bressler N, Brown G, Flynn H, Marmor M, Anderson L, Grand M. Retina and vitrous. In: American Academy of Ophthalmology's basic skills course section 12. Foundation of the American Academy of Ophthalmology, 2000:49-70.

Bressler NM. Age-related macular degeneration is the leading cause of blindness. JAMA 2004;291(15):1900-1.

Bressler NM. Early detection and treatment of neovascular age-related macular degeneration. J Am Board Fam Pract 2002;15(2):142-52.

Bressler NM. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials—TAP report no. 2. Arch Ophthalmol 2001b;119(2):198-207.

Bressler NM, Gills JP. Age-related macular degeneration. New hope for a common problem comes from photodynamic therapy. BMJ 2000;321(7274):1425-7.

Brigelius-Flohe R, Traber MG. Vitamin E: function and metabolism. FASEB J 1999;13(10): 1145-55.

Brown GC, Brown MM, Sharma S. Difference between ophthalmologists' and patients' perceptions of quality of life associated with age-related macular degeneration. Can J Ophthalmol 2000a;35(3):127-33.

Brown GC, Sharma S, Brown MM, Kistler J. Utility values and age-related macular degeneration. Arch Ophthalmol 2000b;118(1):47-51.

Brown KM, Morrice PC, Duthie GG. Erythrocyte vitamin E and plasma ascorbate concentrations in relation to erythrocyte peroxidation in smokers and nonsmokers: dose response to vitamin E supplementation. Am J Clin Nutr 1997;65(2):496-502.

Brown SB, Mellish KJ. Verteporfin: a milestone in ophthalmology and photodynamic therapy. Expert Opin Pharmacother 2001;2(2):351-61.

Burton GW, Ingold KU. Vitamin E as an in vitro and in vivo antioxidant. Ann N Y Acad Sci 1989;570:7-22.

Bush AI, Pettingell WH, Multhaup G, Paradis M, Vonsattel JP, Gusella JF, et al. Rapid induction of Alzheimer A beta amyloid formation by zinc. Science 1994;265(5177):1464-7.

Butler RN, Faye EE, Guazzo E, Kupfer C. Keeping an eye on vision: primary care of age-related ocular disease. Part 1. Geriatrics 1997a;52(8):30-41.

Butler RN, Faye EE, Guazzo E, Kupfer C. Keeping an eye on vision: new tools to preserve sight and quality of life. A roundtable discussion, Part 2. Geriatrics 1997b;52(9):48-56.

Canadian Task Force on the Periodic Health Examination. Periodic health examination, 1995 update: 3. Screening for visual problems among elderly patients. CMAJ 1995;152(8): 1211-22.

Casson EJ, Racette L. Vision standards for driving in Canada and the United States. A review for the Canadian Ophthalmological Society. Can J Ophthalmol 2000;35(4):192-203.

Casten RJ, Rovner BW, Tasman W. Age-related macular degeneration and depression: a review of recent research. Curr Opin Ophthalmol 2004;15(3):181-3.

Chang AA, Tan W, Beaumont PE, Zeldovich A. Limited macular translocation for subfoveal choroidal neovascularization in age-related macular degeneration. Clin Experiment Ophthalmol 2003;31(2):103-9.

Char DH, Irvine AI, Posner MD, Quivey J, Phillips TL, Kroll S. Randomized trial of radiation for age-related macular degeneration. Am J Ophthalmol 1999;127(5):574-8.

Chen KF, Frenkel M. Dynamic visual field testing using the Amsler grid patterns. Trans Am Acad Ophthalmol Otolaryngol 1975;79(6):OP761-71.

Cheng AS, Vingrys AJ. Visual losses in early age-related maculopathy. Optom Vis Sci 1993; 70(2):89-96.

Cho E, Hung S, Willett WC, Spiegelman D, Rimm EB, Seddon JM, et al. Prospective study of dietary fat and the risk of age-related macular degeneration. Am J Clin Nutr 2001; 73(2):209-18.

Christen WG, Glynn RJ, Manson JE, Ajani UA, Buring JE. A prospective study of cigarette smoking and risk of age-related macular degeneration in men. JAMA 1996; 276(14):1147-51.

Ciulla TA, Danis RP, Klein SB, Malinovsky VE, Soni PS, Pratt LM, et al. Proton therapy for exudative age-related macular degeneration: a randomized, sham-controlled clinical trial. Am J Ophthalmol 2002;134(6):905-6.

Congdon NG, Friedman DS, Lietman T. Important causes of visual impairment in the world today. JAMA 2003;290(15):2057-60.

Coscas G, Soubrane G, Ramahefasolo C, Fardeau C. Perifoveal laser treatment for subfoveal choroidal new vessels in age-related macular degeneration. Results of a randomized clinical trial. Arch Ophthalmol 1991;109(9):1258-65.

Cote J, Rosner B, Seddon JM. Smoking and ARMD: results from a prospective study of men and women. The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting, Fort Lauderdale, USA, May 2002. Abstract 4391.

Crafoord S, Geng L, Seregard S, Algvere PV. Experimental transplantation of autologous iris pigment epithelial cells to the subretinal space. Acta Ophthalmol Scand 2001;79(5):509-14.

Cruickshanks KJ, Klein R, Klein BE. Sunlight and age-related macular degeneration. The Beaver Dam Eye Study. Arch Ophthalmol 1993;111(4):514-8.

Cunningham JJ, Fu A, Mearkle PL, Brown RG. Hyperzincuria in individuals with insulin-dependent diabetes mellitus: concurrent zinc status and the effect of high-dose zinc supplementation. Metabolism 1994;43(12):1558-62.

D'Amico DJ, Goldberg MF, Hudson H, Jerdan JA, Krueger DS, Luna SP, et al. Anecortave acetate as monotherapy for treatment of subfoveal neovascularization in age-related macular degeneration: twelve-month clinical outcomes. Ophthalmology 2003a;110(12): 2372-5.

D'Amico DJ, Goldberg MF, Hudson H, Jerdan JA, Krueger S, Luna S, et al. Anecortave acetate as monotherapy for the treatment of subfoveal lesions in patients with exudative age-related macular degeneration (ARMD): interim (month 6) analysis of clinical safety and efficacy. Retina 2003b;23(1):14-23.

de Juan E. Retinal translocation: rationale and results. Ophthalmologica 2001;215(Suppl 1):10-9.

Delcourt C, Carriere I, Ponton-Sanchez A, Fourrey S, Lacroux A, Papoz L. Light exposure and the risk of age-related macular degeneration: the Pathologies Oculaires Liées à l'Âge (POLA) study. Arch Ophthalmol 2001;119(10):1463-8.

Delcourt C, Diaz JL, Ponton-Sanchez A, Papoz L. Smoking and age-related macular degeneration. The Pathologies Oculaires Liées à l'Âge (POLA) study. Arch Ophthalmol 1998;116(8):1031-5.

Desmettre T, Cohen SY, Mordon S. Thérapie photodynamique et DMLA en 2000. J Fr Ophtalmol 2001;24(1):82-93.

EDCC Study Group. Antioxidant status and neovascular age-related macular degeneration. Eye Disease Case-Control Study Group. Arch Ophthalmol 1993;111(1):104-9.

EDCC Study Group. Risk factors for neovascular age-related macular degeneration. The Eye Disease Case-Control Study Group. Arch Ophthalmol 1992;110(12):1701-8.

Esmail N, Walker M. Waiting your turn: hospital waiting lists in Canada (12th edition), 2002. The Fraser Institute. Vancouver, Canada. Available at: http://www.fraserinstitute.ca/shared/readmore.asp?sNav=pb&id=413 (2 Aug 2004).

Essex RW, Qureshi SH, Cain MS, Harper CA, Guymer RH. Photodynamic therapy in practice: a review of the results of the first 12 months experience with verteporfin at the Royal Victorian Eye and Ear Hospital. Clin Experiment Ophthalmol 2003;31(6):476-81.

Esterbauer H, Dieber-Rotheneder M, Striegl G, Waeg G. Role of vitamin E in preventing the oxidation of low-density lipoprotein. Am J Clin Nutr 1991;53(Suppl 1):314S-21S.

Eyetech Study Group. Anti-vascular endothelial growth factor therapy for subfoveal choroidal neovascularization secondary to age-related macular degeneration: phase II study results. Ophthalmology 2003;110(5):979-86.

Eyetech Study Group. Preclinical and phase 1A clinical evaluation of an anti-VEGF pegylated aptamer (EYE001) for the treatment of exudative age-related macular degeneration. Retina 2002;22(2):143-52.

Fine AM, Elman MJ, Ebert JE, Prestia PA, Starr JS, Fine SL. Earliest symptoms caused by neovascular membranes in the macula. Arch Ophthalmol 1986;104(4):513-4.

Fine BS, Yanoff M. Ocular Histology. A Text and Atlas. 2nd ed. Hagerstown, MD: Harper and Row, 1979.

Fine SL, Berger JW, Maguire MG, Ho AC. Age-related macular degeneration. N Engl J Med 2000;342(7):483-92.

Flaxel CJ. Use of radiation in the treatment of age-related macular degeneration. Ophthalmol Clin North Am 2002;15(4):437-44.

Food and Nutrition Board. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc. Washington, DC: National Academy Press, 2002.

Food and Nutrition Board. Dietary reference intakes for vitamin C, vitamin E, selenium and carotenoids. Washington, DC: National Academy Press, 2000.

Friedman DS, Katz J, Bressler NM, Rahmani B, Tielsch JM. Racial differences in the prevalence of age-related macular degeneration: the Baltimore Eye Survey. Ophthalmology 1999; 106(6):1049-55.

Gillies MC, Simpson JM, Luo W, Penfold P, Hunyor AB, Chua W, Mitchell P, Billson F. A randomized clinical trial of a single dose of intravitreal triamcinolone acetonide for neovascular age-related macular degeneration: one-year results. Arch Ophthalmol 2003; 121(5):667-73.

Gottfredsdottir MS, Sverrisson T, Musch DC, Stefansson E. Age-related macular degeneration in monozygotic twins and their spouses in Iceland. Acta Ophthalmol Scand 1999;77(4):422-5.

Green WR. Clinicopathologic studies of treated choroidal neovascular membranes. A review and report of two cases. Retina 1991;11(3):328-56.

Guyer DR. Age-related macular degeneration, 1997. Available at: http://www.vrmny.com/ ARMD. htm (2 Aug 2004).

Hamdi HK, Kenney C. Age-related macular degeneration: a new viewpoint. Front Biosci 2003; 8:e305-14.

Hamdi HK, Reznik J, Castellon R, Atilano SR, Ong JM, Udar N, et al. Alu DNA polymorphism in ACE gene is protective for age-related macular degeneration. Biochem Biophys Res Commun 2002;295(3):668-72.

Harasymowycz P, Kamdeu Fansi AA. Le dépistage du glaucome primitif à angle ouvert : mise à jour. Rapport préliminaire remis à l'Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). Rapport inédit.

Hart PM, Chakravarthy U, Mackenzie G, Chisholm IH, Bird AC, Stevenson MR, et al. Visual outcomes in the subfoveal radiotherapy study: a randomized controlled trial of teletherapy for age-related macular degeneration. Arch Ophthalmol 2002;120(8):1029-38.

Heeschen C, Jang JJ, Weis M, Pathak A, Kaji S, Hu RS, et al. Nicotine stimulates angiogenesis and promotes tumor growth and atherosclerosis. Nat Med 2001;7(7):833-9.

Heier JS, Greene WL, rhuFab Study Group. RhuFabV2 (an anti-VEGF antibody fragment) in neovascular ARMD: safety and tolerability of multiple intravitreal injections. The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. Fort Lauderdale, USA, May 2002. Abstract 2520.

Hogan MJ, Alvarado JA, Weddell JE. Histology of the human eye. An atlas and textbook. Philadelphia, PA: WB Saunders; 1971.

Holz FG, Bindewald A, Schutt F, Specht H. Intraocular microablation of choroidal tissue by a 308 nm AIDA excimer laser for RPE-transplantation in patients with age-related macular degeneration. Biomed Tech (Berl) 2003;48(4):82-5.

Holz FG, Piguet B, Minassian DC, Bird AC, Weale RA. Decreasing stromal iris pigmentation as a risk factor for age-related macular degeneration. Am J Ophthalmol 1994;117(1):19-23.

Hooper CY, Guymer RH. New treatments in age-related macular degeneration. Clin Experiment Ophthalmol 2003;31(5):376-91.

Hunt DW, Margaron P. Status of therapies in development for the treatment of age-related macular degeneration. IDrugs 2003;6(5):464-9.

Husain D, Kramer M, Kenny AG, Michaud N, Flotte TJ, Gragoudas ES, Miller J. Effects of photodynamic therapy using verteporfin on experimental choroidal neovascularization and normal retina and choroid up to 7 weeks after treatment. Invest Ophthalmol Vis Sci 1999;40(10):2322-31.

Institut de la statistique du Québec. Perspectives démographiques Québec et régions, 2001-2051, édition 2003. Québec: ISQ, 2003. Available at: http://www.stat.gouv.qc.ca/donstat/societe/demographie/persp_poplt/pers2001-2051/index.htm (2 Aug 2004).

Institut de la statistique du Québec. Espérance de vie à la naissance et à 65 ans selon le sexe, Québec, 1970-1972 à 2000-2002. Québec: ISQ, 2002. Available at: http://www.stat.gouv.qc.ca/donstat/societe/demographie/naisn_deces/4p1.htm (2 Aug 2004).

Ip M, Kroll A, Reichel E. Transpupillary thermotherapy. Semin Ophthalmol 1999;14(1):11-8.

Ivers RQ, Cumming RG, Mitchell P, Attebo K. Visual impairment and falls in older adults: the Blue Mountains Eye Study. J Am Geriatr Soc 1998;46(1):58-64.

JAT Study Group. Japanese age-related macular degeneration trial: 1-year results of photodynamic therapy with verteporfin in Japanese patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration. Am J Ophthalmol 2003;136(6):1049-61.

Jennings BJ, Mathews DE. Adverse reactions during retinal fluorescein angiography. J Am Optom Assoc 1994;65(7):465-71.

Jialal I, Traber M, Devaraj S. Is there a vitamin E paradox? Curr Opin Lipidol 2001;12(1):49-53.

Johnson RN, McDonald HR, Schatz H. Rash, fever, and chills after intravenous fluorescein angiography. Am J Ophthalmol 1998;126(6):837-8.

Jonas JB, Kreissig I, Hugger P, Sauder G, Panda-Jonas S, Degenring R. Intravitreal triamcinolone acetonide for exudative age-related macular degeneration. Br J Ophthalmol 2003; 87(4):462-8.

Kaven C, Spraul CW, Zavazava N, Lang GK, Lang GE. Thalidomide and prednisolone inhibit growth factor-induced human retinal pigment epithelium cell proliferation in vitro. Ophthalmologica 2001;215(4):284-9.

Kimura K, Isashiki Y, Sonoda S, Kakiuchi-Matsumoto T, Ohba N. Genetic association of manganese superoxide dismutase with exudative age-related macular degeneration. Am J Ophthalmol 2000;130(6):769-73.

Kirwan JF, Constable PH, Murdoch IE, Khaw PT. Beta irradiation: new uses for an old treatment: a review. Eye 2003;17(2):207-15.

Klaver CC, Assink JJ, van Leeuwen R, Wolfs RC, Vingerling JR, Stijnen T, et al. Incidence and progression rates of age-related maculopathy: the Rotterdam Study. Invest Ophthalmol Vis Sci 2001;42(10):2237-41.

Klaver CC, Wolfs RC, Assink JJ, van Duijn CM, Hofman A, de Jong PT. Genetic risk of age-related maculopathy. Population-based familial aggregation study. Arch Ophthalmol 1998;116(12):1646-51.

Klein ML, Mauldin WM, Stoumbos VD. Heredity and age-related macular degeneration. Observations in monozygotic twins. Arch Ophthalmol 1994;112(7):932-7.

Klein R, Klein BE, Jensen SC, Cruickshanks KJ. The relationship of ocular factors to the incidence and progression of age-related maculopathy. Arch Ophthalmol 1998a; 116(4):506-13.

Klein R, Klein BE, Moss SE. Relation of smoking to the incidence of age-related maculopathy. The Beaver Dam Eye Study. Am J Epidemiol 1998b;147(2):103-10.

Klein R, Klein BE, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. Ophthalmology 1997;104(1):7-21.

Klein R, Rowland ML, Harris MI. Racial/ethnic differences in age-related maculopathy. Third National Health and Nutrition Examination Survey. Ophthalmology 1995;102(3):371-81.

Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology 1992;99(6):933-43.

Kobayashi H, Kobayashi K. Age-related macular degeneration: long-term results of radiotherapy for subfoveal neovascular membranes. Am J Ophthalmol 2000;130(5):617-35.

Kramer M, Miller JW, Michaud N, Moulton RS, Hasan T, Flotte TJ, Gragoudas ES. Liposomal benzoporphyrin derivative verteporfin photodynamic therapy. Selective treatment of choroidal neovascularization in monkeys. Ophthalmology 1996;103(3):427-38.

Kubota A, Ohji M, Kusaka S, Hayashi A, Hosohata J, Fujikado T, Tano Y. Evaluation of the peripheral visual field after foveal translocation. Am J Ophthalmol 2001;132(4):581-4.

Kuzniarz M, Mitchell P, Flood VM, Wang JJ. Use of vitamin and zinc supplements and age-related maculopathy: the Blue Mountains Eye Study. Ophthalmic Epidemiol 2002; 9(4):283-95.

Kvanta A, Shen WY, Sarman S, Seregard S, Steen B, Rakoczy E. Matrix metalloproteinase (MMP) expression in experimental choroidal neovascularization. Curr Eye Res 2000; 21(3):684-90.

Kwiterovich KA, Maguire MG, Murphy RP, Schachat AP, Bressler NM, Bressler SB, Fine SL. Frequency of adverse systemic reactions after fluorescein angiography. Results of a prospective study. Ophthalmology 1991;98(7):1139-42.

Lacour M, Kiilgaard JF, Nissen MH. Age-related macular degeneration: epidemiology and optimal treatment. Drugs Aging 2002;19(2):101-33.

Lambert V, Munaut C, Jost M, Nœl A, Werb Z, Foidart JM, Rakic JM. Matrix metalloproteinase-9 contributes to choroidal neovascularization. Am J Pathol 2002;161(4):1247-53.

Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. CMAJ 1992;146(4):473-81.

Lee IM. Antioxidant vitamins in the prevention of cancer. Proc Assoc Am Physicians 1999; 111(1):10-5.

Lee PP, Feldman ZW, Ostermann J, Brown DS, Sloan FA. Longitudinal prevalence of major eye diseases. Arch Ophthalmol 2003;121(9):1303-10.

Lees M, Davey P, Aldridge G, Schulz M, Aristides M. Economic evaluation of photodynamic therapy with verteporfin for predominantly classic, subfoveal CNV secondary to age-related macular degeneration. ISPOR Seventh Annual International Meeting, May 19-22, 2002, Arlington, VA:248.

Leu ST, Batni S, Radeke MJ, Johnson LV, Anderson DH, Clegg DO. Drusen are cold spots for proteolysis: expression of matrix metalloproteinases and their tissue inhibitor proteins in age-related macular degeneration. Exp Eye Res 2002;74(1):141-54.

Lin SC, Lin CP, Feld JR, Duker JS, Puliafito CA. The photodynamic occlusion of choroidal vessels using benzoporphyrin derivative. Curr Eye Res 1994;13(7):513-22.

Liu M, Regillo CD. A review of treatments for macular degeneration: a synopsis of currently approved treatments and ongoing clinical trials. Curr Opin Ophthalmol 2004;15(3):221-6.

Lopez-Saez MP, Ordoqui E, Tornero P, Baeza A, Sainza T, Zubeldia JM, Baeza ML. Fluorescein-induced allergic reaction. Ann Allergy Asthma Immunol 1998;81(5 Pt 1): 428-30.

Maguire MG, Fine SL, Maguire SA. Results of the age-related macular degeneration and thalidomide study (ARMDATS). Invest Ophthalmol Vis Sci 2001(42):S233.

Mainster MA, Reichel E. Transpupillary thermotherapy for age-related macular degeneration: long-pulse photocoagulation, apoptosis, and heat shock proteins. Ophthalmic Surg Lasers 2000;31(5):359-73.

Marcus DF, Bovino JA, Williams D. Adverse reactions during intravenous fluorescein angiography. Arch Ophthalmol 1984;102(6):825.

Marcus DM, Maguire MG, Maguire AM, Fine SL. The age-related macular degeneration radiotherapy trial: baseline characteristics. The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting, Fort-Lauderdale, USA, May 2002. Abstract 1207.

Mares-Perlman JA, Brady WE, Klein R, Klein BE, Bowen P, Stacewicz-Sapuntzakis M, Palta M. Serum antioxidants and age-related macular degeneration in a population-based case-control study. Arch Ophthalmol 1995;113(12):1518-23

Margherio RR, Margherio AR, DeSantis ME. Laser treatments with verteporfin therapy and its potential impact on retinal practices. Retina 2000;20(4):325-30.

Mauget-Faysse M, Coquard R, Francais-Maury C, Milea D, Chiquet C, Martin P et al. Radiothérapie dans la dégénérescence maculaire liée à l'âge : facteurs de risque de survenue des complications, prévention et traitement des effets secondaires. J Fr Ophtalmol 2000;23(2):127-36.

Mayne ST. Beta-carotene, carotenoids, and disease prevention in humans. FASEB J 1996; 10(7):690-701.

McCarty CA, Mukesh BN, Fu CL, Mitchell P, Wang JJ, Taylor HR. Risk factors for age-related maculopathy: the Visual Impairment Project. Arch Ophthalmol 2001;119(10):1455-62.

McLauchlan R, Waterman H, Waterman C, Hillier V, Dodd C. Ethnic variation in fluorescein angiography induced nausea and vomiting. Eye 2001;15(Pt 2):159-62.

Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C. Clinical effectiveness and cost utility of photodynamic therapy for wet age-related macular degeneration. West Midlands Health Technology Assessment Group, Birmingham, England: University of Birmingham, 1997.

Medical Services Advisory Committee (MSAC). Photodynamic therapy with verteporfin for macular degeneration. Assessment report. Canberra, Australia: MSAC, 2001.

Meyers SM, Greene T, Gutman FA. A twin study of age-related macular degeneration. Am J Ophthalmol 1995;120(6):757-66.

Miller JW, Schmidt-Erfurth U, Sickenberg M, Pournaras CJ, Laqua H, Barbazetto I, et al. Photodynamic therapy with verteporfin for choroidal neovascularization caused by age-related macular degeneration: results of a single treatment in a phase 1 and 2 study. Arch Ophthalmol 1999;117(9):1161-73.

Miller JW, Walsh AW, Kramer M, Hasan T, Michaud N, Flotte TJ, et al. Photodynamic therapy of experimental choroidal neovascularization using lipoprotein-delivered benzoporphyrin. Arch Ophthalmol 1995;113(6):810-8.

Mitchell P, Wang JJ, Foran S, Smith W. Five-year incidence of age-related maculopathy lesions: the Blue Mountains Eye Study. Ophthalmology 2002a;109(6):1092-7.

Mitchell P, Wang JJ, Smith W, Leeder SR. Smoking and the 5-year incidence of age-related maculopathy: the Blue Mountains Eye Study. Arch Ophthalmol 2002b;120(10):1357-63.

Mitchell P, Smith W, Wang JJ. Iris color, skin sun sensitivity, and age-related maculopathy. The Blue Mountains Eye Study. Ophthalmology 1998;105(8):1359-63.

Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. Ophthalmology 1995;102(10):1450-60.

Mittra RA, Singerman LJ. Recent advances in the management of age-related macular degeneration. Optom Vis Sci 2002;79(4):218-24.

MPS Group. Risk factors for choroidal neovascularization in the second eye of patients with juxtafoveal or subfoveal choroidal neovascularization secondary to age-related macular degeneration. Macular Photocoagulation Study Group. Arch Ophthalmol 1997; 115(6):741-7.

MPS Group. Occult choroidal neovascularization. Influence on visual outcome in patients with age-related macular degeneration. Macular Photocoagulation Study Group. Arch Ophthalmol 1996;114(4):400-12.

MPS Group. Evaluation of argon green vs krypton red laser for photocoagulation of subfoveal choroidal neovascularization in the macular photocoagulation study. Macular Photocoagulation Study (MPS) Group. Arch Ophthalmol 1994;112(9):1176-84.

MPS Group. Argon laser photocoagulation for neovascular maculopathy. Five-year results from randomized clinical trials. Macular Photocoagulation Study Group. Arch Ophthalmol 1991;109(8):1109-14.

MPS Group. Persistent and recurrent neovascularization after krypton laser photocoagulation for neovascular lesions of age-related macular degeneration. Macular Photocoagulation Study Group. Arch Ophthalmol 1990;108(6):825-31.

MPS Group. Recurrent choroidal neovascularization after argon laser photocoagulation for neovascular maculopathy. Macular Photocoagulation Study Group. Arch Ophthalmol 1986;104(4):503-12.

Mukesh BN, Dimitrov PN, Leikin S, Wang JJ, Mitchell P, McCarty CA, Taylor HR. Five-year incidence of age-related maculopathy: the Visual Impairment Project. Ophthalmology 2004;111(6):1176-82.

National Eye Institute. Submacular Surgery Trials (SST). Bethesda, MD: NEI. Available at: http://www.nei.nih.gov/neitrials/static/study52.asp (2 Aug 2004).

National Institute for Clinical Excellence (NICE). Guidance on the use of photodynamic therapy for age-related macular degeneration. Technical appraisal guidance. London, United Kingdom: NICE, 2003.

Newsom RS, McAlister JC, Saeed M, McHugh JD. Transpupillary thermotherapy (TTT) for the treatment of choroidal neovascularisation. Br J Ophthalmol 2001;85(2):173-8.

Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 1996a;334(18):1150-5.

Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. J Natl Cancer Inst 1996b;88(21):1550-9.

Ordre des optométristes du Québec. Une vision globale intéressante mais inadaptée au secteur oculo-visuel. Recommandations et commentaires relatifs au deuxième rapport ministériel sur les professions de la santé et des relations humaines intitulé « Une vision renouvelée du système professionnel en santé et en relations humaines ». Québec; 2002. Available at: http://www.ooq.org/communication/GTMrap.pdf (2 Aug 2004).

Ordre des optométristes du Québec. Pour des services optométriques efficaces et de qualité : un nouveau cadre organisationnel à la mesure des nouvelles réalités. Québec, 2001. Available at: http://www.ooq.org/communication/GTMMemoire7.pdf (2 Aug 2004).

Pacurariu RI. Low incidence of side effects following intravenous fluorescein angiography. Ann Ophthalmol 1982;14(1):32-6.

Palozza P, Calviello G, Serini S, Maggiano N, Lanza P, Ranelletti FO, Bartoli GM. Beta-carotene at high concentrations induces apoptosis by enhancing oxy-radical production in human adenocarcinoma cells. Free Radic Biol Med 2001;30(9):1000-7.

Palozza P. Prooxidant actions of carotenoids in biologic systems. Nutr Rev 1998;56(9):257-65.

Patrick L. Beta-carotene: the controversy continues. Altern Med Rev 2000;5(6):530-45.

Patterson RE, White E, Kristal AR, Neuhouser ML, Potter JD. Vitamin supplements and cancer risk: the epidemiologic evidence. Cancer Causes Control 1997;8(5):786-802.

PTMD Study Group. Interferon alfa-2a is ineffective for patients with choroidal neovascularization secondary to age-related macular degeneration. Results of a prospective randomized placebo-controlled clinical trial. Pharmacological Therapy for Macular Degeneration Study Group. Arch Ophthalmol 1997;115(7):865-72.

QLT Inc. Visudyne®: Approval Status. Vancouver, BC, 2004. Available at: http://www.qltinc.com/Qltinc/main/mainpages.cfm?InternetPageID=75 (2 Aug 2004).

RAD Study Group. A prospective, randomized, double-masked trial on radiation therapy for neovascular age-related macular degeneration (RAD Study). Radiation Therapy for Age-related Macular Degeneration Study Group. Ophthalmology 1999;106(12):2239-47.

Ranson NT, Danis RP, Ciulla TA, Pratt L. Intravitreal triamcinolone in subfoveal recurrence of choroidal neovascularisation after laser treatment in macular degeneration. Br J Ophthalmol 2002;86(5):527-9.

Raz I, Karsai D, Katz M. The influence of zinc supplementation on glucose homeostasis in NIDDM. Diabetes Res 1989;11(2):73-9.

Reichel E, Berrocal AM, Ip M, Kroll AJ, Desai V, Duker JS, Puliafito CA. Transpupillary thermotherapy of occult subfoveal choroidal neovascularization in patients with age-related macular degeneration. Ophthalmology 1999;106(10):1908-14.

Rivellese MJ, Baumal CR. Photodynamic therapy of eye diseases. J Ophthalmic Nurs Technol 2000;19(3):134-41.

Roodhooft J. No efficacious treatment for age-related macular degeneration. Bull Soc Belge Ophtalmol 2000;276:83-92.

Rulon LL, Robertson JD, Lovell MA, Deibel MA, Ehmann WD, Markesber WR. Serum zinc levels and Alzheimer's disease. Biol Trace Elem Res 2000;75(1-3):79-85.

Schachat A, VIP Study Group. Visual outcomes in patients with occult but no classic choroidal neovascularisation (CNV): Rationale for the Visudyne in Occult CNV (VIO) Trial. The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting, Fort Lauderdale, USA, May 2001.

Schmidt-Erfurth U, Hasan T. Mechanisms of action of photodynamic therapy with verteporfin for the treatment of age-related macular degeneration. Surv Ophthalmol 2000;45(3):195-214.

Schuchard RA. Validity and interpretation of Amsler grid reports. Arch Ophthalmol 1993;111(6): 776-80.

Scott LJ, Goa KL. Verteporfin. Drugs Aging 2000;16(2):139-48.

Seddon JM, Rosner B, Sperduto RD, Yannuzzi L, Haller JA, Blair NP, Willett W. Dietary fat and risk for advanced age-related macular degeneration. Arch Ophthalmol 2001;119(8):1191-9.

Seddon JM, Ajani UA, Mitchell BD. Familial aggregation of age-related maculopathy. Am J Ophthalmol 1997;123(2):199-206.

Seddon JM, Willett WC, Speizer FE, Hankinson SE. A prospective study of cigarette smoking and age-related macular degeneration in women. JAMA 1996;276(14):1141-6.

Seddon JM, Ajani UA, Sperduto RD, Hiller R, Blair N, Burton TC, et al. Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group. JAMA 1994;272(18):1413-20.

Seigel D. AREDS investigators distort findings. Arch Ophthalmol 2002;120(1):100-1.

Sharma S, Bakal J, Oliver-Fernandez A, Blair J. Photodynamic therapy with verteporfin for subfoveal choroidal neovascularization in age-related macular degeneration: results of an effectiveness study. Arch Ophthalmol 2004;122(6):853-6.

Sharma S. Update in retina: photodynamic therapy for the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration. Can J Ophthalmol 2001;36(1):7-10.

Sharma S, Brown GC, Brown MM, Hollands H, Shah GK. The cost-effectiveness of photodynamic therapy for fellow eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. Ophthalmology 2001;108(11):2051-9.

Sharma S, Brown GC, Brown MM, Shah GK, Snow K, Brown H, Hollands H. Converting visual acuity to utilities. Can J Ophthalmol 2000;35(5):267-72.

Shuler MF, Borrillo JL, Ho AC. Photodynamic therapy update. Curr Opin Ophthalmol 2001; 12(3):202-6.

Sickenberg M. Early detection, diagnosis and management of choroidal neovascularization in age-related macular degeneration: the role of ophthalmologists. Ophthalmologica 2001;215(4):247-53.

Smiddy WE, Fine SL, Quigley HA, Hohman RM, Addicks EA. Comparison of krypton and argon laser photocoagulation. Results of stimulated clinical treatment of primate retina. Arch Ophthalmol 1984;102(7):1086-92.

Smith DH, Fenn P, Drummond M. Cost effectiveness of photodynamic therapy (PTD) with verteporfin in the UK. ISPOR Seventh Annual International Meeting, Arlington, VA, May 2002: 247.

Smith W, Assink J, Klein R, Mitchell P, Klaver CC, Klein BE, et al. Risk factors for age-related macular degeneration: Pooled findings from three continents. Ophthalmology 2001; 108(4):697-704.

Smith W, Mitchell P, Webb K, Leeder SR. Dietary antioxidants and age-related maculopathy: the Blue Mountains Eye Study. Ophthalmology 1999;106(4):761-7.

Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making 1993;13(4):322-38.

Soubrane G, Souied E, Haddad W, Razavi S, Roquet W, Coscas G. Thérapeutiques alternatives des néovaisseaux choroïdiens de la dégénérescence maculaire liée à l'âge. J Fr Ophtalmol 2003;26(8):876-8.

Soubrane G. Thérapie photodynamique des néovaisseaux choroïdiens. J Fr Ophtalmol 2001; 24(4):411-3.

Soubrane G, Bressler NM. Treatment of subfoveal choroidal neovascularisation in age-related macular degeneration: focus on clinical application of verteporfin photodynamic therapy. Br J Ophthalmol 2001;85(4):483-95.

Soubrane G, Kuhn D, Oubraham H, Quaranta M, Coscas G. Recent therapies for age-related macular degeneration. J Soc Biol 2001;195(2):115-8.

Souied E, Kaplan J, Coscas G, Soubrane G. DMLA et génétique. J Fr Ophtalmol 2001;24(8):875-85.

Souied EH, Ducroq D, Rozet JM, Gerber S, Perrault I, Munnich A, et al. ABCR gene analysis in familial exudative age-related macular degeneration. Invest Ophthalmol Vis Sci 2000; 41(1):244-7.

Souied EH, Benlian P, Amouyel P, Feingold J, Lagarde JP, Munnich A, et al. The epsilon4 allele of the apolipoprotein E gene as a potential protective factor for exudative age-related macular degeneration. Am J Ophthalmol 1998;125(3):353-9.

Spaide RF, Sorenson J, Maranan L. Combined photodynamic therapy with verteporfin and intravitreal triamcinolone acetonide for choroidal neovascularization. Ophthalmology 2003;110(8):1517-25.

SST Group. Submacular Surgery Trials randomized pilot trial of laser photocoagulation versus surgery for recurrent choroidal neovascularization secondary to age-related macular degeneration: I. Ophthalmic outcomes Submacular Surgery Trials pilot study report number 1. Am J Ophthalmol 2000a;130(4):387-407.

SST Group. Submacular Surgery Trials randomized pilot trial of laser photocoagulation versus surgery for recurrent choroidal neovascularization secondary to age-related macular degeneration: II. Quality of life outcomes Submacular Surgery Trials pilot study report number 2. Am J Ophthalmol 2000b; 130(4):408-18.

Steinmetz RL, Haimovici R, Jubb C, Fitzke FW, Bird AC. Symptomatic abnormalities of dark adaptation in patients with age-related Bruch's membrane change. Br J Ophthalmol 1993;77(9):549-54.

Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). Lancet 1996;347(9004):781-6.

Tano Y, JAT Study Group. The Japanese ARMD Trial (JAT): preliminary results of verteporfin therapy in Japanese age-related macular degeneration patients. The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting, Fort Lauderdale, USA, May 2002.

TAP and VIP Study Group. Guidelines for using verteporfin (Visudyne) in photodynamic therapy to treat choroidal neovascularization due to age-related macular degeneration and other causes. Retina 2002;22(1):6-18.

TAP Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials—TAP report. Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Arch Ophthalmol 1999;117(10):1329-45.

Taylor HR, Tikellis G, Robman LD, McCarty CA, McNeil JJ. Vitamin E supplementation and macular degeneration: randomised controlled trial. BMJ 2002;325(7354):11.

Thach AB, Sipperley JO, Dugel PU, Sneed SR, Park DW, Cornelius J. Large-spot size transpupillary thermotherapy for the treatment of occult choroidal neovascularization associated with age-related macular degeneration. Arch Ophthalmol 2003;121(6):817-20.

The Medical Letter. Antioxidant vitamins and zinc for macular degeneration. Med Lett Drugs Ther 2003;45(1158):45-6.

The Norwegian Centre for Health Technology Assessment (SMM). Photodynamic therapy for age-related macular degeneration. SMM-report n^{o} 3/2000. Oslo, Norway. Available at: http:///www.oslo.sintef.no/smm/Publications/Engsmdrag/photodynamic_therapy_for_age.htm (2 Aug 2004).

Thomas MA, Dickinson JD, Melberg NS, Ibanez HE, Dhaliwal RS. Visual results after surgical removal of subfoveal choroidal neovascular membranes. Ophthalmology 1994; 101(8):1384-96.

Thumann G, Aisenbrey S, Schraermeyer U, Lafaut B, Esser P, Walter P, Bartz-Schmidt KU. Transplantation of autologous iris pigment epithelium after removal of choroidal neovascular membranes. Arch Ophthalmol 2000;118(10):1350-5.

Tomany SC, Cruickshanks KJ, Klein R, Klein BE, Knudtson MD. Sunlight and the 10-year incidence of age-related maculopathy: the Beaver Dam Eye Study. Arch Ophthalmol 2004a;122(5):750-7.

Tomany SC, Wang JJ, Van Leeuwen R, Klein R, Mitchell P, Vingerling JR, Klein BE, Smith W, De Jong PT. Risk factors for incident age-related macular degeneration: pooled findings from 3 continents. Ophthalmology 2004b;111(7):1280-7.

Toth CA, Freedman SF. Macular translocation with 360-degree peripheral retinectomy impact of technique and surgical experience on visual outcomes. Retina 2001;21(4):293-303.

Tuo J, Bojanowski CM, Chan CC. Genetic factors of age-related macular degeneration. Prog Retin Eye Res 2004;23(2):229-49.

van Leeuwen R, Ikram MK, Vingerling JR, Witteman JC, Hofman A, de Jong PT. Blood pressure, atherosclerosis, and the incidence of age-related maculopathy: the Rotterdam Study. Invest Ophthalmol Vis Sci 2003a;44(9):3771-7.

van Leeuwen R, Klaver CC, Vingerling JR, Hofman A, de Jong PT. The risk and natural course of age-related maculopathy: follow-up at 6 1/2 years in the Rotterdam study. Arch Ophthalmol 2003b;121(4):519-26.

VandenLangenberg GM, Mares-Perlman JA, Klein R, Klein BE, Brady WE, Palta M. Associations between antioxidant and zinc intake and the 5-year incidence of early age-related maculopathy in the Beaver Dam Eye Study. Am J Epidemiol 1998;148(2):204-14.

Vingerling JR, Hofman A, Grobbee DE, de Jong PT. Age-related macular degeneration and smoking. The Rotterdam Study. Arch Ophthalmol 1996;114(10):1193-6.

Vingerling JR, Dielemans I, Bots ML, Hofman A, Grobbee DE, de Jong PT. Age-related macular degeneration is associated with atherosclerosis. The Rotterdam Study. Am J Epidemiol 1995a;142(4):404-9.

Vingerling JR, Dielemans I, Hofman A, Lafaut B, Esser P, Walter P, Bartz-Schmidt KU. The prevalence of age-related maculopathy in the Rotterdam Study. Ophthalmology 1995b; 102(2):205-10.

Vingerling JR, Klaver CC, Hofman A, de Jong PT. Epidemiology of age-related maculopathy. Epidemiol Rev 1995c;17(2):347-60.

VIP 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(5):541-60.

Wall M, May DR. Threshold Amsler grid testing in maculopathies. Ophthalmology 1987;94(9): 1126-33.

Wang F, Tielsch JM, Ford DE, Quigley HA, Whelton PK. Evaluation of screening schemes for eye disease in a primary care setting. Ophthalmic Epidemiol 1998;5(2):69-82.

Wang JJ, Foran S, Smith W, Mitchell P. Risk of age-related macular degeneration in eyes with macular drusen or hyperpigmentation: the Blue Mountains Eye Study cohort. Arch Ophthalmol 2003;121(5):658-63.

Watkins ML, Erickson JD, Thun MJ, Mulinare J, Heath CW. Multivitamin use and mortality in a large prospective study. Am J Epidemiol 2000;152(2):149-62.

Weinberg RB, VanderWerken BS, Anderson RA, Stegner JE, Thomas MJ. Pro-oxidant effect of vitamin E in cigarette smokers consuming a high polyunsaturated fat diet. Arterioscler Thromb Vasc Biol 2001;21(6):1029-33.

West S, Vitale S, Hallfrisch J, Munoz B, Muller D, Bressler S, Bressler NM. Are antioxidants or supplements protective for age-related macular degeneration? Arch Ophthalmol 1994; 112(2):222-7.

Williams RA, Brody BL, Thomas RG, Kaplan RM, Brown SI. The psychosocial impact of macular degeneration. Arch Ophthalmol 1998;116(4):514-20.

World Health Organization (WHO). Cécité : Vision 2020 – Initiative mondiale pour l'élimination de la cécité évitable (1), 2000. Available at: http://www.who.int/mediacentre/factsheets/fs213/fr/ (2 Aug 2004).

World Health Organization (WHO). Cécité et la déficience visuelle, partie IV: aspects socio-économiques, 1997. Available at: http://www.who.int/docstore/bulletin/bu1094.pdf.

World Health Organization (WHO). The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), 1977. Available at: http://www.cdc.gov/nchs/about/otheract/icd9/abticd9.htm (2 Aug 2004).

Yannuzzi LA, Rohrer KT, Tindel LJ, Sobel RS, Costanza MA, Shields W, Zang E. Fluorescein angiography complication survey. Ophthalmology 1986;93(5):611-7.

Yusuf S, Dagenais G, Pogue J, Bosch J, Sleight P. Vitamin E supplementation and cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342(3):154-60.

Zanlonghi X. Conduite de véhicules et handicap visuel : aspects fonctionnels. Available at: http://www.ophtalmo.net/bv/GP/IndexGP/G/CONDUITE/path_et_cond.htm (2 Aug 2004).

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