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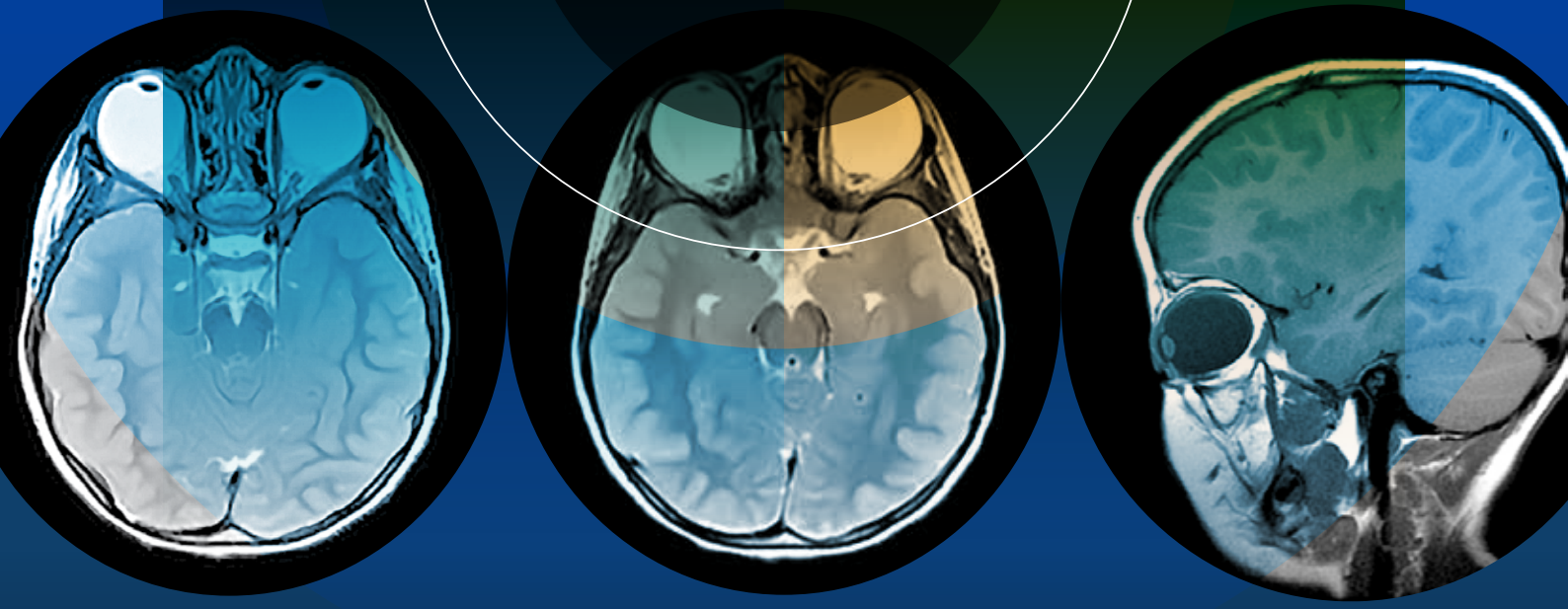
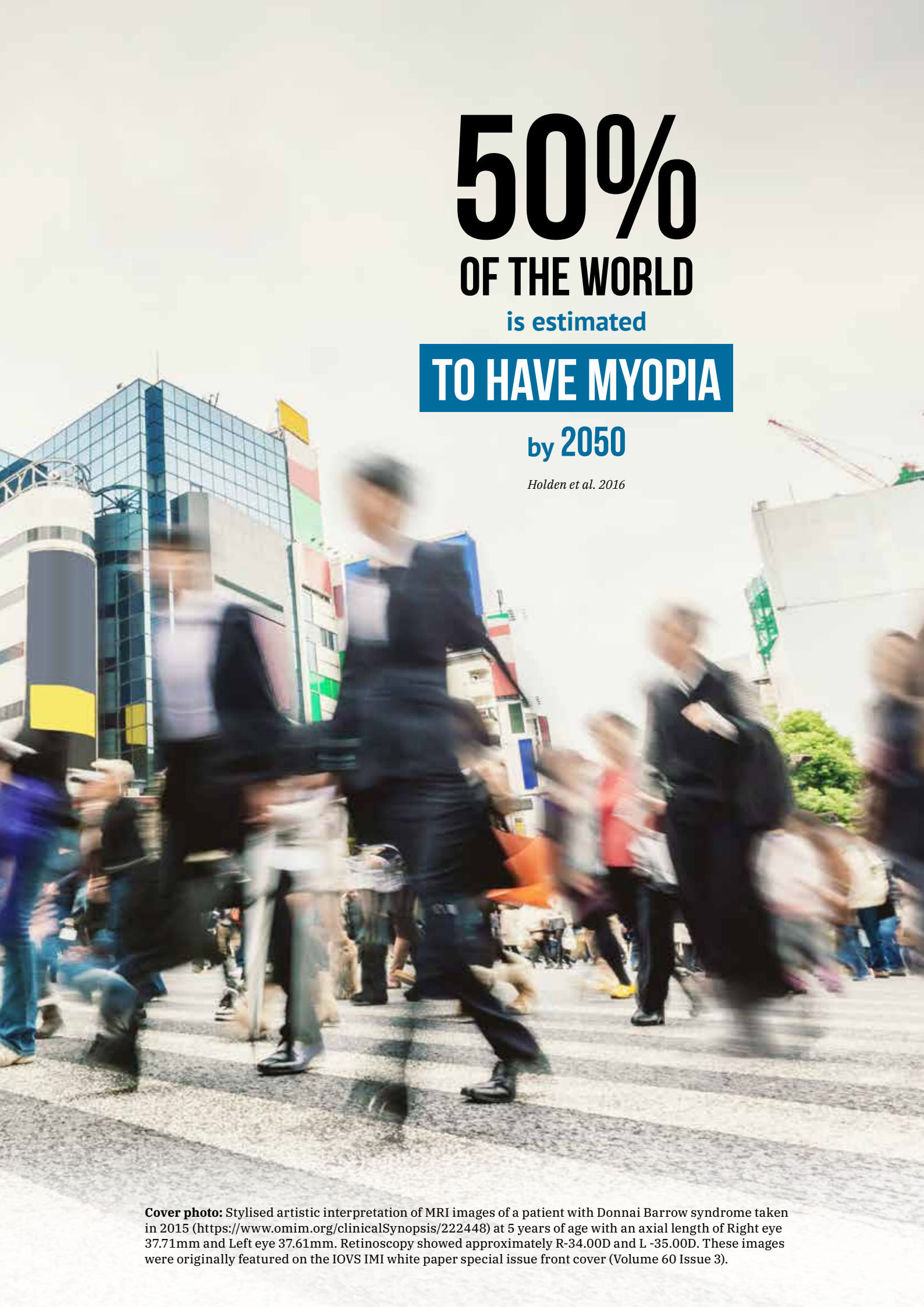
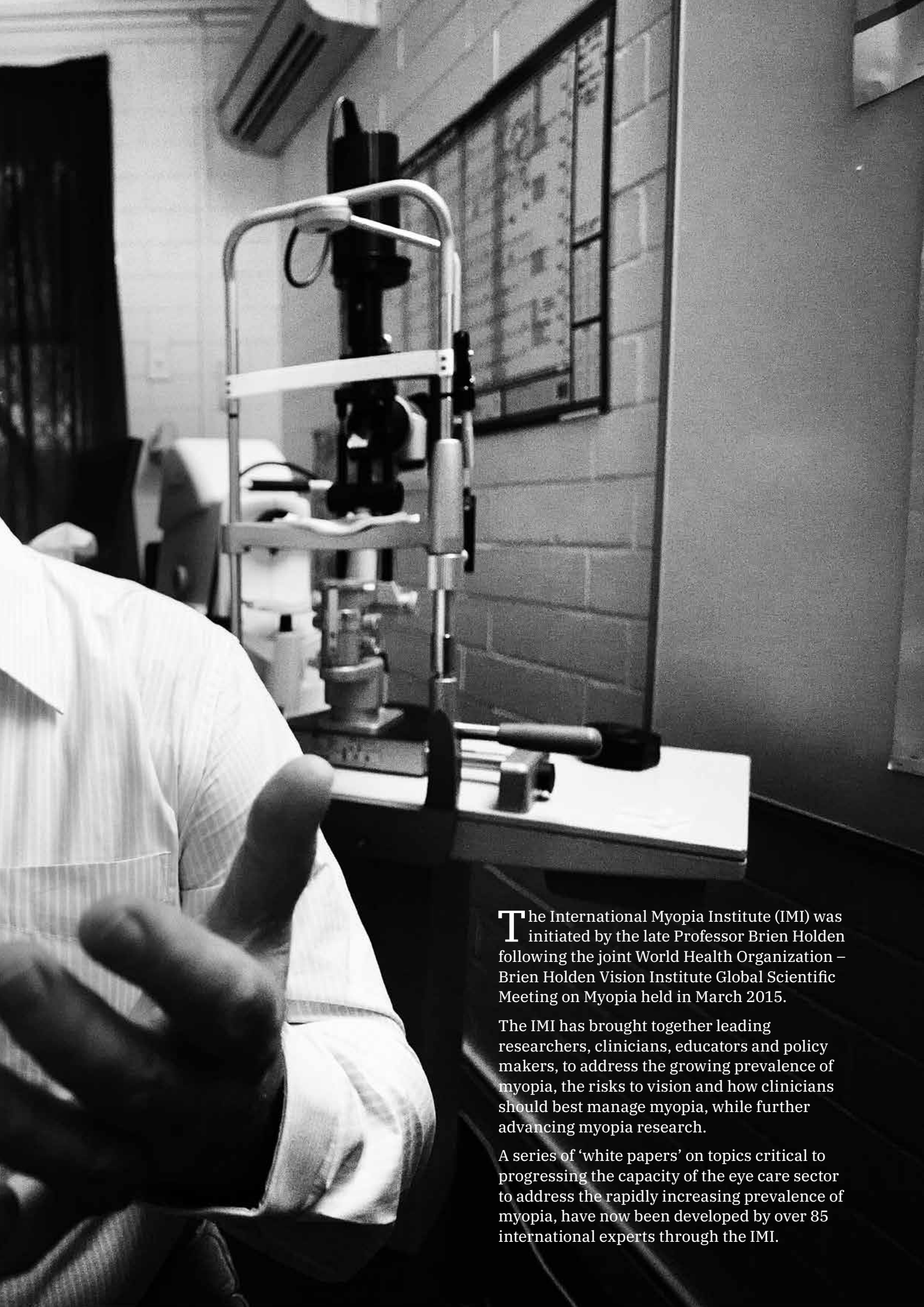


White Papers



Cover photo: Stylised artistic interpretation of MRI images of a patient with Donnai Barrow syndrome taken in 2015 (https://www.omim.org/clinicalSynopsis/222448) at 5 years of age with an axial length of Right eye 37.71mm and Left eye 37.61mm. Retinoscopy showed approximately R-34.00D and L -35.00D. These images were originally featured on the IOVS IMI white paper special issue front cover (Volume 60 Issue 3).

Late Professor Brien Holden attends the Brien Holden Vision Institute Vision Centre, Danila Dilba Health Centre, Darwin, Australia.



The International Myopia Institute (IMI) was initiated by the late Professor Brien Holden following the joint World Health Organization – Brien Holden Vision Institute Global Scientific Meeting on Myopia held in March 2015.

The IMI has brought together leading researchers, clinicians, educators and policy makers, to address the growing prevalence of myopia, the risks to vision and how clinicians should best manage myopia, while further advancing myopia research.

A series of 'white papers' on topics critical to progressing the capacity of the eye care sector to address the rapidly increasing prevalence of myopia, have now been developed by over 85 international experts through the IMI.

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The publication costs of the International Myopia Institute reports
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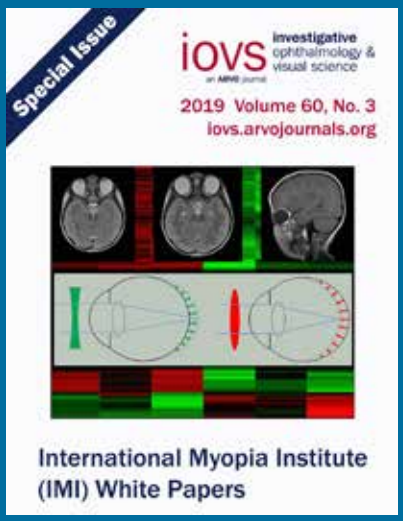

These papers are featured in iovs.arvojournals.org:
IOVS IMI Special Issue. Volume 60, Issue 3.

Individual papers can be downloaded from: https://www.myopiainstitute.org
https://iovs.arvojournals.org/issues.aspx

Original front cover image of the IOVS IMI white papers special issue published at Investigative Ophthalmology & Visual Science February 2019;60:M1–M19. https://doi.org/10.1167/iovs.18-25980. The MRI images were taken in 2015 from a patient with Donnai Barrow syndrome (https://www.omim.org/clinicalSynopsis/222448). They were 5 years of age and had an axial length in the right eye 37.71mm and left eye 37.61mm. Retinoscopy showed myopia of approximately R-34.00D and L -35.00D. Image supplied by JR Polling. Background image shows differential gene expression (red shows upregulated genes; green shows down-regulated genes) in retinas experimentally exposed to either imposed hyperopic (left) or myopic (right) defocus. Adapted from Tkatchenko, Troilo, Benavente, and Tkatchenko, 2018, PLOS Biology; https://doi.org/10.1371/journal.pbio.2006021.

iovs.arvojournals.org j ISSN: 1552-5783

Contents

Editorial

Myopia

A 21st Century Public Health Issue

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Citation: Resnikoff S, Jonas JB, Friedman D, et al. Myopia – a 21st century public health issue. *Invest Ophthalmol Vis Sci.* 2019;60:Mi–Mii. https://doi.org/10.1167/iovs.18-25983

Keywords: myopia, myopic progression, clinical guidelines, definition, interventions, burden, refractive error, prevalence, myopic macular degeneration.

Based on the growing prevalence of myopia around the world, in particular in the young generations in East and Southeast Asia, it was the vision of the late Professor Brien Holden to initiate the International Myopia Institute. For long, Professor Holden, who already had founded and led the Brien Holden Vision Institute in Sydney, had realized the need to address the issues of myopia and myopia-related risks to vision, how clinicians could best manage myopia, and how further myopia research could be advanced. Myopia needed to be recognized as a public health issue if there was to be a change in the approach to this condition, and only a collaborative effort across all eye care professions and researchers could bring this about. Under the auspices of the International Myopia Institute, experts from different myopia-related fields have come together, so that synergistic effects could develop and to make their latest research accessible and easy to understand for practitioners, governments, policy makers, educators, and the general public. Starting with a World Health Organization (WHO)–associated global scientific meeting on myopia, which was held at the Brien Holden Vision Institute in Sydney, Australia in 2015, subgroups of researchers within The International Myopia Institute formed to address the major aspects of myopia. These include the public health issues of myopia, sequelae of myopia, such as the increased risks of sightthreatening complications due to glaucoma, retinal detachment, and myopic macular degeneration, the classification of myopia, prevention of myopia and its complications, and evidence for treatments. With myopia projected to affect 50% of the world population by 2050 and the fear that myopia could become the most common cause of irreversible blindness worldwide,[1] The International Myopia Institute, thus, is a collaborative effort to bring together individuals from across all areas of myopia research.

As a first major step, The International Myopia Institute has edited in this special IOVS issue a series of white papers on defining and classifying myopia, potential interventions, clinical trials and instrumentation, industry guidelines and ethical considerations, clinical management guidelines, experimental models of emmetropization and myopia, and the genetics of myopia. These articles, summarizing the current knowledge in the field and showing trends for future developments, may form a basis for further research, bridging gaps, and connecting people who so far had not intensively exchanged information and ideas. The IMI Myopia white paper reports initiative was chaired by Earl Smith and James Wolffsohn and facilitated by Monica Jong.

The future initiatives and role of The International Myopia Institute will be to foster these scientific cooperations, to be a platform for further harmonization of definitions and guidelines, and also to promote the connections between the scientific world and the public, ultimately supporting the advocacy of this issue at the level of governments, peak health and regulating bodies.

Acknowledgments

Supported by the International Myopia Institute.

The publication costs of the International Myopia Institute reports were supported by donations from the Brien Holden Vision Institute, Carl Zeiss Vision, CooperVision, Essilor, Alcon, and Vision Impact Institute.

Disclosure: **S. Resnikoff**, Brien Holden Vision Institute (C); **J.B. Jonas**, P; **D. Friedman**, None; **M. He**, None; **M. Jong**, None; **J.J. Nichols**, None; **K. Ohno-Matsui**, Novartis (F), Bayer (F), Santen (F), Senju (F); **E.L. Smith III**, Brien Holden Vision Institute (F), Tree House Eyes (C), SightGlass Vision (C), P; **C.F. Wildsoet**, P; **H.R. Taylor**, None; **J.S. Wolffsohn**, Alcon (F), Allergan (F), Aston EyeTech (F), Bausch & Lomb (F), BetterVision Ltd (F), CooperVision (F, C), Eaglet Eye (F), European Union (F), Eyebag (F), EMPharma (F), EyeDocs (F), Gelflex (F), Innovate UK (F), Johnson & Johnson Vision Care (F, C, R), Lenstec (F), Medmont (F), Rayner (F), Tearlab (F), Thea (F), Optimec (F), Visioncare Research (F, C), Aston EyeTech (I), Atiya Vision (C), British Contact Lens Association (C), University of Houston (C), Shire (C), Santen (C, R), RB (C), Santen (R), P; **T.Y. Wong**, Allergan (C), Bayer (C), Genentech (C), Novartis (C), Roche (C)

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IMI

Myopia Control Reports Overview and Introduction

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Submitted: October 16, 2018

Accepted: October 20, 2018

Citation: Wolffsohn JS, Flitcroft DI, Gifford KL, et al.
IMI – Myopia control reports overview and introduction. *Invest Ophthalmol Vis Sci.* 2019;60:M1–M19. https://doi.org/10.1167/iovs.18-25980

Abstract

With the growing prevalence of myopia, already at epidemic levels in some countries, there is an urgent need for new management approaches. However, with the increasing number of research publications on the topic of myopia control, there is also a clear necessity for agreement and guidance on key issues,

including on how myopia should be defined and how interventions, validated by well-conducted clinical trials, should be appropriately and ethically applied. The International Myopia Institute (IMI) reports the critical review and synthesis of the research evidence to date, from animal models, genetics, clinical studies, and randomized controlled trials, by more than 85 multidisciplinary experts in the field, as the basis for the recommendations contained therein. As background to the need for myopia control, the risk factors for myopia onset and progression are reviewed. The seven generated reports are summarized: (1) Defining and Classifying Myopia, (2) Experimental Models of Emmetropization and Myopia, (3) Myopia Genetics, (4) Interventions for Myopia Onset and Progression, (5) Clinical Myopia Control Trials and Instrumentation, (6) Industry Guidelines and Ethical Considerations for Myopia Control, and (7) Clinical Myopia Management Guidelines.

Keywords: myopia control, myopic progression, clinic al guidelines, definition, interventions.

1. Previous Guidance on Myopia Control

While eye care professionals have put forward views on how to slow myopia progression for centuries, the first evidence-based review to make clinical recommendations appears to have been in 2002, based on the only 10 randomized controlled trials to have been conducted at that time. This report concluded that bifocal spectacle lenses and soft contact lenses are not recommended for slowing the progression of myopia in children, nor is the routine use of atropine eye drops.[1] Since that time, more than 170 peer-reviewed articles on myopia control have been published, making it difficult for clinicians to keep abreast of the latest findings and how they should affect the optimum management of their patients. Few, if any, professional bodies have issued documented guidance on the treatment of myopia (in contrast to the correction of the refractive error). While eye care practitioners from across the globe seem concerned about the increasing levels of myopia in their practices, especially in Asia, and report relatively high levels of activity in controlling myopia, most still prescribe single-vision spectacles and contact lenses to their progressing myopes.[2] Hence, there is a need for evidence-based intervention strategies, informed by animal model and genetic studies, with agreement on how myopia should be defined, validated by well-designed and ethically applied clinical trials. The International Myopia Institute (IMI) reports represent the work of more than 85 multidisciplinary experts in the field, who set out to critically review, synthesize, and summarize the research evidence to date (Table 1), and serve to inform both clinical practice and future research.

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CREAM, the international Consortium for Refractive Error and Myopia.

2. The IMI Report Generation Process

As highlighted in the accompanying editorial, the foundation of the IMI was an outcome of the World Health Organization–associated global scientific meeting on Myopia, held at the Brien Holden Vision Institute in Sydney, Australia, in 2015. As part of the IMI's mission to address identified key issues related to myopia, they approached a group of experts to produce two white papers in November 2015, one focused on Myopia Interventions (optical, pharmaceutical, and behavioral/environmental) and the other on Definitions and Classification of Myopia (high myopia, pathologic myopia, and myopic macular degeneration). An IMI steering and an advisory board were established also in November 2015 at the American Academy of Ophthalmology meeting in Las Vegas to oversee the process. A separate initiative at a similar time, led by James Wolffsohn and Nicola Logan of Aston University (Birmingham, UK), approached leading experts in the field to establish a steering committee to put together an evidence-based global consensus on myopia control, in particular to inform clinicians, based on the well-established approach taken by the Tear Film and Ocular Surface Society. The two groups agreed to bring the initiatives together at a meeting at The Association for Research in Vision and Ophthalmology (ARVO)

in May 2016 in Seattle. It was agreed that Earl Smith and James Wolffsohn would chair the initiative supported by the IMI. Monica Jong from the Brien Holden Vision Institute facilitated the entire process. In March 2017, the new white papers to accompany the original two had been agreed on and potential chairs approached.

In developing this set of reports, the IMI has collaborated closely with the past and present organizers of The International Myopia Conference (IMC), an international event that has been in existence since 1964 and is now a biennial event (Table 2). The IMC is devoted to promoting all aspects of myopia research at the basic level through to translational research and clinical myopia research, thereby bringing together a wide range of disciplines.

The attendance at the congress reflects the diversity of persons involved in myopiarelated activities,

TABLE 2. Past International Myopia Conferences

1st*	New York, New York, United States (1964)
2nd†	Yokohama, Japan (1978)
3rd†	Copenhagen, The Netherlands (1980)
2nd*	San Francisco, California, United States (1984)
3rd*	Rome, Italy (1986)
4th	Singapore (1990)
5th	Toronto, Ontario, Canada (1994)
6th	Hakone, Japan (1996)
7th	Taipei, Taiwan (1998)
8th	Boston, Massachusetts, United States (2000)
9th	Hong Kong, Guangzhou (2002)
10th	Cambridge, United Kingdom (2004)
11th	Singapore (2006)
12th	Cairns, Australia (2008)
13th	Tubingen, Germany (2010) ¨
14th	Asilomar, California, United States (2013)

* Organized by the Myopia International Research Foundation.
† Independently organized by local organizing committees. (Not recognized by the Myopia International Research Foundation.)

including researchers, academics, practitioners, policy makers, industry representatives, and students. The IMC started more than 50 years ago; however, it was Sek Jin Chew in collaboration with Josh Wallman who was instrumental in reviving the conference in 1990. The site-hosting organization and organizing committee change for each meeting, thus ensuring diversity at many levels. Chew and Wallman re-established the IMC meetings, using local organizing committees beginning in 1990, adopting the numbering based on the original Myopia International Research Foundation sponsored meetings.

Experts in the field (as identified by the IMI and IMC) were approached for expressions of interest to contribute to one of the reports of their choice. An inclusive approach was adopted, while limiting the number of participants from any one research group to ensure a balanced representation. Discussion between the chairs resulted in report selection for each individual, based on their expertise. The then IMI steering board (David Friedman, Mingguang He, Jonas Jost, OhnoMatsui Kyoko, Kovin Naidoo [chair], Jason Nichols, Serge Resnikoff, Earl Smith, Hugh Taylor, Christine Wildsoet, James Wolffsohn, Tien Wong) and the chairs met at ARVO in May 2017 in Baltimore. The steering committee was responsible for developing the specific aims and mission, along with the strategy for these reports, and agreed on the topics, conflict of interest policy, chairs, and committee members. The chairs (Table 3) presented to a special session at the IMC in Birmingham, United Kingdom, in September 2017 and the report committee membership was expanded based on further interest and feedback. The report committees also met to finalize their paper's outline and to allocate the workload immediately after the meeting. Shortly after this meeting an agreement was put in place to publish all the reports in a special issue of Investigative Ophthalmology & Visual Science (IOVS).

By early 2018, the draft report was put together from the contributions of each committee, and authorship was determined on the basis of contribution. The draft reports were circulated to that committee to review as a whole, to ensure all issues were adequately addressed. In March 2018, the report drafts were circulated to all 88 members of the IMI committees (who came from

17 countries) for review by July. At ARVO in May 2018 the IMI steering committee received reports from each of the committee chairs. Reviewer comments were received by the report chairs and addressed one by one, as occurs in a traditional peer review of academic manuscripts, to ensure all views were considered. Experts in the field who work for industry were not excluded from the report committees owing to their valuable experience, but the review process outlined ensured no undue influence. The sponsors contributed to publication costs of the International Myopia Reports. The appointed harmonizer to each report (see Table 3) was then responsible for ensuring the reviewers' comments had been adequately addressed, that overlap between the reports was minimized (with appropriate cross-referencing), and that the report styles were unified as much as possible.

The harmonizers had a meeting in August 2018 and subsequent email communication to resolve any issues arising. It was acknowledged that some areas of overlap would remain where aspects were approached from a different angle (such as crafting a clinical trial protocol as compared to clinical guidance). The imperative of promoting myopia control as an ethical imperative, due to the evidence-based risk of complications from higher levels of myopia and the availability of treatments with proven effectiveness (compared to the risk of complications from the treatment modality), was of particular note. Hence, the reports promote open communication with patients and their parents/guardians regarding the risk versus benefits, such that a fully informed, joint decision on treatment adoption can be made. Finalized harmonized reports were submitted for publication in IOVS in October 2018.

3. Background to the Need for Myopia Control

3.1 Refractive Development

From birth, eye growth continues and refractive state normally undergoes a gradual shift toward emmetropia. In the first 6 months of life, human newborns typically have a variable, but low hyperopic, cycloplegic refractive error with mean of approximately +2.00 diopters (D) (±SD 2.75 D), which shows a normal distribution in the population.[3–6] Emmetropization over the subsequent 6 to 12 months of age leads to a reduction in hyperopia, and the normal distribution of refractive errors seen in neonates becomes more leptokurtic as the eye matures.[7] For the next several years, hyperopic refractive error will reduce slowly such that, by 5 to 7 years of age, most children will have a refractive error in the low hyperopic range (plano to +2.00 D).[3,6,8,9] In populations with relatively low to modest education levels, refractive error is likely to endure at this level throughout the teenage and adult years.[10] In some individuals, for reasons not well understood, the refractive error will become myopic and is likely to progress for a period of time.

TABLE 3. Report Committees, Chairs, and Harmonizers

Report Subcommittee	Chair(s)	Harmonizer(s)
Defining and Classifying Myopia	Ian Flitcroft	Earl Smith
Experimental Models of Emmetropization and Myopia	David Troilo & Earl Smith	Lyndon Jones
Myopia Genetics	Caroline Klaver	Earl Smith
Interventions for Myopia Onset and Progression	Christine Wildsoet	James Wolffsohn
Clinical Myopia Control Trials and Instrumentation	James Wolffsohn	Kovin Naidoo
Industry Guidelines and Ethical Considerations for Myopia Control	Lyndon Jones	Serge Resnikoff & Kate Gifford
Clinical Myopia Management Guidelines	Kate Gifford	Padmaja Sankaridurg

3.2 Myopia Onset

In children younger than 6 years the prevalence of myopia is low.[11–19] Even in East Asia and Singapore, where the prevalence of myopia is considered to be alarmingly high in young adults, most studies[12,14,15,17,20–22] show a prevalence rate of myopia in the pre–6-year-old age group to be less than 5%. In certain populations, myopia has been found in more than 5% of children younger than 6 years, although the prevalence rarely exceeds 10%.[11,14,23] Recent studies have reported that the incidence of myopia in this age group may be increasing. Fan et al.[23] report that the prevalence of myopia in Hong Kong preschoolers (mean age, 4.6 ± 0.9 years; range, 3–6 years) has increased significantly from 2.3% to 6.3% over 10 years.

The incidence of myopia increases dramatically in at-risk populations from approximately 6 years of age.[24] Previous studies have linked this change with the beginning of primary school education, and a link between the intensity of the education system and myopia onset has been determined.[10,24,25] The annual incidence of myopia onset is reasonably constant between the ages of approximately 7 and 15 years in Chinese populations and, by the age of 18 years, some 80% of the urban-based Han population in China is myopic, regardless of geographic locality.[17,26–28] Singapore, Hong Kong, Taiwan, South Korea, and Japan show similar patterns, although incidence may be higher in Singapore, Taiwan, and Hong Kong at younger ages.[29–37] A systematic review and meta-analysis by Rudnicka et al.[37] has reported an increase of 23% in the prevalence of myopia over the last decade among East Asians.

In Western societies and countries other than those mentioned above, the incidence of myopia onset during childhood years, and thus the corresponding prevalence, is much lower.[37] Most of the myopia cases identified in one study in the United Kingdom was considered to be late onset (16 years or older).[38] Figure 1 illustrates the marked difference in prevalence between East Asian and white children from the meta-analysis of Rudnicka et al.[37] Of ethnicities reported in the meta-analysis, populations in south Asian, black populations in Africa, and Hispanics tended to have lower prevalence than Western white populations, with South-East Asians, black populations not in Africa, Middle Eastern/North African populations, Native Hawaiians, and American Indians showing higher prevalence than white populations, but still much lower than East Asians.[37]

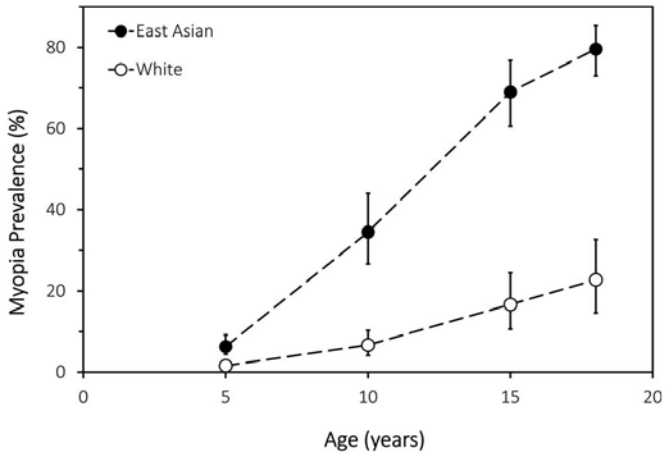

FIGURE 1. Modeled prevalence of myopia by age for East Asian and white children and teenagers from a systematic review and quantitative meta-analysis fitted to the year 2005. Graph created from data in Table 3 of Rudnicka et al.[37]

Models, such as those reviewed in the accompanying IMI – Defining and Classifying Myopia Report,[39] are likely to be efficient in predicting myopia onset, due in part at least, to identification of a process of myopic shift already under way. Since the predominant refractive error of young children is usually a low degree of hyperopia, and the consensus diagnostic criterion for myopia is 0.50 D, there is clearly a transition stage of refractive development for those destined to become myopic.[40] The onset of the myopic trajectory is relatively sudden compared to a subtle loss of hyperopia seen in those who remain emmetropic.[41–43] The myopic shift and acceleration of axial elongation that precedes the onset of myopia may be evident up to 4 years earlier and does not seem to vary between different ethnicities.[42] The high predictive value of the models of Zadnik et al.[44] and Zhang et al.[45] is therefore likely based on detection of values of refractive error and ocular biometry during the transition phase, which depart from those found in emmetropes of the same age.

3.3 Myopia Progression

Progression of myopic refractive error tends to be studied less frequently than onset and prevalence in population-based studies. However,

understanding the mechanisms and risk factors for both onset and progression, and the degree to which they vary, are important, so the phenomena are considered separately here. Longitudinal studies are optimal, but are resource intensive and consequently uncommon. Cross-sectional studies are useful when the mean refractive errors of myopes are segregated by age.

Donovan and colleagues[46] have conducted a meta-analysis of studies reporting myopia progression rates in children of Asian or European descent living in urban areas and corrected with single-vision spectacles. The analysis uses data from 20 studies, 14 intervention trials, and 6 longitudinal observation studies, to predict the progression of myopia and shows that among existing myopes, progression rate declines with increasing age. For example, according to the equation provided in the study of Donovan et al.,[46] progression declines from –1.12 D/y at age 7 years to –0.50 D/y at age 12 years among Asian children.

The progression rates presented by Donovan et al.[46] arise principally from control groups of intervention trials, which may not be representative of the general population. For example, parents of participants in such trials may have enrolled them because of concern that their children's myopia was progressing at a rapid rate when compared with their peers. Population-based and school-based studies tend to report somewhat slower progression. In a rural district in China with baseline data collected in 1998, a total of 4662 myopic (≤–0.5 D) children with a mean age of 9.8 years showed –0.84 D progression during 28.5 months, an average annual progression rate of –0.35 D.[47] The timing of the study and rural habitation of this population may explain some of the difference in myopic progression rate compared with the metadata reported by Donovan et al.[46] The average annual progression rate for a sample including more than 7500 myopic children aged 5 to 16 (mean, 9.3) years in Hong Kong was reported at –0.63 D.[12] Chua et al.[48] have plotted annual changes in refractive error for 928 myopic Singaporean children of mixed ethnicity from age 7 to 11 years, stratified by age of myopia onset. Mean progression rate at a given age is remarkably consistent across the groups, irrespective of age of onset. These mean progression rates are slightly slower than those reported by Donovan et al.[46] (Fig. 2).

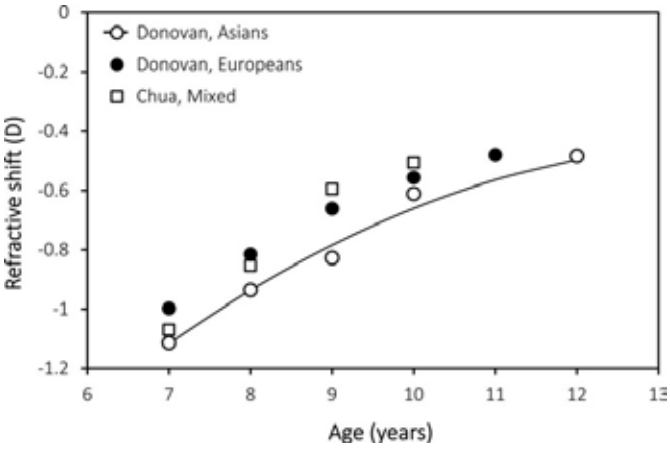

FIGURE 2. Refractive shift among myopic children by age. Data from Donovan et al.[46] were digitized by using ImageJ (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA) and replotted, and the best fit line for Asians was taken from the equation provided in their article. Data for Chua et al.[48] were obtained by averaging progression rates for given ages from their Figure 2.

In a large population-based study in Yongchuan District of Chongqing City, Western China, children aged 6 to 15 years in 2006–2007 have been followed up for an average of 5.2 years.[49] The authors report mean progression of –3.56 D (average, –0.68 D/y) among myopes (≤–0.50 D) during this time. While presentation of the data does not allow direct comparison, these progression rates may well be closer to those reported by Donovan et al.[46] Kim and colleagues[50] have retrospectively analyzed refractive error progression among a population of 221 myopic South Korean children aged 3 to 9 years for an average of 11.2 years.

While this was a hospital-based study, and therefore not necessarily representative of the population at large, the progression rate of approximately –0.50 D/y between the ages of 7 and 13 years was surprisingly modest. Hsu and coworkers[51] have reviewed a population-based cohort in Taiwan of 3256 myopic children, of average age 7.5 years, after 1 year and noted average progression in the group of only –0.42 D, well below that predicted by Donovan et al.[46] Some of these children were being treated with cycloplegics to slow myopia progression and all had been exposed to a large-scale eye care education program, which may explain the lower progression rate. Most recently, Wu et al.[52] have found annual progression of –0.79 D among a school-based control population of 89 myopes aged 6 and 7 years in Taiwan.

This is also less than predicted by Donovan et al.,[46] but it should be noted that those in the sample population receiving myopia treatment were excluded from the analysis.

Further details of likely progression can be obtained from centile progression curves. Chen et al.[53] have constructed reference age-specific centile curves of refraction from cross-sectional population-based data from the Guangzhou Refractive Error Study in Children. However, apparent progression among the myopes between ages of 7 and 12 years is observed to be only approximately −0.5 to −0.6 D/y, comparatively constant across ages, and less again than that of Donovan et al.,[46] particularly at a younger age. The implications of these differences are not clear. Tideman et al.[54] have also produced age-specific centile curves for axial length. The relative functionality of these curves compared to those for refractive error is yet to be determined.

Based on the above literature review, greater myopia progression rates are expected at younger ages (i.e., −0.50 to −1.00 D/y for 6- to 9-year-olds) than at older ages (i.e., −0.35 to −0.75 D for those older than 10 years).

3.4 High Myopia

One of the major ethical challenges for practitioners is accurate identification of those at risk of becoming highly myopic or, at the very least, of those whose myopia is progressing at an unacceptably fast rate. Few analyses are available on this topic, but the breakdown by Chua et al.[48] probably represents the most comprehensive data available. They have found age of onset of myopia to be the strongest predictor of high myopia among Singaporean children.[48] As expected, duration of myopia progression was also important in predicting high myopia. For children with high myopia at age 11 years, there was an 87% chance that the child became myopic at 7 years of age or younger or had a duration of myopia progression of 4 years or more. Reports from other countries (Denmark, Argentina, United Kingdom) reliably reproduce this observation.[55–57] However, in contrast to the report by Chua and colleagues,[48] Williams et al.[57] have found that age of onset only accounts for a modest proportion (approximately 15%) of the variance in severity of myopia.

3.5 Adult-Onset Myopia and Progression

Most of the myopia cases in one study in Britain were considered to be late onset (16 years or older).[38] Although myopia onset past the adolescent stage of life is of clinical interest and has shown an association with environmental factors,[58] eye care practitioners are generally more concerned from an ethical standpoint with identifying patients at risk for development of higher degrees of myopia, which typically involves juvenile-onset myopia and its associated potential to progress to sight-threatening pathology.

The prevailing perception is that myopia stabilizes in the late teenage years.[41] Certainly, annual progression in most myopic patients slows with time and for many myopes whose condition has progressed through the teenage years, myopia will stabilize before they reach 20 years of age. However, there are patients whose myopia will continue to progress through adult years.[58–60] These patients include those doing intense near work, especially students, and those who have higher degrees of myopia. Continued assessment of refraction and initiation of treatment in patients showing continued progression are warranted. Higher levels of myopia will result from continued progression through adulthood, placing these individuals at higher risk for development of myopia-associated pathologies.

3.6 Genetic and Environmental Risk

Risk factors for myopia onset have been identified and included in a number of multivariate models, although to our knowledge there is currently no comprehensive clinical model that provides good predictive value, aside from those using refractive or biometric information. McMonnies[61] has provided a review of risk factors for onset and progression of myopia and produced a comprehensive table of those factors and how they may influence the prognosis and treatment decisions for individual patients. However, he also notes that the lack of clinical data on the topic of risk "undermines the confidence with which individual prognoses and clinical decisions about interventions can be made."

3.6.1 Myopia Onset

Genetics and Personal Characteristics

Heritability statistics can be used to estimate the

proportion of variation in a phenotypic trait of a population that is due to genetics, and further details can be found in the accompanying IMI – Myopia Genetics Report.[62] Heritability estimates for myopia vary from 0.11 to 0.98, the latter higher value being found among a highly specific group of Finnish female twins aged 28 to 29 years.[63,64] A meta-analysis[65] places heritability at 0.71 for refractive error, which would suggest that the majority of influence is from genetics rather than environment.

Genome-wide association studies (GWAS)[66] have demonstrated complex inheritance of refractive error traits, with identification of more than 150 gene loci associated with myopia and good correlation between studies. However, the identified loci explain a meagre percentage of the variance in refractive error.[67] For example, a genetic risk score (GRS) has estimated that these loci explain only 0.6% and 2.3% of the variance in refractive error at ages 7 and 15 years, respectively.[68] The difference between heritability from twin studies and GWAS is known as "missing heritability" or the "heritability gap" and is a well-known characteristic of other phenotypes and diseases.[66]

While the nature versus nurture debate continues in relation to myopia development, recognition of the importance of gene-environment interactions in phenotypic expression has been a significant step forward. Fan et al.[68] have tested for evidence of interactions between near work or time spent outdoors and 39 previously identified loci from GWAS in refractive development in a pediatric cohort. Five variants have shown apparent interaction with near work, while neither variant nor GRS effects were altered with time outdoors.[68]

The most useful clinical indicator for genetic risk short of genetic testing is parental history of myopia. Older studies demonstrating this association have been reviewed by Goss and Jackson.[69] Studies since that time show significant association between number of myopic parents and incident myopia, as summarized in a recent meta-analysis.[70] Odds ratios (ORs) ranging from 1.44 to 2.96 for having a myopic child compared to not having a myopic child were calculated, depending on the number of myopic parents and adjustment for bias and missing studies.[70] More recent studies confirm the connection.[27,71–76] Parental myopia has also been found to interact with other risk factors. In one study of 1770 grade-7 Chinese students, those with close reading distances and two myopic parents have a 26-fold higher odds for prevalent myopia than children with reading distances of greater than 20 cm and no myopic parents.[77,78] Also, unsurprisingly, parental myopia correlates with certain ocular components, particularly axial length.[79,80]

There are some further considerations around parental myopia as a risk factor. The additive genetic portion of phenotypic variance is smaller in younger families, reflecting the trend for increasing environmental influences.[81] The odds of a child with two myopic parents becoming myopic is thus different to the odds of a myopic child having two myopic parents. In part, this stems from increased myopia prevalence, meaning that there will likely be more children with myopia than there are parents with myopia.[43] Number of myopic parents is a relatively gross instrument and a knowledge of degree of myopia in family members may be a more useful factor for predicting progression.[61,82] Because of these factors, the sensitivity of number of myopic parents in predicting childhood myopia is correspondingly low.[82,83]

Rudnicka et al.[37] also have found that sex differences emerge in myopia prevalence at approximately 9 years of age in whites and East Asians. By 18 years of age, white females have 2.0 (95% confidence interval [CI], 1.4–2.9) times the odds of myopia as white males, and East Asian females have 2.3 (95% CI, 2.0–2.6) times the odds of myopia as East Asian males. Others[27,71,73] since have confirmed the propensity for greater myopia prevalence among females. The extent to which this influence is environmental as opposed to genetic has yet to be determined.

Environment

Ramamurthy and colleagues[84] have reviewed the large number of environmental risk factors for myopia. Two key environmental influences upon myopia development are time spent outdoors and amount of near work. The reason time spent outdoors is protective against myopia development remains unexplained. Although there is some evidence from animal studies showing that high light levels or chromaticity might be the critical factor,[84] Flitcroft[85] and Ngo et al.[86] present a counter-argument as to why

the dioptric field, perhaps in an interaction with the high light level, is central to protection from time spent outdoors. Xiong et al.[87] have reviewed multiple studies and suggest a clear connection between time spent outdoors and myopia onset. However, differentiation between consequence and causality can only be shown in prospective randomized studies. As spending time outdoors is an intervention to prevent or delay myopia development, detailed description of this risk factor for myopia onset is presented in the accompanying IMI – Interventions for Controlling Myopia Onset and Progression Report.[88]

Despite some indications that near work may not be directly related to myopia, more recent evidence suggests a clear link.[89] "Near work" has been defined and measured in a multitude of ways across different studies (e.g., education level, duration of continuous study time, time spent reading books for pleasure, number of books read per week, time spent on reading and close work, time spent indoors studying, closer working distance, short reading distance, distance from near work, font size, and screen-viewing activities) and is, by its nature, difficult to quantify. Nonetheless, in a systematic review and meta-analysis, Huang et al.[89] have found more time spent on near-work activities is associated with higher odds of myopia, increasing by 2% for every additional diopter-hour of near work per week. Multiple subsequent articles not included in this meta-analysis also confirm the association of some index of near work with development and progression of myopia, often independently from time spent outdoors in multivariate analyses.[27,51,52,72,75,76,78,90–92] French and coworkers[93] have presented data that illustrate a strong interaction between the effect of time spent outdoors and near work. In children with baseline mean age of 6 years, those who spend low amounts of time outdoors and perform high levels of near work have dramatically increased odds of incident myopia by age 12 years (OR, 15.9; 95% CI, 3.5–73.4) as compared with those who spend high amounts of time outdoors and low amount of time involved in near work.

Both country and location of residency (urban versus rural) of an individual are associated with the likelihood of myopia. Rose et al.[94] have found that the prevalence of myopia in 6- to 7-year-old children of Chinese ethnicity is significantly lower in Sydney, Australia (3.3%) than Singapore (29.1%). In their large meta-analysis of childhood myopia prevalence from population-based surveys, Rudnicka et al.[37] have shown striking differences in prevalence among school-aged children of Eastern Chinese ancestry, based on their country of residence (Fig. 3). Among South Asian children living in Australia, England, or Singapore, myopia was five times as likely compared to those living in India or Nepal. There was no apparent difference in prevalence of myopia among white children in studies from Europe, United States, and Oceania.

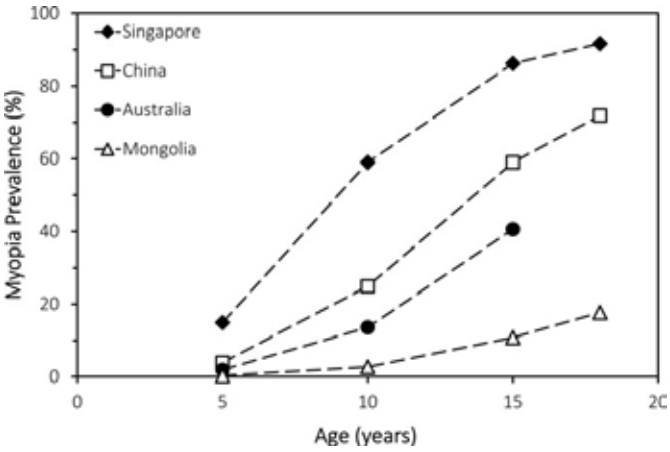

FIGURE 3: Modeled prevalence of myopia by age for East Asians by selected country of residence from a systematic review and quantitative meta-analysis adjusted to the year 2005 (except for Mongolia, which is 2003). Graph created from data in Table 4 of Rudnicka et al.[37]

The authors also determined that children from urban environments have 2.6 (95% CI, 1.8–3.9) times higher odds of myopia than those from rural environments.[37] Consistent with this finding, population density, home size, and housing type are also significantly associated with refractive error and axial length.[95,96] The mediating factors for all of the environmental effects are likely to be a combination of education, near work, and time spent outdoors.

Physical attributes (height, weight, and body mass index),[29,97,98] prenatal history,[99] birth season,[100,101] intelligence,[102,103] and socioeconomic status[27,104,105] have all been linked to the likelihood of myopia, with varying strengths of association.

Binocular Vision

It has long been postulated that myopia onset and progression may be related to dysfunctional accommodation and convergence.[106] An elevated accommodation-convergence/accommodation (AC/A) ratio has been observed before the onset of myopia.[44,107] In a large, ethnically diverse group of children followed up for an extensive period of time, Mutti and colleagues[108] have found the AC/A ratios of those who become myopic begin to increase approximately 4 years before myopia diagnosis, continue increasing until diagnosis, and then plateau at a level higher than those who remain emmetropic.

Another feature of accommodation that has been observed is that measured lag of accommodation is larger among myopes than nonmyopes.[109,110] It was thought that the presence of lag before onset may produce hyperopic retinal defocus, stimulating myopia onset. However, this effect only appears at the time of onset, not before, and does not seem to impact progression.[108,111] An aspect of accommodative lag worthy of mention is that spurious measurement of accommodative error is well documented.[112–114] So-called lag may be substantially a function of the measurement technique, where depth of focus and increasing negative spherical aberration with accommodation and developing myopia are not taken into account.

The shift in refraction (in terms of a reduction in hyperopia) observed in those who will become myopic compared to those who remain emmetropic begins several years before diagnosis. Changes to the AC/A ratio merely seem to parallel such changes. Accommodative lag does not seem to appear until myopia onset.[115] Thus, while binocular vision attributes are an interesting research adjacency in the onset and development of myopia, from our current knowledge they do not seem to add any additional benefit in risk assessment over refraction and biometric parameters, genetics, or environmental effects.

3.6.2 Myopia Progression

Compared with onset, there is a lower volume of literature describing risk of progression for existing myopes other than age and initial refractive error. Some studies have looked at group progression, including emmetropes and hyperopes as well as myopes in their analyses, which does not allow specific interpretation regarding progression among myopes.

Genetics and Personal Characteristics

Donovan et al.[46] report that myopia in European children progresses more slowly on average than in Asians (–0.55 D/y and –0.82 D/y, respectively, at mean age of 9.3 years), although age-specific progression data by baseline age for Europeans in their analysis are derived from a single article. For studies conducted in somewhat homogeneous Western societies, the analysis of Mutti et al.[42] supports the ethnic differences in progression rates found in the study by Donovan and colleagues,[46] although French et al.[116] did not establish significance of an ethnicity effect. Gwiazda and colleagues[117] have looked at risk factors for high myopia, which can be considered a corollary of fast progression. Reporting on an ethnically diverse population of children aged 6 to 11 years with initial myopia between –4.50 and –1.25 D at four sites within the United States, they did not find an effect of ethnicity on progression rates. Environment is also likely to play a role in myopic progression rates, which may be inferred from higher degrees of myopia among Asian children living in Asia compared to those living in Western societies; however, a thorough review of differences in progression rates between ethnically similar populations in different environments does not seem to have been undertaken.

In their study, Gwiazda et al.[117] found that the number of myopic parents is a risk factor for high myopia. Some studies support the proposition that parental myopia is associated with faster progression rates, where others do not.[91,118,119]

Females show faster progression than males according to Donovan et al.[46] (–0.80 D/y and –0.71 D/y, respectively, at mean age 8.8 years) and Zhou et al.[49] (OR, 1.45; 95% CI, 1.12–1.84). However, such a difference is not evident in the study of Gwiazda et al.[117]

Environment

In their meta-analysis, Xiong et al.[87] report that outdoor time is not effective in slowing progression in eyes that are already myopic. However, a more recent prospective study[52] suggests that outdoor time does have a protective effect on rate of

progression. Subsequent cohort studies[51,74,118,120] yield mixed results. Support for the protective effect of time spent outdoors on myopia progression may be inferred from numerous studies that have found a seasonal variation in myopia progression;[121–123] see the accompanying Interventions for Controlling Myopia Onset and Progression Report.[88]

Many of the same environmental factors that are linked to the incidence or prevalence of myopia are also related to progression. Multiple articles link near work, with various descriptors of activity, to myopia progression.[51,52,72,74,91,119,120] Other associations include urbanization and increasing family income.[90,91]

Binocular Vision

Two studies that have considered binocular vision effects as part of the treatment protocol (esophoria or low lag of accommodation) have had good success, suggesting that some aspect of binocular function may be a risk factor for progression.[124,125]

3.7 Summary of Findings on Risk Factors

The observations reported above present an unambiguous message. The younger the age of onset of myopia, the greater the likelihood that a child will experience progression to vision-threatening levels of myopia. Practitioners and parents should be active in addressing both myopia onset and progression at as young an age as possible. No formal procedures have been identified that recognize those at risk of myopia onset before the triggering of the steady progression in refractive error that ultimately leads to myopia diagnosis. However, it is clear, for example, that Chinese children living in urban regions of Asia, who are immersed in an intensive education environment and have two myopic parents, have a much greater risk for onset and development of significant myopia than a Caucasian living in a rural environment in Australia with no myopic parents. Not all children who are young at myopia onset will experience progression to high myopia, but age of onset is the current best determinant for identifying children at risk of progression. While noting the risk of high myopia is greatest in those with early onset, practitioners should also be cognizant that the condition of some individuals with later onset (say 11 years or older) may also progress to higher degrees of myopia, where the rate of progression is high. Practitioners should be vigilant in identifying and treating those at risk of rapid progression, regardless of age of onset.

4. Subcommittees and Their Report Focus and Advancements

4.1 IMI – Defining and Classifying Myopia Report[39]

Myopia has been the topic of scientific study for more than 400 years, but it is only more recently that it has been recognized as a serious public health issue, owing to its being a significant cause of visual loss and a risk factor for a range of pathologic ocular conditions. Its prevalence is increasing on a global basis and has reached epidemic levels in much of Asia. Myopia has been defined in a wide variety of ways in the past, such as based on its assumed etiology, age of onset, progression rate, degree of myopia (in diopters), and structural complications. This has led to a confusing accumulation of terms. Hence this subcommittee's aim was to provide a standardized set of terminology, definitions, and thresholds of myopia and its main ocular complications. A critical review of current terminology and choice of myopia thresholds was undertaken to ensure that the proposed standards are appropriate for clinical research purposes, relevant to the underlying biology of myopia, acceptable to researchers in the field, and useful for developing health policy. It is recommended that the many descriptive terms of myopia be consolidated into the following descriptive categories:

> **Myopia:** A refractive error in which rays of light entering the eye parallel to the optic axis are brought to a focus in front of the retina when ocular accommodation is relaxed. This usually results from the eyeball being too long from front to back, but can be caused by an overly curved cornea, a lens with increased optical power, or both. It is also called nearsightedness.

With qualifying terms:

> **Axial Myopia:** A myopic refractive state that can be attributed to excessive axial elongation.
>
> **Refractive Myopia:** A myopic refractive state that can be attributed to changes in the structure or location of the image-forming structures of the eye (i.e., the cornea and lens).

Secondary Myopia: A myopic refractive state for which a single, specific cause (e.g., drug, corneal disease, or systemic clinical syndrome) can be identified that is not a recognized population risk factor for myopia development.

It was also recommended that in quantitative contexts, myopia should always be treated as a negative value and that mathematical comparison symbols be used in their strict mathematical sense.

To provide a framework for research into myopia prevention, the condition of "premyopia" is defined.

Premyopia: A refractive state of an eye of ≤+0.75 D and >−0.50 D in children where a combination of baseline refraction, age, and other quantifiable risk factors provides a sufficient likelihood of the future development of myopia to merit preventative interventions.

As a quantitative trait it is recommended that myopia be divided into myopia (i.e., all myopia), low myopia, and high myopia as based on the current consensus of publications:

Myopia: A condition in which the spherical equivalent refractive error of an eye is ≤−0.5 D when ocular accommodation is relaxed.

Low Myopia: A condition in which the spherical equivalent refractive error of an eye is ≤−0.5 D and >−6.00 D when ocular accommodation is relaxed.

High Myopia: A condition in which the spherical equivalent refractive error of an eye is ≤−6.00 D when ocular accommodation is relaxed.

Although even low levels of myopia are associated with an increased risk of developing pathologic conditions such as myopia maculopathy and having a retinal detachment, "pathologic myopia" is proposed as the categorical term for the adverse, structural complications of myopia.

Pathological Myopia: Excessive axial elongation associated with myopia that leads to structural changes in the posterior segment of the eye (including posterior staphyloma, myopic maculopathy, and high myopia–associated optic neuropathy) and that can lead to loss of best-corrected visual acuity.

A clinical classification is also proposed to encompass the scope of such structural complications.

4.2 IMI – Experimental Models of Emmetropization and Myopia Report[126]

Much of our current understanding of characteristics and mechanisms of postnatal eye growth and the development of myopia has come from detailed experimental studies using animal models. These models use a wide range of species, from primates to invertebrates, and include macaque and marmoset monkeys, tree shrews, guinea pigs, mice, chickens, fish, and squids. Considering that these phylogenetically wide-ranging species all possess visually guided eye growth despite differences in ecology, ocular anatomy, visual function, and visual acuity, this supports the hypothesis that visually guided eye growth is an evolutionarily conserved process found in camera-type eyes. Each species provides unique experimental advantages to study the mechanisms of visually guided eye growth and the key signalling pathways that regulate refractive eye development across species; however, anatomic and physiological differences must be taken into account when interpreting and translating results to humans.

The report summarizes the anatomic similarities and differences between the eyes of the principal experimental species used for studies of emmetropization and myopia. Surveying more than 800 published reports on the changes in eye growth and refractive state in response to experimental manipulations of visual conditions, the report offers a summary of the evidence supporting the role of vision in eye development and the mechanisms that underlie the visual regulation of eye growth and emmetropization development. Also discussed are the key operating characteristics of experimental emmetropization to experimentally imposed retinal defocus including local retinal mechanisms controlling regional eye growth, the spatial and temporal integration of visual signals, the impact of simultaneous competing defocus signals, the relationships of various ocular circadian rhythms to induced changes in eye growth, and the critical periods for visual experience–invoked myopia. Studies of the characteristics of the visual signals affecting eye growth are also reviewed and discussed, including the intensity of ambient illumination, the spectral composition of light, longitudinal chromatic aberration, higher-order monochromatic aberrations, and astigmatism.

The report reviews the biochemistry of refractive error development, including the roles of various retinal neurotransmitters, neuromodulators, and growth promotors such as dopamine, vasoactive intestinal peptide, melanopsin, glucagon, and insulin, and nitric oxide. Pharmacologic studies of the mechanisms of emmetropization and myopia are discussed including the effects of cholinergic, GABAergic, and adenosine antagonistic drugs and drugs affecting nitric oxide and neuropeptides. Finally, the article reviews the molecular biology of gene expression in the eye and retina and possible gene-environment interactions.

The report reviews and summarizes several confirmed findings from animal models that have provided important proofs of concept that helped to transform treatment strategies for myopia control. These findings include the eye's ability to detect the sign of retinal defocus and undergo compensatory growth, the local retinal control of eye growth, regulatory changes in choroidal thickness, and the identification of biochemical signal cascades regulating postnatal eye growth and refractive state. Experimental animal models continue to provide new insights into the cellular and molecular mechanisms of eye growth control, including the identification of potential new targets for drug development and future treatments needed to stem the increasing prevalence of myopia and the vision-threatening conditions associated with this disease.

4.3 IMI – Myopia Genetics Report[62]

Like other complex traits, myopia has benefitted enormously from the dramatic improvements in DNA technologies and significant reduction in costs for genotyping during the last decade. The IMI – Myopia Genetics Report summarizes the developments in gene identification for refractive error and myopia, and addresses their implications for molecular pathways. An extensive literature search identified almost 200 genetic loci that have been reported for refractive error, myopia, or axial length, and many overlap between these endophenotypes. Risk variants have mostly been identified outside the protein coding regions, and by themselves carry a low risk. Nevertheless, totalling all genetic risk variants in a polygenic risk score shows that those with a high genetic load are >40 times more likely to become myopic, and high myopes and high hyperopes can be separated by their genetic score. The most significant contribution of the current gene dissection is the insights into the molecular machinery underlying eye growth. Functions of the annotated genes include retinal cell physiology, light processing, glutamate receptor signalling, extracellular matrix modulation, anterior segment morphology, but also posttranscriptional regulation indicating control of gene expression at the RNA level. In silico and in vitro experiments have shown that all cell types in the retina, but also RPE, vascular bed, and connective tissue are sites of gene expression. This implies that the retinal signalling cascade responding to a visual trigger and leading to eye growth involves a complex network of molecules from many different cells and tissues. Another lesson learned from the genetic studies is that most genes are not eye specific and have a plethora of effects outside of the eye. A fair number of genes for common myopia are involved in a wide range of syndromes, including neurodegenerative and connective tissue disorders. How this broad spectrum of gene functions leads to scleral remodelling and an increase of axial length remains intriguing. Addressing this "black box" requires taking myopia molecular genetics to the next level: to explore new high-throughput, wide coverage genotyping assays; determine the protein function and the elements that regulate gene expression; investigate how DNA, proteins, and the environment interact to determine eye size; and create possibilities for storage and reuse of massive genomic data. The forecast of understanding and solving myopia makes these challenges worth taking.

4.4 IMI – Interventions for Controlling Myopia Onset and Progression Report[88]

This report examines the evidence basis for various interventions in current use for controlling myopia progression in children, organized under the categories of optical, pharmacologic, environmental (behavioral), and surgical interventions (aimed at stabilizing highly myopic eyes). There is equivocal evidence concerning whether single-vision spectacles cause faster myopic progression than soft contact lenses, but any difference is likely to be clinically irrelevant. Undercorrection is still adopted as a myopia control strategy by some practitioners, yet some but not all clinical trials indicate this strategy has no clinically significant

benefit in slowing myopia. Single-vision spectacle lenses designed to alter peripheral defocus had only a small treatment effect, of less than 14% reduction in myopia progression. The treatment effects on myopia progression of bifocal and progressive addition spectacles tend to be larger, although variable and questioned in terms of clinical significance in some cases (6%–51%). Overall, single-vision contact lenses, whether soft or rigid, seem to have little effect on myopia progression, in contrast to significant treatment effects with contact lenses that impose multifocality. Center-distance multifocal lenses have been used off-label successfully, demonstrating a sample size–weighted average of 38%, slowing both myopia progression and axial elongation, although these two assessment elements did not always correspond tightly. Orthokeratology has also proven to be effective in slowing axial length elongation, by between 30% to 55%.

Pharmacologic myopia control trials have principally used atropine, although other muscarinic antagonists such as M1 selective pirenzepine, ocular hypotensive agents including topical timolol (a nonselective β-adrenergic antagonist), and oral 7-methylxanthine, an adenosine antagonist, have also undergone trial. Although the reduction in myopia progression seems to be higher with 1% atropine (around 60%–80%), more recent atropine studies use much lower doses (e.g., 0.01%), with a reduced effect on refractive error retardation (around 45%) and no apparent effect of axial length compared to historical controls, but with fewer side effects and apparent rebound after discontinuation.

Time outdoors appears to be more effective in preventing incident myopia than slowing progression of existing myopia. However, the evidence for vitamin D levels being related to myopic control is weak. Seasonal trends in myopia progression have also been interpreted as indirect evidence of outdoor effects on myopia progression, based on observed faster myopia progression during the darker winter than the brighter summer months. In one study, every additional hour of outdoor time per week has been found to reduce the risk of developing myopia by 2%. In another study, the time children spend engaged in near work outside of school and time spent outdoor were not found to be related, as might be expected. Deployment of wearable technologies in place of questionnaires as study tools may help to resolve apparent inconsistencies and unresolved questions, including whether the quality of indoor lighting is important.

4.5 IMI – Clinical Myopia Control Trials and Instrumentation Report[127]

Clinical trials on myopia control conducted to date were reviewed to inform a consensus on best practice in the design of clinical trials to assess the effectiveness of treatments and the impact on patients. As myopia control interventions will be applied for multiple years throughout the time during which myopia is progressing, and treatment effects have been shown to often reduce after an initial period, it is important that clinical trials evaluate efficacy over a long period (3 years being the recommendation) to ensure continued efficacy beyond any initial treatment effect. Assessment of rebound should also be considered, with a minimum recommended period of 1 year due to seasonal effects. Typical inclusion criteria are cycloplegic spherical or spherical equivalent myopia of at least −0.75 D; astigmatism ≤ 1.00 D; anisometropia ≤ 1.50 D; ages 6 to 12 years; and 20/20 (0.0 logMAR) minimum visual acuity. Exclusion criteria typically are previous rigid contact lens wear; history of previous myopia control treatment; ocular pathology; binocular vision anomaly; medications that may affect pupil size, accommodation, or have an impact on ocular surface; and systemic disease that may affect vision, vision development, or the treatment modality. Appropriate control group selection depends on the intervention being studied, but often myopia control studies cannot be fully masked. Studies with no control group are unable to demonstrate treatment efficacy; as the rate of myopia progression decreases naturally with age and has seasonal variation, it is not possible to distinguish between naturally declining progression and reduced progression attributable to the treatment, without a simultaneously conducted control group. Randomization should be applied to treatment allocation, and stratification by key factors known to influence myopia progression (such as age and race/ethnicity) should be considered. Ocular health, including a slit lamp examination and baseline/periodic dilated fundus examination, along with standardized adverse event reporting, should

also be embedded in the trial protocol. Binocular vision associations in myopia control treatments have also been found, so should be investigated at baseline and periodic intervals during the study. Other safety-related assessments include visual acuity and dysphotopsia. Finally, there is not a specific minimum percentage reduction in myopia progression that has been published for a treatment effect to be considered clinically meaningful; any such percentage reduction threshold could theoretically vary with multiple other factors, including duration of treatment, sample population, and study design considerations. Sample size estimations based on currently available measurement variability data are provided.

Outcome measures were classified as primary, secondary, and exploratory. Primary outcome measures are refractive error (ideally assessed objectively with autorefraction of the eye cyclopleged in optical intervention studies with 1% tropicamide) or axial length (ideally measured with noncontact interferometry) or both. Secondary outcome measures focus on patient-reported outcomes (usually assessed by questionnaire and can include the parent's/guardian's experience as well as the patient's) and treatment compliance (ideally in real time, such as with text messaging responses or wearable sensors connected to data loggers). Exploratory outcome measures are particularly useful in trying to understand the mechanism of action and associated factors. These include peripheral refraction (such as measured with autorefractors or wavefront aberrometers), accommodative changes (including accommodative lag and dynamics), ocular alignment, pupil size, outdoor activity/lighting levels, anterior and posterior segment structural changes (typically imaged with Scheimpflug imaging, optical coherence tomography, and retinal photography with a particular interest in choroidal thickness changes), and tissue biomechanics (of the sclera and cornea).

4.6 IMI – Industry Guidelines and Ethical Considerations for Myopia Control Report[128]

The aim of this subcommittee was to discuss guidelines and ethical considerations associated with the development and prescription of treatments intended for myopia control. A critical review of published articles and guidance documents was undertaken, with a view to carefully consider the ethical standards associated with the investigation, development, registration, marketing, prescription, and use of myopia control treatments.

From an ethical standpoint, deciding whether to implement a myopia control strategy represents a classical medical risk versus benefit ratio. A principal motivation for slowing myopia progression is based on the premise that limiting myopia progression reduces risk of the development of vision-threatening disease in later life. However, conclusive evidence that this is the case is unlikely to be available for decades. Nonetheless, if this assumption is correct, then the benefits could be substantial, given the clear relationship between myopia-related ocular pathology and the degree of myopia. Thus, the risk-benefit analysis must take account of the outcomes arising from nonintervention in deciding if implementation of a myopia control strategy with an individual patient is warranted. Other factors to consider include the known improvements in quality-of-life issues arising from the use of corrective devices; adults with pathologic myopia and associated visual impairment report significant social and emotional impacts and reduced life satisfaction. Additional factors that must be accounted for in the decision to undertake myopia control include the regulatory status of the treatment being considered, availability of the treatment, access to appropriate eye care services, and pricing and convenience of the treatment, which are all potential barriers to accessing the myopia control treatment being considered.

These considerations place a burden of responsibility on the practitioner to be fully cognizant of the risks for the patient of developing different levels of myopia, the implications that progression to higher levels of myopia may have, the likely benefits of treatment, the side effects of treatment and other associated factors, so as to provide appropriate advice and care.

Researchers and clinicians often partner with companies to conduct myopia control studies. However, there is a risk for these partnerships to introduce bias, and practitioners should be aware of the importance of evaluating any real (or perceived) conflict of interest when recommending a management plan for myopia control. The interactions between researchers, practitioners,

and manufacturers of myopia control treatments should meet the highest possible standards of integrity and transparency and must be declared in the reporting of the results obtained. Relationships between clinicians and patients should not be compromised by commercial or other interests that could subvert the principle that the interests of patients are of primary concern.

Most myopia control treatments are currently off-label in many countries. Most regulatory bodies do not restrict practitioners from discussing off-label treatment uses with their patients. However, given that patients and their families generally assume that a treatment prescribed by their clinician has been proven safe and effective and is supported by scientific evidence, it is recommended that practitioners ensure that a formal informed consent process is adopted, to ensure that the patient (and parents/guardians in some cases) is aware of the risks, benefits, and alternatives for any myopia control treatment discussed.

Regulatory bodies, manufacturers, academics, practitioners, and patients are all stakeholders and play an important role in ensuring the appropriate prescribing and success of myopia control treatments. Approval of a treatment by a regulatory body relies on the risk-benefit assessment and is informed by science, medicine, policy, and judgment, in accordance with applicable legal and regulatory standards. Manufacturers have a large part to play in the ethical decisions around the practitioner's prescribing of myopia control treatments by ensuring that the discussion of the efficacy of a treatment is appropriately reported and that the treatments are manufactured by using rigorous methods to ensure their quality. Academics have an important role in disseminating scientific information related to myopia control treatments, which is typically undertaken in the form of peer-reviewed journal articles, in addition to abstracts and presentations at major scientific conferences. Practitioners have a responsibility to care for their patients by recommending myopia control treatments using evidence-based practice. With a condition as multifactorial and individual as myopia, this means using published evidence along with clinical judgment to determine the best course of action for the young myopic patient. Finally, patients should be well informed about the nature of the product's marketing authorization status for the intended use and, in case of off-label/unlicensed treatments, that the risks associated with the treatment might be unknown. Such information should be provided in a neutral, balanced, and nonbiased way by the practitioner and be accompanied by easily accessible online and printed information.

Undertaking myopia control treatment in minors creates an ethical challenge for a wide variety of stakeholders. Regulatory bodies, manufacturers, academics, and clinicians all share an ethical responsibility to ensure that the products used for myopia control are safe and efficacious and that patients understand the benefits and potential risks of such products.

4.7 IMI – Clinical Myopia Management Guidelines Report[129]

This report draws on the evidence basis outlined principally in the IMI – Interventions for Controlling Myopia Onset and Progression Report[88] for establishing clinical guidelines to inform the management of the progressing myopic patient. This includes risk factor identification from the assessment of refractive error, binocular visual function, parental refraction, and visual environment (such as educational intensity and time spent outdoors) at around ages 6 to 11 years; discussion of the prospect of developing myopia and the associated risks, along with treatment option efficacy, risks, and additional correction benefits with the parents/guardians and the patient in lay terms; setting realistic expectations; gaining informed consent; agreement of compliance and a follow-up schedule; and off-label considerations. Key baseline examination procedures include a detailed ocular and general health history (including parental refractive error, myopia onset, any previous correction/treatment, and time spent outdoors/doing detailed near work), subjective refraction (objective refraction following cycloplegia when indicated), visual acuity, binocular vision (principally vergence) and accommodation (particularly lag and amplitude) assessment, corneal topography (if considering orthokeratology), slit lamp biomicroscopy of the anterior eye (including signs of dry eye disease), intraocular pressure measurement (if considering pharmaceutical treatment), dilated fundus examination, and ideally noncontact axial length

measurement. Exploratory tests that may be used clinically in future include uncorrected relative peripheral refraction, ocular aberrations, pupil size, subfoveal choroidal thickness, and wearable devices to track visual habits and the environment.

Treatment strategies need to be agreed upon in conjunction with the patient and parents/guardians with aspects such as their risks/benefits, the patient's lifestyle, and ease of compliance taken into account. Myopia "calculators" can be useful to visualize the average potential outcome based on research studies, but it must be noted that projections are based on carefully selected subjects examined for between 2 and 5 years only. Owing to the inherent risks of any treatment (contact lens, pharmaceuticals), treatment is not generally advisable until the myopia is visually significant (−0.50 D to −0.75 D), and baseline refractive error will determine the availability and potential effectivity of treatment. Although undercorrecting myopia is still practiced in some countries, most robust studies show it to either have no effect or increase the rate of myopia progression, hence children should be encouraged to wear their myopic correction full time. Children should not be prevented from participating in near-work activity, but regular breaks and fixation changes from intense near work should be encouraged, along with sufficient time (8–15 hours/week) outdoors.

Treatments are likely to be most effective at younger ages, when rapid progression is underway; the efficacy of some treatments may wane after the first 6 months to 2 years of treatment and the effects could rebound after cessation (particularly with higher-dose pharmaceuticals). The guidelines recommend 6 monthly follow-ups to monitor safety and efficacy of the myopia control treatment, performing the same tests as at baseline, but with cycloplegic refraction and dilated fundus examination conducted annually or on indication. The future research directions of myopia interventions and treatments are discussed, along with the provision of clinical references, resources, and recommendations for continuing professional education in this growing area of clinical practice.

Acknowledgments

The authors thank David Sullivan, the chief executive of the Tear Film and Ocular Surface Society, for sharing his expertise in putting together global consensuses. An individual who contributed significantly to this paper wishes to remain anonymous and declined authorship or acknowledgment.

Supported by the International Myopia Institute. The publication costs of the International Myopia Institute reports were supported by donations from the Brien Holden Vision Institute, Carl Zeiss Vision, CooperVision, Essilor, Alcon, and Vision Impact Institute.

Disclosure: J.S. Wolffsohn, Alcon (F), Allergan (F), Aston EyeTech (F, I), Atiya Vision (C), Bausch & Lomb (F), BetterVision Ltd. (F), British Contact Lens Association (C), CooperVision (F, C), Eaglet Eye (F), European Union (F), Eyebag (F), EMPharma (F), EyeDocs (F), Gelflex (F), Innovate UK (F), Johnson & Johnson Vision Care (F, C, R), Lenstec (F), Medmont (F), Optimec (F), Rayner (F), RB (C), Santen (C, R), Shire (C), Tearlab (F), Théa (F), University of Houston (C), Visioncare Research (F, C), P; **D.I. Flitcroft**, None; **K.L. Gifford**, Myopia Profile Pty Ltd. (I), CooperVision (C), Menicon (C), Alcon (R), CooperVision (R), Menicon (R), Visioneering Technologies (R); **M. Jong**, None; **L. Jones**, Alcon (F, C, R), Allergan (F), Contamac (F), CooperVision (F, C, R), Essilor (F), GL Chemtec (F), Inflamax Research (F), J&J Vision (F, C, R), Menicon (F), Nature's Way (F), Novartis (F, C, R), Ophtecs (C, R), Safilens (F), Santen (F), Shire (F), SightGlass (F), TearLab (F), TearScience and Visioneering (F); **C.C.W. Klaver**, Topcon (F), Thea Pharma (C); **N.S. Logan**, CooperVision, Visioncare Research (F); **K. Naidoo**, None; **S. Resnikoff**, Brien Holden Vision Institute (C); **P. Sankaridurg**, Brien Holden Vision Institute (E), P; **E.L. Smith III**, Brien Holden Vision Institute (F), Tree House Eyes, SightGlass Vision (C), P; **D. Troilo**, Johnson & Johnson Vision (C), P; **C.F. Wildsoet**, P

IMI – Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiologic Studies

Disclosure: D.I. Flitcroft, None; **M. He**, None; **J.B. Jonas**, P; **M. Jong**, None; **K. Naidoo**, None; **K. Ohno-**

Matsui, Bayer (F), Japanese Society for Promotion of Science (F), Novartis (F), Santen (F), Senju (F); **J. Rahi**, None; **S. Resnikoff**, Brien Holden Vision Institute (C); **S. Vitale**, None; **L. Yannuzzi**, None

IMI – Report on Experimental Models of Emmetropization and Myopia

Disclosure: D. Troilo, Alcon (C), Essilor (C), Johnson & Johnson (C), P; **E.L. Smith III**, Brien Holden Vision Institute (F), SightGlass Vision (C), Tree House Eyes (C), P; **D. Nickla**, None; **R. Ashby**, P; **A. Tkatchenko**, P; **L.A. Ostrin**, None; **T.J. Gawne**, None; **M.T. Pardue**, None; **J.A. Summers**, P; **C. Kee**, None; **F. Schroedl**, None; **S. Wahl**, Carl Zeiss Vision International (E); **L. Jones**, Alcon (F, C, R), Allergan (F), Contamac (F), CooperVision (F, C, R), Essilor (F), GL Chemtec (F), Inflamax Research (F), Johnson & Johnson Vision (F, C, R), Menicon (F), Nature's Way (F), Novartis (F, C, R), Ophtecs (C, R), Safilens (F), Santen (F), Shire (F), SightGlass (F), TearLab (F), TearScience (F), Visioneering (F)

IMI – Myopia Genetics Report

M.S. Tedja, None; **A.E.G. Haarman**, None; **M.A. Meester-Smoor**, None; **J. Kaprio**, None; **D.A. Mackey**, None; **J.A. Guggenheim**, None; **C.J. Hammond**, None; **V.J.M. Verhoeven**, None; **C.C.W. Klaver**, Bayer (C), Novartis (C), Optos (C), Topcon (F), Thea Pharma (C)

IMI – Interventions for Controlling Myopia Onset and Progression Report

Disclosure: C.F. Wildsoet, P; **A. Chia**, None; **P. Cho**, None; **J.A. Guggenheim**, None; **J.R. Polling**, None; **S. Read**, Cylite Pty Ltd. (F), P; **P. Sankaridurg**, Brien Holden Vision Institute (E), P; **S.-M. Saw**, P; **K. Trier**, Theialife (I), P; **J.J. Walline**, Bausch & Lomb (F), SightGlass (C); **P.-C. Wu**, None; **J.S. Wolffsohn**, Alcon (F), Allergan (F), Aston EyeTech (F, I), Atiya Vision (C), Bausch & Lomb (F), BetterVision Ltd. (F), British Contact Lens Association (C), CooperVision (F, C), Eaglet Eye (F), European Union (F), Eyebag (F), EMPharma (F), EyeDocs (F), Gelflex (F), Innovate UK (F), Johnson & Johnson Vision Care (F, C, R), Lenstec (F), Medmont (F), Rayner (F), Santen (C, R), Shire (C), Tearlab (F), Théa (F), Optimec (F), University of Houston (C), Visioncare Research (F, C), P

IMI – Clinical Myopia Control Trials and Instrumentation Report

Disclosure: J.S. Wolffsohn, Alcon (F), Allergan (F), Aston EyeTech (F, I), Atiya Vision (C), Bausch & Lomb (F), BetterVision Ltd. (F), British Contact Lens Association (C), CooperVision (F, C), Eaglet Eye (F), European Union (F), Eyebag (F), EMPharma (F), EyeDocs (F), Gelflex (F), Innovate UK (F), Johnson & Johnson Vision Care (F, C, R), Lenstec (F), Medmont (F), Rayner (F), Santen (C, R), Shire (C), Tearlab (F), Théa (F), Optimec (F), University of Houston (C), Visioncare Research (F, C), P; **P.S. Kollbaum**, Alcon (F), Allergan (F), CooperVision (F, C, R), Johnson & Johnson Vision Care (F, R), Luminopia (F), P; **D.A. Bernsten**, Bausch & Lomb (F), Visioneering Technologies (C); D.A. Atchison, Carl Zeiss Vision (F), Cylite Optics (F), ForgetSpecs (F), P; **A. Benavente**, None; **A. Bradley**, CooperVision (F, C), Alcon (F, C), Vistakon (F, C), Allergan (F, C); **H. Buckhurst**, None; **M. Collins**, Johnson & Johnson Vision Care (F, C, R), Cylite (F), Johnson & Johnson Vision (F), P; **T. Fujikado**, Nidek (F), Topcon (F), Menicon (F), Hoya (F), P; **T. Hiraoka**, Johnson & Johnson Vision Care (F), Seed (F), Alpha Corporation (F), Menicon (R), Santen (R); **M. Hirota**, None; **D. Jones**, CooperVision (C), Shire (C), Alcon (C); **N.S. Logan**, CooperVision (F), Visioncare Research (F); **L. Lundström**, Abbott (F), Alcon (C), P; **H. Torii**, P, **S.A. Read**, Cylite Pty Ltd. (F), P; **K. Naidoo**, None

IMI – Industry Guidelines and Ethical Considerations for Myopia Control Report

Disclosure: L. Jones, Alcon (F, C, R), Allergan (F), Contamac (F), CooperVision (F, C, R), Essilor (F), GL Chemtec (F), Inflamax Research (F), Johnson & Johnson Vision (F, C, R), Menicon (F), Nature's Way (F), Novartis (F, C, R), Ophtecs (C, R), Safilens (F), Santen (F), Shire (F), SightGlass (F), TearLab (F), TearScience (F), Visioneering (F); **B. Drobe**, Essilor (E), P; **J.M. González-Méijome**, Alcon (F, C, R), Bausch & Lomb (C, R), CooperVision (F, C, R), Essilor (F), Johnson & Johnson Vision (F), Menicon (F), Paragon Vision Science (F), Procornea (F, C, R); **L. Gray**, None; **T. Kratzer**, Carl Zeiss Vision GmbH (E), P; **S. Newman**, Menicon Co. Pty Ltd. (E), P; **J.J. Nichols**, Alcon, (C, R), Bruder Healthcare (F, C), Allergan (F, C), Kala Pharmaceuticals (F, C), Olympic Ophthalmics (C), Shire (C), Johnson & Johnson Vision Care (F), Sun Pharmaceuticals (C), ScienceBased Health (C), Oyster Point (C), Sight

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IMI – Clinical Management Guidelines Report

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APPENDIX 1

TABLE A1. Consolidated Acronymn/Abbreviation List for IMI – Reports

Abbreviation	Definition
7-MX	7-Methylxanthine
AC/A	Accommodative convergence to accommodation
ACES	Anyang Childhood Eye Study
Add	Bifocal addition
ADTN	(+/–)-2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene
AF	Retinal autofluorescence
AL	Axial length
ALSPAC	Avon Longitudinal Study of Parents and Children
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
APLP2	Amyloid-like protein-2
AREDS	Age-Related Eye Disease Study
ATOM	Atropine in the treatment of myopia
atRA	All-trans-retinoic acid
b	Regression coefficient
BAK	Benzalkonium chloride
BF	Bifocal
BHVI	Brien Holden Vision Institute
BMES	Blue Mountain Eye Study
BMP	Bone morphogenic protein
BS	British standard
C	Control group
CA	repeats Cytosine-adenine repeats
cAMP	Cyclic adenosine monophosphate
CCL	Collagen cross-linking
CE	Conformité Européenne
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
CLEERE	Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error
CNV	Choroidal neovascularization
COI	Conflict of interest
COMET	Correction of Myopia Evaluation Trial
CPD	Continuing professional development
CREAM	Consortium for Refractive Error and Myopia
D	Dioptres
DA	Dopamine
DFP	Diisopropylfluorophosphate
ECM	Extracellular matrix
ECP	Eye care practitioners
EN	European standard
eNOS	Endothelial nitric oxide synthase
ENSLI	Enkephalin-, neurotensin-, and somatostatin-like immunoreactive amacrine cells
EOM	Early onset myopia
Eso	Esophoria
EU	European Union
FA	Fluorescein angiography
FC	Full correction
FDA	Food and Drug Administration
FDM	Form deprivation myopia
FGF	Fibroblast growth factor
FRD	Foveal RD
FU	Follow-up
GABA	Gamma-amminobutyric acid
GAG	Glycosaminoglycan
GCP	Good clinical practice
GCTA	Genome-wide complex trait analysis
GEWIS	Genome-environment-wide interaction studies
GLP	Good laboratory practice
GLP-1	Glucagon-like peptide-1
GMP	Good manufacturing practice
GOAL	Guangzhou Outdoor Activity Longitudinal Study
GP	Gas permeable rigid contact lens
GRS	Genetic risk score
GWAS	Genome Wide Association Studies
GxE	Gene-environment interaction
HCP	Healthcare professional
HM-PRO	High myopia-partial reduction orthokeratology
HOA	Higher-order aberrations
Hrs	Hours
ICD	International Classification of Disease
ICG	Indocyanine green angiography
IOP	Intraocular pressure
IRB	Institutional review board
ISO	International Organization for Standardization
KORA	Cooperative Health Research in the Region Augsburg
LCA	Longitudinal chromatic aberration
L-DOPA	Levodopa (L-3,4 dihydroxyphenylalanine)
LED	Llight emitting diode
LIH	Lens induced hyperopia
LIM	Lens induced myopia

Abbreviation	Definition
L-NAME	N omega-nitro-L-arginine methyl ester (NOS inhibitor)
L-NIO	N5-(1-Iminoethyl)-L-ornithine (NOS inhibitor)
L-NMMA	NG-methyl-L-arginine acetate (NOS inhibitor)
LogMAR	Logarithm minimum angle of resolution
LOM	Late onset myopia
LORIC	Longitudinal orthokeratology research in children
MC	Myopia control
META-PM	Meta-Analysis for Pathologic Myopia Study Group
MF	Multifocal
MFSCL	Multifocal soft contact lens
MM	Myopic maculopathy
mm	Millimetres
MMD	Myopic macular degeneration
MMP	Matrix metalloprotease
MR	Mendelian randomization
MRI	Magnetic resonance image
MT	Muscarinic toxin
MTF	Modulation transfer function
MX	Methylxanthine
NA	Not applicable
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NOS	Nitric oxidase synthase
NP	Not provided
N-PLA	Nω-propyl-L-arginine (NOS inhibitor)
OCT	Ocular coherence tomography
OK	Orthokeratology
OLSM	Orinda Longitudinal Study of Myopia
OMIM	Online Mendelian Inheritance in Man database
OR	Odds ratio
PAL	Progressive addition spectacle lenses
PA-PAL	Peripheral aspherized, progressive addition spectacle
PG	Proteoglycan
PMA	Premarket approval
PMDA	Pharmaceuticals and Medical Devices Agency
PPG	Pre-proglucagon
PR	Partial reduction
PRO	Patient reported outcomes
PSR	Posterior scleral reinforcement

Abbreviation	Definition
QOL	Quality of life
QTL	Quantitative trait locus
r	Correlation coefficient
RA	Retinoic acid
RAAB	Rapid assessment of avoidable blindness
RALDH2	Retinaldehyde dehydrogenase 2
RAR	Retinoic acid receptor
RCT	Randomized clinical trial/Randomized controlled trial
RCUK	Research Council of the United Kingdom
ROC	Recess outside the classroom
ROMIO	Retardation of myopia in orthokeratology
RPE	Retinal pigment epithelium
SAVES	Sydney Adolescent Vascular and Eye Study
SCL	Soft contact lenses
SCN	Suprachiasmatic nucleus
SCORM	Singapore Cohort Study of Risk Factors for Myopia
SER	Spherical equivalent refraction
SMS	Sydney Myopia Study
SNP	Single nucleotide polymorphism
Specs	Spectacles
SSGAC	Social Science Genetic Association Consortium
SSI	Injection-based scleral strengthening
STARS	Strabismus, Amblyopia and Refractive Error Study in Young Singaporean Children
SV	Single vision
TGF	Transforming growth factor
TIMP	Tissue inhibitor of metalloprotease
TO-SEE	Toric orthokeratology slowing eye elongation
UC	Under-corrected
UK	United Kingdom
USA	United States
UV	Ultraviolet
VEGF	Vascular endothelial growth factor
VIP	Vasoactive intestinal peptide
WES	Whole-exome sequencing
WGS	Whole-genome sequencing
WHO	World Health Organization
Yr	Year/years
ΔBF	Bifocal with base-in prism

APPENDIX 2

The following tables are from ***IMI – Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiologic Studies***

https://iovs.arvojournals.org/article.aspx?articleid=2727312

TABLE 2. Summary of Proposed General and Quantitative Thresholds for Myopia

Term	Definition
Qualitative definitions	
Myopia	A refractive error in which rays of light entering the eye parallel to the optic axis are brought to a focus in front of the retina when ocular accommodation is relaxed. This usually results from the eyeball being too long from front to back, but can be caused by an overly curved cornea and/or a lens with increased optical power. It also is called nearsightedness.
Axial myopia	A myopic refractive state primarily resulting from a greater than normal axial length.
Refractive myopia	A myopic refractive state that can be attributed to changes in the structure or location of the image forming structures of the eye, i.e. the cornea and lens.
Secondary myopia	A myopic refractive state for which a single, specific cause (e.g., drug, corneal disease or systemic clinical syndrome) can be identified that is not a recognized population risk factor for myopia development.
Quantitative definitions	
Myopia	A condition in which the spherical equivalent refractive error of an eye is ≤ −0.50 D when ocular accommodation is relaxed.
Low myopia	A condition in which the spherical equivalent refractive error of an eye is ≤ −0.50 D and > −6.00 D when ocular accommodation is relaxed.
High myopia	A condition in which the spherical equivalent refractive error of an eye is ≤ −6.00 D when ocular accommodation is relaxed.
Pre-myopia	A refractive state of an eye of ≤ +0.75 D and > −0.50 D in children where a combination of baseline refraction, age, and other quantifiable risk factors provide a sufficient likelihood of the future development of myopia to merit preventative interventions.

TABLE 3. Definitions for the Structural Complications of Myopia

Term	Definition
Descriptive definitions	
Pathologic myopia	Excessive axial elongation associated with myopia that leads to structural changes in the posterior segment of the eye (including posterior staphyloma, myopic maculopathy, and high myopia-associated optic neuropathy) and that can lead to loss of best-corrected visual acuity.
Myopic macular degeneration (MMD)	A vision-threatening condition occurring in people with myopia, usually high myopia that comprises diffuse or patchy macular atrophy with or without lacquer cracks, macular Bruch's membrane defects, CNV and Fuchs spot.
Diagnostic subdivisions of MMD	
Myopic maculopathy	Category 0: no myopic retinal degenerative lesion. Category 1: tessellated fundus. Category 2: diffuse chorioretinal atrophy. Category 3: patchy chorioretinal atrophy. Category 4: macular atrophy. "Plus" features (can be applied to any category): lacquer cracks, myopic choroidal neovascularization, and Fuchs spot.
Presumed myopic macular degeneration	A person who has vision impairment and vision acuity that is not improved by pinhole, which cannot be attributed to other causes, and: • The direct ophthalmoscopy records a supplementary lens < −5.00 D and shows changes such as "patchy atrophy" in the retina or, • The direct ophthalmoscopy records a supplementary lens < −10.00 D.
Specific clinical conditions characteristic of pathologic myopia	
Myopic traction maculopathy (MTM)	A combination of macular retinoschisis, lamellar macula hole and/or foveal retinal detachment (FRD) in eyes with high myopic attributable to traction forces arising from adherent vitreous cortex, epiretinal membrane, internal limiting membrane, retinal vessels, and posterior staphyloma.
Myopia-associated glaucoma-like optic neuropathy	Optic neuropathy characterized by a loss of neuroretinal rim and enlargement of the optic cup, occurring in eyes with high myopia eyes with a secondary macrodisc or peripapillary delta zone at a normal IOP

The following tables are from ***IMI – Interventions for Controlling Myopia Onset and Progression Report***
https://iovs.arvojournals.org/article.aspx?articleid=2727315

Table 1. A summary of results from previous spectacle myopia control studies reported in the peer-reviewed literature.

Study (Country)	Sample Size [Age Range, y]	Control	Study Design [Duration, y]	% Loss to Follow-Up	% Slowing Myopia Progression	% Slowing Axial Elongation	Baseline Age, y	Myopia Range, D	Average Myopia, D
Undercorrection									
Li et al., 2015[13] (China)	253 [10-16]	FC specs	Non-randomized, observational [1]	NA	5.8	0	FC: 12.7 ± 0.4 UC: 12.7 ± 0.5	NP	FC: −3.75 ± 1.23 UC: −3.12 ± 1.29
Adler & Millodot, 2006[12] (UK)	48 [6-15]	FC specs	Randomized [1.5]	22.5	Worse with UC: 20.7	NC	FC: 10.2 ± 2.2 UC: 9.9 ± 2.7	FC: 1.06 to −4.50 UC: −1.37 to −5.30	FC: −2.82 ± 1.06 −2.95 ± 1.25
Chung et al., 2002[10] (Malaysia)	94 [9-14]	FC specs	Randomized [2]	NP	Worse with UC: 29.8	NP	FC: 11.5 ± 1.5 UC: 11.6 ± 1.5	Greater than −0.50	FC: −2.68 ± 1.17 −2.68 ± 1.41
Koomson et al., 2016[11] (Ghana)	150 [10-15]	FC specs	Randomized [2]	0.6	7.4	12.5	FC: 12.4 ± 1.2 UC: 12.4 ± 1.4	−1.25 to −4.00	FC: −1.96 ± 0.57 −2.02 ± 0.54
Bifocals									
Fulk et al., 2000[15] (USA)	82 [6-13]	SV specs	Randomized [2.5]	8.5	20.2	18.4	BF: 10.7 ± 1.3 SV: 10.8 ± 1.4	Greater than −0.50 and near point Esophoria	BF: −2.12 ± 1.16 −2.52 ± 1.40
Goss et al., 1986[16] (USA)	112 NP	SV specs	Non-randomized [NP]	NA	15.9	NA	NP	NP	NP
Pärssinen et al., 1989[17] (Finland)	240 [9-11]	SV specs-distant SV specs-continuous	Randomized [variable]	NP	20.2 vs. SV* 8.2 worse vs. SV cont*	NA	SV Distant: 10.9 SV Cont: 10.9 BF: 10.9	NP	SV Distant: LE: −1.3 SV Cont: LE: −1.5 BF: LE: −1.5
Grosvenor et al., 1987[18] (USA)	207 [6-15]	SV specs	Randomized [3]	40.1	+1.00 Add: worse 5.8 +2.00 Add: 5.8	N/A	NP	Greater than −0.25	NP
Cheng et al., 2014[26] (Canada)	135 [8-13]	SV specs	Randomised [3]	5.2	ΔBF: 51.0 BF: 39.3	ΔBF: 34.1 BF: 30.5	ΔBF: 10.4 ± 0.3 BF: 10.1 ± 0.3 SV: 10.3 ± 0.3	−1.00 or more with ≥ 0.5D progression in preceding year	ΔBF: −3.27 ± 0.16 BF: −3.03 ± 0.16 SV: −2.92 ± 0.19
Progressive Addition Spectacles									
Leung et al., 1999[19] (Hong Kong)	80 [9-12]	SV specs	Non-randomized [2]	15.0	PAL +1.50: 38.2 PAL +2.00: 46.3	PAL + 1.50: 33.7 PAL + 2.00: 44.5	PAL +1.50: 10.5 PAL +2.00: 10.2 SV: 10.4	−1.00 to −5.00	PAL +1.50: −3.73 ± 1.13 PAL +2.00: −3.67 ± 0.97 SV: −3.67 ± 1.15

Study (Country)	Sample Size [Age Range, y]	Control	Study Design [Duration, y]	% Loss to Follow-Up	% Slowing Myopia Progression	% Slowing Axial Elongation	Baseline Age, y	Myopia Range, D	Average Myopia, D
Progressive Addition Spectacles (Continued)									
Edwards et al., 2002[20] (Hong Kong)	298 [7-10.5]	SV specs	Randomized [2]	14.7	11.1	3.1	PAL: 9.2 SV: 8.9	−1.25 to −4.50	PAL: −2.82 ± 0.99 SV: −2.92 ± 0.99
Yang et al., 2009[21] (China)	178 [7-13]	SV specs	Randomized [2]	16.3	17.3	15.7	All: 11.0 ± 1.6	−0.50 to −3.00	PAL: −1.60 ± 0.63 SV: −1.78 ± 0.68
Gwiazda et al., 2003[22] (USA)	469 [6-11]	SV specs	Randomized [3]	1.5	13.5	14.6	PAL: 9.3 ± 1.3 SV: 9.4 ± 1.3	−1.25 to −4.50	PAL: −2.40 ± 0.75 SV: −2.37 ± 0.84
Hasebe et al., 2008[23] (Japan)	92 [6-12]	SV specs	Randomized crossover [1.5]	7.0	25.8 (phase I)	NA	PAL: 10.0 SV: 9.7	−1.25 to −6.00	PAL: −3.17 SV: −3.31
COMET 2011[24] (USA)	118 [8-12]	SV Specs	Randomized [3]	7.0	24.3	NA	PAL: 10.2 ± 1.1 SV: 10.0 ± 1.1	−0.75 to −2.50	PAL: −1.50 ± 0.45 SV: −1.45 ± 0.47
Berntsen et al., 2012[25] (USA)	85 [6-11]	SV specs	Randomized [1]	1.1	34.6	28.5	PAL: 9.6 ± 1.2 SV: 10.1 ± 1.5	−0.75 to −4.50	PAL: −1.95 ± 0.64 SV: −2.04 ± 0.91
Peripheral defocus management									
Sankaridurg et al., 2010[27] (China)	210 [6-16]	SV specs	Randomized [1]	4.4	Type I: Worse 3.8 Type II: Worse 3.8 Type III: 15.4	Type I: 0 Type II: 2.8 3.8 Type III: 13.9	Type I: −10.7 ± 2.4 Type II: −11.1 ± 2.2 Type III: −11.4 ± 2.3 SV: 10.8 ± 2.5	−0.75 to −3.50; cyl ≤ 1.50	Type I: −1.82 ± 0.62 Type II: −1.81 ± 0.67 Type III: −1.82 ± 0.66 SV: −1.87 ± 0.68
Hasebe et al., 2014[28] (China / Japan)	197 [6-12]	SV specs	Randomized [2]	14.3	PA-PAL +1.0: 13.7 PA-PAL +1.5: 20	PA-PAL +1.0: 7.3 PA-PAL +1.5: 11.7	PA-PAL + 1.0: 10.6 ± 1.5 PA-PAL + 1.5: 10.0 ± 1.5 SV: 10.4 ± 1.2	−0.50 to −4.50	PA-PAL + 1.0: −2.52 ± 1.01 PA-PAL +1.5: −2.80 ± 1.02 SV: −2.61 ± 1.00

BF, bifocal; FC, full correction; NA, not applicable; NP, not provided; PA-PAL, peripheral aspherized PAL; Specs, spectacles; UC, undercorrection; NC, no change; cont, continuous wear.

* Left eye rather than average across both eyes compared.

Table 2. A summary of results from previous soft multifocal contact lens myopia control studies reported in the peer-reviewed literature and comparison of baseline variables to the BLINK Study.

Study (Country)	Sample Size [Age Range, y]	Control Treatment	Study Design [Duration, y]	% Loss to Follow-Up	% Slowing Myopia Progression	% Slowing Axial Elongation	Baseline Age, y	Myopia Range, D	Average Myopia, D
Anstice et al., 2011[48] (New Zealand)	70 [11-14]	Contact lens	Contralateral [0.8]	12.5	36.2	50.0	Unknown	−1.25 to −4.50	−2.71 ± 1.10
Sankaridurg et al., 2011[53] (China)	82 [7-14]	Spectacles	Prospective [1]	18.0	35.7	38.5	MF: 11.6 ± 1.5 Spec: 10.8 ± 1.9	−0.75 to −3.50	MF: −2.24 ± 0.79 Spec: −1.99 ± 0.62
Walline et al., 2013[54] (USA)	54 [8-11]	Contact lens	Historical Control [2]	19.4	50.5	29.3	MF: 10.8 ± 1.0 SV: 10.8 ± 0.7	−1.00 to −6.00	MF: −2.24 ± 1.02 SV: −2.35± 1.05
Fujikado et al., 2014[50] (Japan)	24 [10-16]	Contact lens	Randomized crossover [1]	0	26.2	25.0	MF: 14.3 ± 1.3 SV: 13.1 ± 1.9	−0.75 to −3.50	MF: −2.52 ± 1.69 SV: −3.61 ± 0.98
Lam et al., 2014[51] (Hong Kong)	128 [8-13]	Contact lens	Randomized [2]	42.1	25.3	32.4	MF: 11.1 ± 1.6 SV: 10.9 ± 1.7	−1.00 to −5.00	MF: −2.90 ± 1.05 SV: −2.08 ± 1.03
Paune et al., 2015[52] (Spain)	40 [9-16]	Spectacles	Prospective [2]	43.7	42.9	20	MF: 13.3 ± 2.0 SV: 13.1 ± 2.8	−0.75 to −7.00	MF: −2.44 ± 0.91 SV: −2.64 ± 1.1
Aller et al., 2016[47] (USA)	79 [8-18]	Contact lens	Randomized [1]	8.1	77.2	79.2	MF: 13.0 ± 2.5 SV: 13.5 ± 2.2	−0.50 to −6.00	MF: −2.57 ± 1.34 SV: −2.81 ± 1.46
Cheng et al., 2016[49] (USA)	109 [8-11]	Contact lens	Randomized [1]	14.2	20.6	38.9	MF: 9.7 ± 1.1 SV: 9.7 ± 1.1	−0.75 to −4.00	MF: −2.44 ± 0.91 SV: −2.52 ± 1.46
Ruiz-Pomeda et al., 2018[55] (Spain)	89 [8-13]	Spectacles	Randomized [2]	16.9	39.32	36.04	MF: 11.0 ± 1.2 Spec: 10.1 ± 1.3	−0.75 to −4.00	MF: −2.16 ± 0.94 Spec: −1.75 ± 0.94

BLINK, Bifocal Lenses in Nearsighted Kids; MF, multifocal contact lens; Spec, single-vision spectacle; SV, single-vision contact lens.

Table 3. Summary of results of published papers on orthokeratology for myopia control

Study (Country)	Sample Size [Age Range, y]	Control Treatment	Study Design [Duration, y]	Loss to Follow-Up, %	Axial Elongation, mm	Slowing in Axial Elongation, %	Baseline Age, y	Baseline Myopia [SER, D]
Cho et al., 2005[69] (Hong Kong)	43 [+35 historical controls] 7-12	SV specs	Historical control [2]	19.0	OK: 0.29 ± 0.27 C: 0.54 ± 0.27	46	OK: 9.6 ± 1.5 C: 9.6 ± 0.69	OK: [–2.27 ± 1.09] C: [–2.55 ± 0.98]
Walline et al., 2009[70] (United States)	40 [+28 historical controls] 8-11	SCL	Historical control [2]	30.0	OK: 0.25 ± 0.27 C: 0.57 ± 0.27	55	OK: 10.5 ± 1.1 C: 10.5 ± 1.0	Unknown
Kakita et al., 2011[74] (Japan)	105 8-16	SV specs	Non-randomized [2]	12.4	OK: 0.39 ± 0.27 C: 0.61 ± 0.24	36	OK: 12.1 ± 2.6 C: 11.9 ± 2.1	OK: [–2.55 ± 1.82] C: [–2.59 ± 1.66]
Hiraoka et al., 2012[75] (Japan)	59 ≤12	SV specs	Non-randomized [5]	27.1	OK: 0.99 ± 0.47 C: 1.41 ± 0.68	30	OK: 10.04 ± 1.43 C: 9.95 ± 1.59	OK: [–1.89 ± 0.82] C: [–1.83 ± 1.06]
Santodomingo et al., 2012[71] (Spain)	61 6-12	SV specs	Non-randomized [2]	13.1	OK: 0.47 C: 0.69	32	OK: 9.9 ± 1.6 C: 9.9 ± 1.9	OK: –2.15 ± 1.12 C: –2.08 ± 1.23
Cho and Cheung, 2012[72] (Hong Kong)	102 6-10	SV specs	Randomized [2]	23.5	OK: 0.36 ± 0.24 C: 0.63 ± 0.26	43	OK: 9.4 ± 1.4 C: 8.9 ± 1.6	OK: –2.05 ± 0.72 C: –2.23 ± 0.84
Chen et al., 2013[73] (Hong Kong)	80 6-12	SV specs	Non-randomized [2]	27.5	OK: 0.31 ± 0.27 C: 0.64 ± 0.31	52	OK: 9.4 ± 1.4 C: 8.9 ± 1.6	OK: –2.46 ± 1.32 C: –2.04 ± 1.09
Charm and Cho, 2013[89] (Hong Kong)	52 8-11	SV specs	Randomized [2]	46.2	OK: 0.19 ± 0.21 C: 0.51 ± 0.32	63	OK: Median 10, range 9.0 - 11.0 C: Median 10, range 8.0 - 11.0	OK: Median 6.50, range 6.0 - 8.30 C: Median 6.13, range 5.0 - 8.30
Swarbrick et al., 2015[61] (Australia)	32 8-16	GP	Contralateral eye Randomized crossover [1]	25	Phase 1 OK: −0.02 ± 0.05 C: 0.04 ± 0.06 Phase 2 OK: −0.04 ± 0.08 C: 0.09 ± 0.09	–	13.4 ± 1.9	Phase 1 OK: –2.43 ± 0.98 GP: –2.39 ± 0.93 Phase 2 OK: –2.60 ± 1.21 GP: –2.22 ± 1.10
Pauné et al., 2015[52] (Spain)	70 9-16	SV Specs	Non-randomized [2]	44.3	OK: 0.32 ± 0.20 C: 0.52 ± 0.22	38	OK: 12.27 ± 1.76 C: 13.09 ± 2.79	OK: [–3.51 ± 2.13] C: [–3.61 ± 0.98]

SCL, soft contact lenses; SER, spherical equivalent refraction; C, control group; GP, gas-permeable rigid contact lenses.

Table 4. Summary of design and key results from randomized trials involving topical atropine for myopia control.

Study (Country)	Size; Duration, y	Treatments	Age Range, y	Baseline Age, y*	Myopia Range, D	Average Myopia, D*	Change in SER*#	Change in AL, mm*#	Loss to follow-up, %
Yen et al., (1989)[113] (Taiwan)	247; 1	A 1% and Cyclo 1% vs. Saline	6, 14	10.5 10.0 10.4	−0.5, −4	−1.5 (0.9) −1.4 (0.8) −1.6 (0.9)	−0.2 D (76%) −0.6 D (37%) −0.9 D	–	61
Shih et al., (1999)[114] (Taiwan)	200; 2	A 0.5% A 0.25% A 0.1% vs. Trop 0.5%	6, 13	9.8 9.7 8.9 8.3	−0.5, −7	−4.9 (2.1) −4.2 (1.7) −4.1 (1.5) −4.5 (1.8)	−0.04 D/y (61%) −0.45 D/y (49%) −0.47 D/y (42%) −0.61 D/y	–	7
Chua et al., (2006)[118] (Singapore)	400; 2	A 1% vs. Placebo	6, 12	9.2 9.2	−1, −6	−3.6 (1.2) −3.4 (1.4)	−0.3 (0.9) (77%) −1.2 (0.7)	−0.02 (0.35) (105%) 0.38 (0.38)	13
Chia et al., (2016)[119] (Singapore)	400; 2	A 0.5% A 0.1% A 0.01%	6, 12	9.5 (1.5) 9.7 (1.6) 9.7 (1.5)	−2, −6	−4.5 (1.5) −4.8 (1.5) −4.7 (1.8)	−0.3 (0.6) (75%) −0.4 (0.6) (67%) −0.5 (0.6) (58%)	0.27 (0.25) 0.28 (0.28) 0.41 (0.32)	11
Wang et al., (2017)[121] (China)	126; 1	A 0.5% vs. Placebo	5, 10	9.1 (1.4) 8.7 (1.5)	−0.5, −2	−1.3 (0.4) −1.2 (0.3)	−0.8 (160%) −2.0	−1.1 (300%) +0.50	13
Yi et al., (2015)[120] (China)	140; 1	A 1% vs. Placebo	7, 12	9.9 (1.4) 9.7 (1.4)	−0.5, −2	−1.2 (0.3) −1.2 (0.3)	+0.3 (0.2) (138%) −0.9 (0.5)	−0.03 (0.07) (109%) 0.32 (0.15)	6
Yam et al., (2018)[122] (Hong Kong)	438; 1	A 0.05% A 0.025% A 0.01% vs. Placebo	4, 12	8.45 (1.81) 8.54 (1.71) 8.23 (1.83) 8.42 (1.72)	−1 (min)	−3.98 (1.69) −3.71 (1.85) −3.77 (1.85) −3.85 (1.95)	−0.27 (0.61) −0.46 (0.45) −0.59 (0.61) −0.81 (0.53)	0.20 (0.25) 0.29 (0.20) 0.36 (0.29) 0.41 (0.22)	12

Cyclo, cyclopentolate; min, minimum; Trop, tropicamide.
* Standard deviations in brackets.
# Percent change from placebo.

Table 6. Outdoor intervention studies for myopia prevention and progression

Author (Year), Study Location, Study Design	Type of Intervention	Age at Baseline, Refraction	Main Findings
He et al. (2015)[177] China, School-based, randomized clinical trial (GOAL study); *N* = 1848	Intervention group: One additional 40-minute class of outdoor activities on each school day. Control group: No additional class. 3-year RCT	6-7 y, Cycloplegic auto-refraction	Myopia incidence rate: Intervention group: 30.4%; Control group: 39.5%; Diff: −9.1 (95% CI, −14.1 to −4.1); *P*<0.001) after 3 y Myopia progression rates: Intervention group: −1.42 D (95% CI: −1.58 to −1.27 D); Control group: −1.59 D (95% CI, −1.76 to −1.43 D) Diff: 0.17 D (95% CI, 0.01 to 0.33D); *P*=0.04 after 3 yr Lost to follow-up: 4.7%
Jin et al., (2015)[178] China, school-based, prospective, interventional study; *N* = 3051	Intervention group: Two additional 20-minute Recess Outside the Classroom (ROC) programs, in the morning & afternoon. Control group: No program. 1-year RCT	6-14 y, Cycloplegic auto-refraction	Myopia incidence rate: Intervention group: 3.7%; Control group: 8.5%; Diff: 4.8% (*P*=0.048) after 1 year Myopia progression rate: Intervention group: −0.10 ± 0.65 D; Control group: −0.27 ± 0.52 D; Diff: 0.17 D (*P* = 0.005) after 1 year Lost to follow-up rate: 10.7%
Wu et al., (2013)[176] Taiwan, school-based, interventional trial; *N*=571	Intervention group: Two additional 40-min. Recess Outside the Classroom (ROC) programs, in the morning & afternoon. Control group: No program. 1-year RCT	7-11 y, Cycloplegic auto-refraction	Myopia incidence rate: Intervention group: 8.41%; Control group: 17.65%; Diff: 9.24% (*P*=0.001) after 1 year Myopia progression rate: Intervention group: −0.25 ± 0.68 D; Control group: −0.38 ± 0.69 D; Diff: 0.13 D (*P* = 0.029) after 1 y
Wu et al., (2018)[179] Taiwan, school-based interventional trial; N=693	Intervention group: 40-minute Recess Outside the Classroom (ROC) in morning and encouragement to undertake 4 additional outdoor leisure activity programs; in addition to 120 min./day outdoors during school hours ("Tien-Tien 120"), 150 min./week outdoor sports ("Sport & Health 150"). Control group: 120 min./day outdoors during school hours ("Tien-Tien 120"), 150 min./ week outdoor sports ("Sport and Health 150"). 1-year RCT	6-7 y, Cycloplegic auto-refraction	Myopia incidence: Intervention group: 14.5%; Control group: 17.4%; Diff: 2.9% (*P*=0.054) after 1 year Myopia progression: Intervention group: −0.35 ± 0.58 D; Control group: −0.47 ± 0.74 D; Diff: 0.12 D (95% CI, 0.05 to 0.19; *P*=0.002) after 1 year
GOAL, Guangzhou Outdoor Activity Longitudinal study; ROC, Recess Outside the Classroom; Diff, Difference.			

Table 7. Outdoor studies for myopia prevention and progression

Author (Year) Study Location, Study Design	Age at Baseline, Refraction	Main Findings
Prevention		
Jones et al. (2007)[154] USA (OLSM), cohort study; *N* = 514	8–9 y, cycloplegic auto-refraction	Time outdoors (h/wk) and incident myopia (SER ≤ −0.75 D): OR = 0.91 (0.87 to 0.95); *P* < 0.0001
Guggenheim et al. (2012)[172] UK, cohort study (ALSPAC); *N* = 7747	7 y, noncycloplegic auto-refraction	Time outdoors (h/wk) and incident myopia (SER ≤ −1.00 D): HR = 0.76 (95% CI 0.60–0.96); *P* = 0.02; Lost to follow-up: 37.6%
French et al. (2013)[164] Australia, (SAVES), cohort study; *N* = 2103; 5–6- y follow-up	6 and 12 y, cycloplegic auto-refraction	Time outdoors (h/wk) and incident myopia (SER ≤ −0.50 D): 12-y-olds: OR = 2.84 (95% CI 1.56–5.17) *P* < 0.0001; 17-y-olds: OR = 2.15 (95% CI 1.35–3.42); *P* = 0.001; Lost to follow-up: 51.6%
Mutti et al. (2002)[152] USA (OLSM), cross-sectional; *N* = 336	13–14 y, cycloplegic auto-refraction	Time outdoors (h/d) and myopia (*SER* ≤ −0.75D): OR = 0.92 (95% CI, 0.86 to 0.97); *P* = 0.005
Rose et al. (2008)[155] Australia (SMS), cross-sectional; *N* = 2339	6 and 12 y, cycloplegic auto-refraction	Time outdoors (h/d) and SER: 6-y-olds: β = 0.05; *P* = 0.009; 12-y-olds: β = 0.07; *P* < 0.0003
Dirani et al. (2009)[167] Singapore (SCORM), cross-sectional; *N* = 1249	11–20 y, cycloplegic auto-refraction	Time outdoors (h/d) and myopia (*SER* ≤ −0.50 D): OR = 0.90 (95% CI 0.84–0.96); *P* = 0.004
Low et al. (2010)[168] Singapore (STARS), cross-sectional; *N* = 3009	6–72 mo, cycloplegic auto-refraction	Time outdoors (h/d) and myopia (*SER* ≤ −0.50 D): OR = 0.95 (95% CI 0.85–1.07); *P* = 0.44
Guo et al. (2013)[169] China, crosssectional; *N* = 681	5–13 y, noncycloplegic auto-refraction	Time outdoors (h/d) and myopia (*SER* ≤ −1.00 D): OR = 0.32 (95% CI 0.21–0.48); *P* < 0.001
Progression		
Jones-Jordan et al. (2012)157 USA, cohort study (CLEERE); *N* = 835	6–14 y, cycloplegic auto-refraction	Time outdoors (h/wk) and SER change: β = 0.03 (99% CI −0.03 to 0.08); *P* > 0.01 for additional 10 h of outdoor time/wk
Li et al. (2015)174 China, cohort study; (ACES), *N* = 2267	10–15 y, cycloplegic auto-refraction	Time outdoors (h/d) and AL change: β = 0.036 (95% CI 0.063 to 0.009); *P* = 0.009; Lost to follow-up: 16.6%

ACES, Anyang Childhood Eye study; ALSPAC, Avon Longitudinal Study of Parents and Children; CLEERE, Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error study; HR, hazard ratio; OLSM, Orinda Longitudinal Study of Myopia; OR, odds ratio; SAVES, Sydney Adolescent Vascular and Eye Study; SCORM, Singapore Cohort study of Risk Factors for Myopia; SMS, Sydney Myopia Study; STARS, Strabismus, Amblyopia and Refractive error Study.

The following figures are from ***IMI – Clinical Management Guidelines Report***
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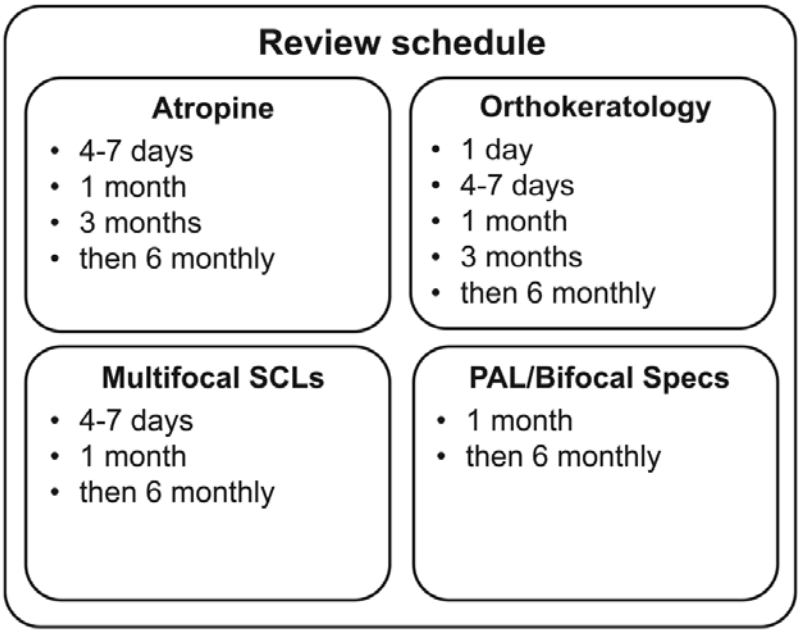

Figure 1. Review schedule for myopia management based on treatment type.

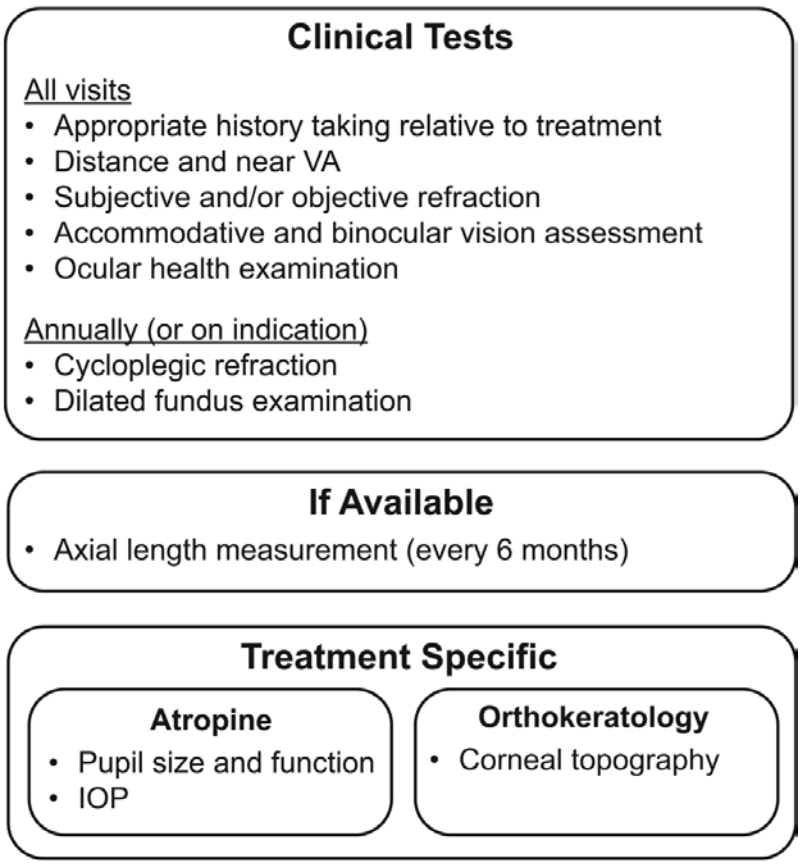

Figure 2. Clinical tests for myopia management.

This image shows some of the work of our committee members in myopia prevention programs in schools. Thank you to Professor Pei-Chang Wu for supplying this image.

Professors Ian Morgan, Kathy Rose and Pei-Chang Wu visiting a kindergarten in Gushan Elementary School, Kaohsiung, Chinese Taipei to promote a myopia prevention program (September 2015).

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