International Myopia Institute (IMI) Myopia Control Reports Overview and Introduction

James S. Wolffsohn, FCOptom PhD
   Ophthalmic Research Group, Aston University, Birmingham, UK

Daniel Ian Flitcroft MB.BS. D.Phil
   Children’s University Hospital, University College Dublin and Dublin Institute of Technology, Ireland

Kate L Gifford, BAppSc(Optom), PhD
   Private Practice and Queensland University of Technology, Australia

Monica Jong BOptom, PhD
   Brien Holden Vision Institute and School of Optometry and Vision Science, University of New South Wales, Sydney, NSW, Australia.

Lyndon Jones FCOptom, PhD, DSc
   Centre for Ocular Research & Education (CORE), School of Optometry & Vision Science, University of Waterloo, Waterloo, Canada.

Caroline C.W. Klaaver MD, PhD
   Department of Ophthalmology, Radboud University Medical Center, Nijmegen, The Netherlands

Nicola S. Logan, MCOptom PhD
   Ophthalmic Research Group, Aston University, Birmingham, UK

Kovin Naidoo OD, PhD
   African Vision Research Institute, Univ. of KwaZulu-Natal, Durban, South Africa

Serge Resnikoff MD, PhD
   Brien Holden Vision Institute and School of Optometry and Vision Science, University of New South Wales, Sydney, NSW, Australia.

Padmaja Sankaridurg BOptom, PhD
   Brien Holden Vision Institute and School of Optometry and Vision Science, University of New South Wales, Sydney, NSW, Australia

Earl L. Smith III, OD, PhD
   College of Optometry, University of Houston, Houston, TX, USA

David Troilo, PhD
   SUNY College of Optometry, State University of New York, New York, NY, USA

Christine F. Wildsoet DipAppSci (Optom), BSc (Hons Pharm), PhD
   Berkeley Myopia Research Group, School of Optometry & Vision Science Program, University of California Berkeley, Berkeley, CA, USA

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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 reports the critical review and synthesis of the research evidence to-date, from animal models, genetics, clinical studies and randomized controlled trials, by over 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: Defining and Classifying Myopia; Experimental Models of Emmetropization and Myopia; Myopia Genetics; Interventions for Myopia Onset and Progression; Clinical Myopia Control Trials and Instrumentation; Industry Guidelines and Ethical Considerations for Myopia Control; Clinical Myopia Management Guidelines.
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 randomised controlled trials to have been conducted at that time. This report concluded that bifocal spectacle lenses and soft contact lenses were not recommended for slowing the progression of myopia in children, nor was the routine use of atropine eye drops.\(^1\) Since that time, over 170 peer-reviewed articles on myopia control have been published, making it difficult for the clinician 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, the vast majority 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, and, validated by well-designed and ethically applied clinical trials. The International Myopia Institute (IMI) reports represent the work of over 85 multidisciplinary experts in the field, who set out to critically review, synthesise and summarize the research evidence to-date, (Table 1), and serve to inform both clinical practice and future research.

Table 1: IMI report Subcommittee Members

**IMI –Defining and Classifying Myopia**

Daniel Ian Flitcroft MB.BS. D.Phil

*Children’s University Hospital, University College Dublin and Dublin Institute of Technology, Ireland*

Mingguang He MD PhD

*Centre for Eye Research Australia; Ophthalmology, Department of Surgery, University of Melbourne, Melbourne, Australia*

Jost B. Jonas MD
Department of Ophthalmology, Medical Faculty Mannheim of the Ruprecht-Karis-University Heidelberg, Mannheim, Germany

Monica Jong PhD

Brien Holden Vision Institute and School of Optometry and Vision Science, University of New South Wales, Sydney, NSW, Australia.

Kovin Naidoo OD, PhD

African Vision Research Institute, Univ. of KwaZulu-Natal, Durban, South Africa

Kyoko Ohno-Matsui, MD, PhD

Tokyo Medical and Dental University, Japan.

Jugnno Rahi, MB BS PhD

Institute of Child Health, University College London and Great Ormond Street Hospital for Children, London, UK

Serge Resnikoff MD, PhD

Brien Holden Vision Institute and School of Optometry and Vision Science, University of New South Wales, Sydney, NSW, Australia.

Susan Vitale PhD, MHS

National Eye Institute, National Institutes of Health, Bethesda, MD, USA

Lawrence Yannuzzi MD

The Vitreous, Retina, Macula Consultants of New York and the LuEsther T. Mertz Retina Research Center, Manhattan Eye, Ear, and Throat Hospital, New York, USA.

IMI –Experimental Models of Emmetropization and Myopia

David Troilo, PhD

SUNY College of Optometry, State University of New York, New York, NY, USA

Earl L. Smith III, OD, PhD

College of Optometry, University of Houston, Houston, TX, USA

Debora Nickla, PhD

Biomedical Sciences and Disease, New England College of Optometry, Boston, MA, USA

Regan Ashby, PhD

University of Canberra, Health Research Institute, Canberra, Australia

Andrei Tkatchenko, MD, PhD

Department of Ophthalmology, Columbia University, New York, NY, USA

Lisa A. Ostrin, OD, PhD

College of Optometry, University of Houston, Houston, TX, USA
Tim J. Gawne, PhD
College of Optometry, University of Alabama Birmingham, Birmingham, AL, USA

Machelle T. Pardue, PhD
Biomedical Engineering, Georgia Tech College of Engineering, Atlanta, GA, USA

Jody A. Summers, PhD
College of Medicine, University of Oklahoma, Oklahoma City, OK, USA

Chea-su Kee, BSc Optom, PhD
School of Optometry, The Hong Kong Polytechnic University, Hong Kong, SAR, China

Falk Schroedl, MD
Department of Ophthalmology and Anatomy, Paracelsus Medical University, Salzburg, Austria

Siegfried Wahl, PhD
Institute for Ophthalmic Research, University of Tuebingen, Zeiss Vision Science Laboratory, Tuebingen, Germany

Lyndon Jones, PhD, DSc, FCOptom
Centre for Ocular Research & Education (CORE), School of Optometry & Vision Science, University of Waterloo, Waterloo, Canada.

**IMI – Myopia Genetics**

Milly S. Tedja MD
Department of Ophthalmology / Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands

Annechien E.G. Haarman MD
Department of Ophthalmology / Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands

CREAM Consortium
Magda A. Meester-Smoor PhD
Department of Ophthalmology / Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands

Jaakko Kaprio MD, PhD
Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland.

David A. Mackey MD, PhD
Jeremy Guggenheim MCOptom, PhD
School of Optometry & Vision Sciences, Cardiff University, Cardiff, UK.

Christopher J. Hammond MD, PhD
Section of Academic Ophthalmology, School of Life Course Sciences, King’s College London, London, UK

Virginie J.M. Verhoeven MD, PhD
Department of Ophthalmology / Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands

Caroline C.W. Klaver MD, PhD
Department of Ophthalmology, Radboud University Medical Center, Nijmegen, The Netherlands

IMI – Interventions for Myopia Onset and Progression
Christine F. Wildsoet DipAppSci (Optom), BSci (Hons Pharm), PhD
Berkeley Myopia Research Group, School of Optometry & Vision Science Program, University of California Berkeley, Berkeley, CA, USA

Audrey Chia Wei Lin FRANZCO, PhD
Singapore Eye Research Institute & Singapore National Eye Center, Singapore.

Pauline Cho BOptom, PhD
School of Optometry, The Hong Kong Polytechnic University, Hong Kong

Jeremy A. Guggenheim MCOptom, PhD
School of Optometry & Vision Sciences, Cardiff University, Cardiff, UK

Jan Roelof Polling BoH
Erasmus MC Dept. Ophthalmology, Rotterdam, Netherlands

Scott Read BAAppSci Optom (Hons), PhD
School of Optometry & Vision Science and Institute of Health & Biomedical Innovation, Queensland University of Technology, Brisbane, Australia

Padmaja Sankaridurg BOptom, PhD
Brien Holden Vision Institute & School of Optometry and Vision Science, University of New South Wales, Sydney, Australia

Seang-Mei Saw MPH, PhD
Saw Swee Hock School of Public Health, National University of Singapore, Singapore

Klaus Trier MD
Trier Research Laboratories, Tingskiftevej 6, DK-2900 Hellerup, Denmark

Jeff J. Walline OD, PhD
The Ohio State University College of Optometry, Columbus, OH, USA

Pei-Chang Wu MD, PhD
Department of Ophthalmology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

James S. Wolffsohn, FCOptom PhD
Ophthalmic Research Group, Aston University, Birmingham, UK

IMI - Clinical Myopia Control Trials and Instrumentation
James S. Wolffsohn, FCOptom PhD
Ophthalmic Research Group, Aston University, Birmingham, UK

Pete S. Kollbaum, OD, PhD
Indiana University, School of Optometry, Bloomington, Indiana, USA

David A. Berntsen, OD PhD
The Ocular Surface Institute, College of Optometry, University of Houston, Houston, Texas, USA

David A. Atchison DSc
School of Optometry & Vision Science and Institute of Health & Biomedical Innovation, Queensland University of Technology, Australia

Alexandra Benavente MCOptom PhD
SUNY College of Optometry, New York, NY, USA.

Arthur Bradley, PhD
Indiana University, School of Optometry, Bloomington, Indiana, USA

Hetal Buckhurst MCOptom PhD
School of Health Professions, Peninsula Allied Health Centre, Plymouth University, Plymouth, UK

Michael Collins Dip App Sc (Optom) PhD
Queensland University of Technology, Australia
IMI – Industry Guidelines and Ethical Considerations for Myopia Control

Lyndon Jones, PhD, DSc, FCOptom

Centre for Ocular Research & Education (CORE), School of Optometry & Vision Science, University of Waterloo, Waterloo, Canada.

Björn Drobe, MSc, PhD

Essilor R&D, Vision Sciences AMERA, Center of Innovation and Technology AMERA, Singapore, Singapore.
José Manuel González-Méijome, OD, PhD  
*Clinical & Experimental Optometry Research Lab, Center of Physics (Optometry), School of Science, University of Minho, Braga, Portugal.*

Lyle Gray PhD, BSc, Dip Optom  
*Department of Vision Sciences, Glasgow Caledonian University, Glasgow, UK.*

Timo Kratzer, Dipl. Phys  
*Carl Zeiss Vision International GmbH, Turnstraße 27, Aalen, 73430, Germany.*

Steve Newman  
*Menicon Company Limited, Nagoya, Japan.*

Jason J Nichols, OD, MPH, PhD  
*University of Alabama at Birmingham, School of Optometry, Birmingham, AL, USA.*

Arne Ohlendorf, PhD  
*Carl Zeiss Vision International GmbH, Turnstraße 27, Aalen, 73430, Germany.*

Stephanie Ramdass, OD, MS  
*Vision Research Institute, Michigan College of Optometry, Ferris State University, Big Rapids, Michigan, USA.*

Jacinto Santodomingo-Rubido, MSc, PhD  
*Menicon Company Limited, Nagoya, Japan.*

Katrina L Schmid, PhD  
*School of Optometry and Vision Science, Institute of Health and Biomedical Innovation, Faculty of Health, Queensland University of Technology, Brisbane, Australia.*

Donald Tan, FRCS  
*Ophthalmology and Visual Sciences Academic Clinical Program, Duke-National University of Singapore Medical School, Singapore Eye Research Institute, Singapore National Eye Centre.*

Kah-Ooi Tan, MBA, PhD  
*Brien Holden Vision Institute, Sydney, Australia.*

Fuensanta A. Vera-Diaz, OD, PhD  
*New England College of Optometry, Boston MA USA.*

Yee-Ling Wong, BSc  
*Essilor R&D, Vision Sciences AMERA, Center of Innovation and Technology AMERA, Singapore, Singapore.*

Kate L Gifford, BAppSc(Optom), PhD  
*Private Practice and Queensland University of Technology, Australia*

Serge Resnikoff MD, PhD
IMI – Clinical Myopia Management Guidelines

Kate L Gifford, BAppSc(Optom), PhD
  Private Practice and Queensland University of Technology, Australia

Kathryn Richdale, OD, PhD
  University of Houston, USA

Pauline Kang, BOptom, PhD
  University of New South Wales, Australia

Thomas A Aller, OD
  Private Practice and University of California, Berkeley, USA

Carly S Lam, BSc, PhD
  Hong Kong Polytechnic University, Hong Kong

Y Maria Liu, OD, PhD
  University of California, Berkeley, USA

Langis Michaud, OD, MSc
  University of Montreal, Canada

Jeroen Mulder, BOptom, MSc
  University of Applied Sciences Utrecht, Netherlands

Janis B Orr, BSc, PhD
  Aston University, Birmingham, UK

Kathryn A Rose, PhD
  University of Technology Sydney, Australia

Kathryn J Saunders, FCOptom, PhD
  Ulster University, Londonderry, UK

Dirk Seidel, PhD
  Glasgow Caledonian University, Glasgow, UK

J Willem Tideman, MD, PhD
  Erasmus Medical Centre, Rotterdam, Netherlands

Padmaja Sankaridurg BOptom, PhD
  Brien Holden Vision Institute & School of Optometry and Vision Science, University of New South Wales, Sydney, Australia
2 The IMI Report Generation Process

As highlighted in the accompanying editorial, the foundation of the IMI was an outcome of the WHO-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 behavioural / environmental) and the other on Definitions and Classification of Myopia (high myopia, pathologic myopia and myopic macular degeneration). An IMI steering and 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 and potential chairs approached.

In developing this set of reports, the IMI has collaborated closely with the past and present organisers 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 myopia-related activities, including researchers, academics, practitioners, policy makers, industry representatives and students. The IMC started over 50 years ago, however it was Dr. Sek Jin Chew in collaboration with Professor Josh Wallman
who were instrumental in reviving the conference in 1990. The site hosting organization and organizing committee change for each meeting, thus ensuring diversity at many levels.

**Table 2:** Past International Myopia Conferences

<table>
<thead>
<tr>
<th>Meeting</th>
<th>Location</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st*</td>
<td>New York, USA</td>
<td>1964</td>
</tr>
<tr>
<td>2nd**</td>
<td>Yokohama, Japan</td>
<td>1978</td>
</tr>
<tr>
<td>3rd**</td>
<td>Copenhagen, Netherlands</td>
<td>1980</td>
</tr>
<tr>
<td>2nd*</td>
<td>San Francisco, USA</td>
<td>1984</td>
</tr>
<tr>
<td>3rd*</td>
<td>Rome, Italy</td>
<td>1986</td>
</tr>
<tr>
<td>4th</td>
<td>Singapore</td>
<td>1990</td>
</tr>
<tr>
<td>5th</td>
<td>Toronto, Canada</td>
<td>1994</td>
</tr>
<tr>
<td>6th</td>
<td>Hakone, Japan</td>
<td>1996</td>
</tr>
<tr>
<td>7th</td>
<td>Taipei, Taiwan</td>
<td>1998</td>
</tr>
<tr>
<td>8th</td>
<td>Boston, Massachusetts, USA</td>
<td>2000</td>
</tr>
<tr>
<td>9th</td>
<td>Hong Kong, Guangzhou</td>
<td>2002</td>
</tr>
<tr>
<td>10th</td>
<td>Cambridge, UK</td>
<td>2004</td>
</tr>
<tr>
<td>11th</td>
<td>Singapore</td>
<td>2006</td>
</tr>
<tr>
<td>12th</td>
<td>Cairns, Australia</td>
<td>2008</td>
</tr>
<tr>
<td>13th</td>
<td>Tübingen, Germany</td>
<td>2010</td>
</tr>
<tr>
<td>14th</td>
<td>Asilomar, California, USA</td>
<td>2013</td>
</tr>
<tr>
<td>15th</td>
<td>Wenzhou, China</td>
<td>2015</td>
</tr>
<tr>
<td>16th</td>
<td>Birmingham, UK</td>
<td>2017</td>
</tr>
</tbody>
</table>

*Organized by the Myopia International Research Foundation.

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

Chew and Wallman re-established the IMC meetings using local organizing committees beginning in 1990, adopting the numbering based on the original MIRF 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; Ohno-Matsui Kyoko; Kovic 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, UK in September 2017 and the report committee membership was expanded based on further interest and feedback. The report committees also met to finalise 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 and Visual Science (IOVS).

By early 2018, the draft report was put together from the contributions of each committee and authorship was determined based on 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 counties) for review by July. At ARVO in May 2018 the IMI steering committee received reports from each of the committee chairs. Reviewer’s 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 due 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 harmoniser to each report (see Table 3) was then responsible for ensuring the reviewers comments had been adequately addressed, that overlap between the reports was minimised (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 e-mail 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.

**Table 3:** Report committees, chairs and harmonizers.

<table>
<thead>
<tr>
<th>Report Subcommittee</th>
<th>Chair(s)</th>
<th>Harmonizer(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defining and Classifying Myopia</td>
<td>Ian Flitcroft</td>
<td>Earl Smith</td>
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</tr>
</tbody>
</table>
3 Background to the need for myopia control

3.1 Refractive development
From birth, eye growth continues and refractive state normally undergoes a gradual shifts towards emmetropia. In the first 6 months of life, human newborns typically have a variable but low hyperopic, cycloplegic refractive error with mean of about +2.00D (± SD 2.75D), which shows a normal distribution in the population.\(^3\)\(^-\)\(^6\) Emmetropization over the subsequent 6-12 months of age, leads to a reduction in hyperopia and the normal distribution of refractive error seen in neonates becomes more leptokurtotic as the eye matures.\(^7\) Over 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 +2.00D).\(^3\)\(^,\)\(^6\)\(^,\)\(^8\)\(^,\)\(^9\) 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.

3.2 Myopia onset
In children younger than 6 years of age 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 show a prevalence rate of myopia in the pre-6 year old age group to be less than 5%.\(^12\)\(^,\)\(^14\)\(^,\)\(^15\)\(^,\)\(^17\)\(^,\)\(^20\)\(^-\)\(^22\)

In certain populations, myopia has been found in more than 5% of children younger than 6 years of age, 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 reported that the prevalence of myopia in Hong Kong preschoolers (mean age 4.6 ± 0.9 years, range: 3 to 6 years) increased significantly from 2.3% to 6.3% over ten years.\(^23\)
The incidence of myopia increases dramatically in at-risk populations from about 6 years of age.\textsuperscript{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.\textsuperscript{10, 24, 25} The annual incidence of myopia onset is reasonably constant between the ages of about 7 and 15 years in Chinese populations and, by the age of 18, some 80\% of the urban-based Han population in China are myopic, regardless of geographic location.\textsuperscript{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.\textsuperscript{29-37} A systematic review and meta-analysis by Rudnicka et al reported an increase of 23\% in the prevalence of myopia over the last decade among East Asians.\textsuperscript{37}

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.\textsuperscript{37} Most of the myopia identified in one study in the UK was considered to be late onset (16 years or older).\textsuperscript{38} Figure 1 illustrates the marked difference in prevalence between East Asian and White children from the meta-analysis of Rudnicka et al.\textsuperscript{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.\textsuperscript{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 amount 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, that 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, 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.\(^46\) The analysis used data from 20 studies, 14 intervention trials and 6 longitudinal observation studies, to predict the progression of myopia and showed that among existing myopes, progression rate declines with increasing age. For example, according to the equation provided in the Donovan study, progression declined from 1.12D/yr at age 7 to 0.50D/yr at age 12 among Asian children.\(^46\)

The progression rates presented by Donovan et al arose 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 were progressing at a rapid rate 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, 4,662 myopic (≤ -0.5D) children with a mean age of 9.8 years showed 0.84D progression over 28.5 months, an average annual progression rate of 0.35D.\(^47\) The timing of the study and rural habitation of this population may explain some of the difference in myopic progression rate compared with the meta-data reported by Donovan et al. The average annual progression rate for a sample of over 7500 myopic children aged 5 to 16 (mean 9.3) years in Hong Kong was 0.63 D.\(^12\) Chua et al plotted annual changes in refractive error for 928 myopic Singaporean children of mixed ethnicity from age 7–11 years, stratified by age of myopia onset.\(^48\) Mean progression rate at a given age was
remarkably consistent across the groups, irrespective of age of onset. These mean progression rates are slightly slower than that reported by Donovan et al (see Figure 2).

In a large population-based study in Yongchuan District of Chongqing City, Western China, children aged 6-15 years in 2006-7 were followed for an average of 5.2 years. The authors reported mean progression of 3.56D (average of 0.68D/yr) among myopes (≤ -0.50D) 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. Kim and colleagues retrospectively analyzed refractive error progression among a population of 221 myopic South Korean children aged 3 to 9 over 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 0.50D/yr between ages of 7 and 13 was surprisingly modest. Hsu and coworkers reviewed a population-based cohort in Taiwan of 3256 myopic children of average age 7.5 years after one year and noted average progression in the group of only 0.42D, well below that predicted by Donovan et al. Some of these children were being treated with cycloplegics to slow myopia progression and all had been exposed to a large-scale eyecare education program, which may explain the lower progression rate. Most recently, Wu et al found annual progression of 0.79D among a school-based control population of 89 myopes aged 6 and 7 years old in Taiwan. This is also less than predicted by Donovan et al, but it should be noted that those in the sample population receiving myopia treatment were excluded from the analysis.
Figure 2: Refractive shift among myopic children by age (Data from Donovan et al\textsuperscript{46} were digitized using ImageJ and replotted, and the best fit line for Asians was taken from the equation provided in their paper. Data for Chua et al\textsuperscript{48} were obtained by averaging progression rates for given ages from their Figure 2). Further details of likely progression can be obtained from centile progression curves. Chen et al constructed reference age-specific centile curves of refraction from cross-sectional population-based data from the Guangzhou Refractive Error Study in Children (RESC).\textsuperscript{53} However, apparent progression among the myopes between ages of 7 and 12 is observed to be only about 0.5 to 0.6D/year, comparatively constant across ages and less again than that of Donovan et al, particularly at a younger age. The implications of these differences are not clear. Tideman et al have also produced age-specific centile curves for axial length.\textsuperscript{54} 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 -1.00D/year for 6 to 9-year olds) compared with older ages (i.e., 0.35 to 0.75D for over 10-year olds).

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, those progressing at an unacceptably fast rate. Few analyses are available on this topic, but the breakdown by Chua et al probably represents the most comprehensive data available.\textsuperscript{48} They found age of onset of myopia to be the strongest predictor of high myopia among Singaporean children.\textsuperscript{48} As expected, duration of myopia progression was also important in predicting high myopia. For children with high myopia at age 11, 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; UK) reliably reproduce this observation.\textsuperscript{55-57} However, in contrast to the report by Chua and
colleagues, Williams et al found that age of onset only accounted for a modest proportion (about 15%) of the variance in severity of myopia.  

3.5 Adult onset myopia and progression

Most of the myopia in one study in Britain was considered to be late onset (16 years or older). Although myopia onset past the adolescent stage of life is of clinical interest and has shown an association with environmental factors, eye care practitioners are generally more concerned from an ethical standpoint with identifying patients at risk for development of higher amounts 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. Certainly, annual progression in most myopic patients slows with time and many myopes who have progressed through the teenage years stabilize prior to reaching 20 years of age. However, there are patients who will continue to progress through adult years. 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 is 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 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 in 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

a) Genetics / 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. 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. A meta-analysis placed 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) 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. For example, a genetic risk score (GRS) estimated that these loci explain only 0.6% and 2.3% respectively of the variance in refractive error at ages 7 and 15. 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.

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 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 showed apparent interaction with near work while neither variant nor GRS effects altered with time outdoors.

The most useful clinical indicator for genetic risk short of genetic testing is parental history of myopia. Older studies demonstrating this association were reviewed by Goss and Jackson. Studies since that time show significant association between number of
myopic parents and incident myopia, as summarized in a recent meta-analysis.\textsuperscript{70} Odds ratios 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.\textsuperscript{70} More recent studies confirm the connection.\textsuperscript{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 had a 26-fold higher odds for prevalent myopia than children with reading distances of greater than 20 cm and no myopic parents.\textsuperscript{77, 78} Also, unsurprisingly, parental myopia correlates with certain ocular components, particularly axial length.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{61, 82} Because of these factors, the sensitivity of number of myopic parents in predicting childhood myopia is correspondingly low.\textsuperscript{83 82}

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

Ramamurthy and colleagues have reviewed the large number of environmental risk factors for myopia.\textsuperscript{84} 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,\textsuperscript{84} Flitcroft presents 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.\textsuperscript{85, 86} Xiong et al reviewed multiple studies that show a clear connection between time spent outdoors and myopia onset.\textsuperscript{87} 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 Myopia Onset and Progression report.\textsuperscript{88}

Despite initial indications that near work may not be directly related to myopia, more recent evidence suggests a clear link.\textsuperscript{89} ‘Near work’ has been defined and measured in a multitude of ways across different studies (for example, 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 found more time spent on near work activities was associated with higher odds of myopia, increasing by 2% for every additional diopter-hour of near work per week.\textsuperscript{89} Multiple subsequent papers 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.\textsuperscript{27, 51, 52, 72, 75, 76, 78, 90-92} French and coworkers presented data that illustrate a strong interaction between the effect of time spent outdoors and near work.\textsuperscript{93} In children with baseline mean age of 6 years, those who spent low amounts of time outdoors and performed high levels of near work had dramatically increased odds
of incident myopia by age 12 years (OR, 15.9; 95% CI, 3.5-73.4) compared with those who spent high amounts of time outdoors and low amount of time involved in near work.

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

The authors also determined that children from urban environments have 2.6 (95% CI 1.8-3.9) times higher odds of myopia compared with those from rural environments. Consistent with this finding, population density, home size and housing type are also significantly associated with refractive error and axial length. The mediating factors for all of the environmental effects are likely to be a combination of education, near-work and time spent outdoors.
Figure 3: Modelled 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).\textsuperscript{37}

Physical attributes (height, weight and body-mass index),\textsuperscript{29, 97, 98} pre-natal history,\textsuperscript{99} birth season,\textsuperscript{100, 101} intelligence\textsuperscript{102, 103} and socio-economic status\textsuperscript{27, 104, 105} have all been linked to the likelihood of myopia, with varying strengths of association.

c) Binocular vision
It has long been postulated that myopia onset and progression may be related to dysfunctional accommodation and convergence.\textsuperscript{106} An elevated accommodation-convergence/accommodation (AC/A) ratio has been observed prior to the onset of myopia.\textsuperscript{44, 107} In a large, ethnically diverse group of children followed up for an extensive period of time, Mutti and colleagues found the AC/A ratios of those who became myopic began to increase about 4 years prior to myopia diagnosis, continued increasing until diagnosis and then plateaued at a level higher than those who remained emmetropic.\textsuperscript{108}

Another feature of accommodation which has been observed is that measured lag of accommodation is larger among myopes than non-myopes.\textsuperscript{109, 110} It was thought that
the presence of lag prior to 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. An aspect of accommodative lag worthy of mention is that spurious measurement of accommodative error is well documented. 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 away from 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. 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.

a) Genetics / personal characteristics

Donovan et al reported that European children progress more slowly on average than Asians (0.55D/yr and 0.82D/yr, respectively, at mean age of 9.3 years), although age-specific progression data by baseline age for Europeans in their analysis was derived from a single paper. For studies conducted in somewhat homogeneous Western societies, the analysis of Mutti et al supports the ethnic differences in progression rates found in the Donovan study, although French et al did not establish significance of an
ethnicity effect.\textsuperscript{42, 116, 117} Gwiazda and colleagues looked at risk factors for high myopia, which can be considered a corollary of fast progression.\textsuperscript{117} Reporting on an ethnically diverse population of children aged 6 to 11 years with initial myopia between -4.50D and -1.25 D at 4 sites within the US, 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 found that the number of myopic parents was a risk factor for high myopia.\textsuperscript{117} Some studies support the proposition that parental myopia is associated with faster progression rates, where others do not.\textsuperscript{91, 118, 119}

Females show faster progression compared with males according to Donovan et al (0.80D/yr and 0.71 D/yr, respectively, at mean age 8.8 yrs) and Zhou et al (OR 1.45; 95% CI, 1.12–1.84).\textsuperscript{46, 49} However, such a difference was not evident in the study of Gwiazda et al.\textsuperscript{117}

b) Environment
In their meta-analysis, Xiong et al reported that outdoor time was not effective in slowing progression in eyes that were already myopic.\textsuperscript{87} However, a more recent prospective study suggests that outdoor time does have a protective effect on rate of progression.\textsuperscript{52} Subsequent cohort studies yield mixed results.\textsuperscript{51, 74, 118, 120} Support for the protective effect of time spent outdoors on myopia progression may be inferred from numerous studies which have found a seasonal variation in myopia progression.\textsuperscript{121-123} See the accompanying IMI – Interventions for Myopia Onset and Progression report.\textsuperscript{88}

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

c) 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.\textsuperscript{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 progress to vision-threatening levels of myopia. Practitioners and parents should be aggressive 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 prior to 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, that 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 progress to high myopia, but age of onset is the current best determinate 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 some individuals with later onset (say 11 years or older) may also progress to higher amounts 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 / advancements

4.1  IMI - Defining and Classifying Myopia report\textsuperscript{39}

Myopia has been the topic of scientific study for over 400 years, but it is only more recently that it has been recognized as a serious public health issue, due to it being a significant cause of visual loss and a risk factor for a range of pathological 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, amount 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 purpose, 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:

\textbf{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:

\textbf{Axial Myopia:} a myopic refractive state that can be attributed to excessive axial elongation.

\textbf{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 “pre-myopia” is defined.

**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.

As a quantitative trait it is recommended that myopia be divided into myopia (i.e. all myopia), low myopia and high myopia 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 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 pathological 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 report of Emmetropization and Myopia

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, anatomical and physiological differences must be taken into account when interpreting and translating results to humans.

The report summarizes the anatomical 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, the 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 paper 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. Pharmacological studies of the mechanisms of emmetropization and myopia are discussed including the effects of cholinergic, GABAergic and adenosine antagonistic drugs and drugs effecting nitric oxide and neuropeptides. Finally, the paper 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

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 based on 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, extra-cellular matrix modulation, anterior segment morphology, but also post-transcriptional 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 Myopia Onset and Progression report

This report examined the evidence-basis for various interventions in current use for controlling myopia progression in children, organized under the categories of optical, pharmacological, environmental (behavioural) 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 to 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. Centre-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%.

Pharmacological myopia control trials has principally used atropine, although other muscarinic antagonists such as M1 selective pirenzepine, ocular hypotensive agents, including topical timolol (a nonselective beta-adrenergic antagonist), and oral 7-methylxanthine (7-MX), an adenosine antagonist, have also been trialled. Although the reduction in myopia progression seems to be higher with 1% atropine (around 60 to 80%), more recent atropine studies use much lower doses (e.g., 0.01%), with a reduced effect on axial elongation (around 42 to 58%), but with fewer side-effects and apparently 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

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 time period of 1 year due to seasonal effects. Typical inclusion criteria are: cycloplegic spherical or spherical equivalent myopia of at least -0.75D; astigmatism ≤1.00D; anisometropia ≤1.50D; aged 6-12 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 exam, along with standardised 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 assessment includes visual acuity and dysphotopsia. Finally, there is not a specific minimum percent reduction in myopia progression that has been published for a treatment effect to be considered clinically meaningful; any such percent reduction threshold could theoretically vary based on 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 non-contact interferometry) or both. Secondary outcome measures focus on patient reported outcomes (usually assessed by questionnaire and can include the parent/guardian’s experience as well as the patient) 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 using 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 using 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

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 papers and guidance documents was undertaken, with a view to carefully considering 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 amount of myopia. Thus, the risk-benefit analysis must take account of the outcomes arising from non-intervention 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 pathological myopia and associated visual impairment report significant social and emotional impacts and reduced life satisfaction. Additional factors which 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.

The majority of myopia control treatments are currently off-label in most 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 their parents/guardians in some cases) are 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 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 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 judgement 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 non-biased 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

This report draws on the evidence-basis outlined principally in the IMI - Interventions for Myopia Onset and Progression report 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 aged 6-11 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 and gaining informed consent and 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 non-contact axial length measurement. Exploratory tests which may be employed clinically in future include uncorrected relative peripheral refraction, ocular aberrations, pupil size, sub-foveal 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 visualise 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. Due to the inherent risks of any treatment (contact lens, pharmaceuticals), treatment is not generally advisable until the myopia is visually significant (-0.50 to -0.75 D) and baseline refractive error will determine the availability and potential effectiveness 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 and 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.

**Consolidated acronym/abbreviation list for IMI – reports**

7-MX 7-methylxanthine
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AC/A</td>
<td>accommodative convergence to accommodation</td>
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<td>ACES</td>
<td>Anyang Childhood Eye study</td>
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<tr>
<td>Add</td>
<td>bifocal addition</td>
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<tr>
<td>AF</td>
<td>retinal autofluorescence</td>
</tr>
<tr>
<td>AL</td>
<td>axial length</td>
</tr>
<tr>
<td>ALSPAC</td>
<td>Avon Longitudinal Study of Parents and Children</td>
</tr>
<tr>
<td>ANSES</td>
<td>French agency for food, environmental and occupational health &amp; safety</td>
</tr>
<tr>
<td>APLP2</td>
<td>amyloid-like protein-2</td>
</tr>
<tr>
<td>AREDS</td>
<td>Age-Related Eye Disease Study</td>
</tr>
<tr>
<td>ATOM</td>
<td>Atropine in the treatment of myopia</td>
</tr>
<tr>
<td>atRA</td>
<td>all-trans-retinoic acid</td>
</tr>
<tr>
<td>b</td>
<td>regression coefficient</td>
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<tr>
<td>BAK</td>
<td>benzalkonium chloride</td>
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<tr>
<td>BF</td>
<td>bifocal</td>
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<tr>
<td>BHVI</td>
<td>Brien Holden Vision Institute</td>
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<tr>
<td>BMES</td>
<td>Blue Mountain Eye Study</td>
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<tr>
<td>BMP</td>
<td>bone morphogenic protein</td>
</tr>
<tr>
<td>BS</td>
<td>British Standard</td>
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<tr>
<td>C</td>
<td>control group</td>
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<tr>
<td>CA repeats</td>
<td>Cytosine- Adenine repeats</td>
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<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
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<tr>
<td>CCL</td>
<td>collagen cross-linking</td>
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<tr>
<td>CE</td>
<td>Conformité Européenne</td>
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<tr>
<td>cGMP</td>
<td>cyclic guanosine monophosphate</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CLEERE</td>
<td>Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error</td>
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<tr>
<td>CNV</td>
<td>choroidal neovascularization</td>
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<tr>
<td>COI</td>
<td>conflict of interest</td>
</tr>
<tr>
<td>COMET</td>
<td>Correction of myopia evaluation trial</td>
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<tr>
<td>CPD</td>
<td>continuing professional development</td>
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<tr>
<td>CREAM</td>
<td>Consortium for Refractive Error and Myopia</td>
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<td>D</td>
<td>dioptres</td>
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<td>DA</td>
<td>dopamine</td>
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<td>ECM</td>
<td>extracellular matrix</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>ECP</td>
<td>Eye Care Practitioners</td>
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<td>EN</td>
<td>European Standard</td>
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<tr>
<td>eNOS</td>
<td>endothelial nitric oxide synthase</td>
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<td></td>
<td>enkephalin-, neurotensin- and somatostatin-like immunoreactive amacrine cells</td>
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<td>ENSLI</td>
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<td>EOM</td>
<td>early onset myopia</td>
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<td>esophoria</td>
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<td>EU</td>
<td>European Union</td>
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<tr>
<td>FA</td>
<td>fluorescein angiography</td>
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<td>FC</td>
<td>full correction</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FDM</td>
<td>form deprivation myopia</td>
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<td>FGF</td>
<td>fibroblast growth factor</td>
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<td>FRD</td>
<td>foveal RD</td>
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<td>FU</td>
<td>follow-up</td>
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<td>GABA</td>
<td>gamma-amminobutyric acid</td>
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<td>GAG</td>
<td>glycosaminoglycan</td>
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<td>GCP</td>
<td>Good clinical practice</td>
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<tr>
<td>GCTA</td>
<td>genome-wide complex trait analysis</td>
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<tr>
<td>GEWIS</td>
<td>genome-environment-wide interaction studies</td>
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<tr>
<td>GLP</td>
<td>Good laboratory practice</td>
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<td>GLP-1</td>
<td>glucagon-like peptide-1</td>
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<td>GMP</td>
<td>Good manufacturing practice</td>
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<td>GOAL</td>
<td>Guangzhou Outdoor Activity Longitudinal study</td>
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<td>GP</td>
<td>Gas permeable rigid contact lens</td>
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<td>GRS</td>
<td>Genetic risk score</td>
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<td>GWAS</td>
<td>Genome wide association studies</td>
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<td>GxE</td>
<td>gene-environment interaction</td>
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<td>HCP</td>
<td>Health care professional</td>
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<td>HM-PRO</td>
<td>High myopia-partial reduction orthokeratology</td>
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<td>HOA</td>
<td>higher-order aberrations</td>
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<tr>
<td>Hrs</td>
<td>hours</td>
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<tr>
<td>ICD</td>
<td>International Classification of Disease</td>
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<td>ICG</td>
<td>indocyanine green angiography</td>
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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  Light emitting diode
LIH  lens induced hyperopia
LIM  lens induced myopia
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)
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>OCT</td>
<td>ocular coherence tomography</td>
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<tr>
<td>OK</td>
<td>orthokeratology</td>
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<tr>
<td>OLSM</td>
<td>Orinda Longitudinal Study of Myopia;</td>
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<tr>
<td>OMIM</td>
<td>Online Mendelian Inheritance in Man database</td>
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<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>PAL</td>
<td>Progressive addition spectacle lenses</td>
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<tr>
<td>PA-PAL</td>
<td>Peripheral asphered Progressive addition spectacle</td>
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<td>PG</td>
<td>proteoglycan</td>
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<td>PMA</td>
<td>Premarket approval</td>
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<td>PMDA</td>
<td>Pharmaceuticals and Medical Devices Agency</td>
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<tr>
<td>PPG</td>
<td>pre-proglucagon</td>
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<tr>
<td>PR</td>
<td>partial reduction</td>
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<tr>
<td>PRO</td>
<td>patient reported outcomes</td>
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<tr>
<td>PSR</td>
<td>posterior scleral reinforcement</td>
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<tr>
<td>QOL</td>
<td>quality of life</td>
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<tr>
<td>r</td>
<td>Correlation coefficient</td>
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<tr>
<td>RA</td>
<td>retinoic acid</td>
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<tr>
<td>RAAB</td>
<td>rapid assessment of avoidable blindness</td>
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<td>RALDH2</td>
<td>retinaldehyde dehydrogenase 2</td>
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<tr>
<td>RAR</td>
<td>retinoic acid receptor</td>
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<tr>
<td>RCT</td>
<td>Randomized clinical trial/Randomized controlled trial</td>
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<tr>
<td>RCUK</td>
<td>Research Council of the United Kingdom</td>
</tr>
<tr>
<td>ROC</td>
<td>recess outside the classroom</td>
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<td>ROMIO</td>
<td>Retardation of myopia in orthokeratology</td>
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<tr>
<td>RPE</td>
<td>retinal pigment epithelium</td>
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<td>SAVES</td>
<td>Sydney Adolescent Vascular and Eye Study</td>
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<td>SCL</td>
<td>soft contact lenses</td>
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<tr>
<td>SCN</td>
<td>suprachiasmatic nucleus</td>
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<td>SCORM</td>
<td>Singapore Cohort study of Risk Factors for Myopia</td>
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<tr>
<td>SER</td>
<td>spherical equivalent refraction</td>
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<tr>
<td>SMS</td>
<td>Sydney Myopia Study</td>
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<tr>
<td>SNP</td>
<td>single nucleotide polymorphism</td>
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<tr>
<td>Specs</td>
<td>spectacles</td>
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<tr>
<td>SSGAC</td>
<td>Social Science Genetic Association Consortium</td>
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</tbody>
</table>
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

Financial disclosures

James S. Wolffsohn
Alcon, Allergan, Aston EyeTech, Bausch & Lomb, BetterVision Ltd, CooperVision, Eaglet Eye, European Union, Eyebag, EMPharma, EyeDocs, Gelflex, Innovate UK, Johnson & Johnson Vision Care, Lenstec, Medmont, Rayner, Tearlab, Théa, Optimec, Visioncare Research (F); Aston EyeTech (I); Atiya Vision, British Contact Lens Association, Johnson and Johnson Vision, University of Houston, Visioncare Research, CooperVision, Shire, Santen, RB (C); Portable Aberrometer, POV Scope, Digital Slit-lamp, Contrast Sensitivity Chart (P); Johnson & Johnson, Santen (R)

Daniel Ian Flitcroft  (N)
Kate L Gifford  
Myopia Profile Pty Ltd (I), Coopervision, Menicon (C), Alcon, CooperVision, Menicon, Visioneering Technologies (R)

Monica Jong (N)

Lyndon Jones  
Consultant for Alcon, CooperVision, J&J Vision, Novartis and Ophtecs (C)  
Honoraria and/or travel reimbursement from Alcon, CooperVision, J&J Vision, Novartis and Ophtecs. (R)

Caroline C.W. Klaver  
Topcon (F); C: Thea Pharma (C)

Nicola S. Logan  
CooperVision, Visioncare Research (F)

Kovin Naidoo (N)

Serge Resnikoff  
Brien Holden Vision Institute (C)

Padmaja Sankaridurg  
Brien Holden Vision Institute (E), (P)

Earl L. Smith III  
(P)  
Brien Holden Vision Institute (F); Tree House Eyes, SightGlass Vision (C)
David Troilo
(P); Johnson & Johnson Vision (C)

Christine F. Wildsoet (P)

**IMI – defining and classifying myopia report**

Ian Flitcroft [N]
Serge Resnikoff Brien Holden Vision Institute
Brien Holden Vision Institute [C]

Jost Jonas [P]
Treatment of eye diseases using encapsulated cells encoding and secreting neuroprotective factor and / or anti-angiogenic factor; Patent number: 20120263794, and Patent application with University of Heidelberg (Heidelberg, Germany) Agents for use in the therapeutic or prophylactic treatment of myopia or hyperopia; European Patent Number: 3 070 101 (P)

Susan Vitale [N]

Monica Jong [N]

Kyoko Ohno-Matsui
Novartis, Bayer, Santen, Senju (F)

Kovin Naidoo (N)
Jugnoo Rahi (N)
Mingguang He (N)
Larry Yannuzzi (N)

IMI – Interventions for Myopia Onset and Progression
Audrey Chia (N)
Pauline Cho N
Jeremy A. Guggenheim N
Jan Roelof Polling
Laboratoires Théa (C)
Scott Read
Treatment of myopia progression (Patent application: US20150036102A1, assignee Queensland University of Technology) (P); Cylite Pty Ltd. (F)
Padmaja Sankaridurg E, P
Seang-Mei Saw Inventor of the FitSight watch (P)
Klaus Trier Theialife (I), P
Jeff Walline
Bausch + Lomb (F) SightGlass (C)
Christine Wildsoet P
Pei-Chang Wu N

IMI - Clinical Myopia Control Trials and Instrumentation report

James S. Wolffsohn
Alcon, Allergan, Aston EyeTech, Bausch & Lomb, BetterVision Ltd, CooperVision, Eaglet Eye, European Union, Eyebag, EMPharma, EyeDocs, Gelflex, Innovate UK, Johnson & Johnson Vision Care, Lenstec, Medmont, Rayner, Tearlab, Théa, Optimec, Visioncare Research (F); Aston EyeTech (I); Atiya Vision, British Contact Lens Association, Johnson and Johnson Vision, University of Houston,
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Pete S. Kollbaum
Alcon, Allergan, CooperVision, Johnson & Johnson Vision Care, Luminopia (F); CooperVision (C); multifocal contact lens designs (P); CooperVision, Johnson & Johnson Vision Care (R);

Pete S. Kollbaum
Alcon, Allergan, CooperVision, Johnson & Johnson Vision Care, Luminopia (F); CooperVision (C); multifocal contact lens designs (P); CooperVision, Johnson & Johnson Vision Care (R);

David A. Berntsen
Bausch & Lomb (F), Visioneering Technologies (C)

David A. Atchison
Carl Zeiss Vision, Cylite Optics, ForgetSpecs (F); visual displays, retinal imaging (P)

Alexandra Benavente MCOptom PhD
N

Arthur Bradley, PhD
Cooper Vision, Alcon, Vistakon, Allergan (F); Cooper Vision, Alcon, Vistakon, Allergan (C)

Hetal Buckhurst
N

Michael Collins
Johnson & Johnson Vision Care, Cylite, Johnson & Johnson Vision (F); (C) Johnson & Johnson Vision Care (C); QUT Bluebox, Johnson & Johnson Vision Care (P); Johnson & Johnson Vision Care (R)

Takashi Fujikado
Nidek, Topcon, Menicon, Hoya (F); Nidek, Topcon (P)

Takahiro Hiraoka
Johnson & Johnson Vision Care, Seed, Alpha Corporation (F); Menicon, Santen (R)
Masakazu Hirota (N)
Debbie Jones
Coopervision, Shire, Alcon (C)
Nicola S. Logan
CooperVision, Visioncare Research (F)
Linda Lundström
Abbott (F); Alcon (C); Lens design (P)
Scott A. Read
Treatment of myopia progression (Patent application: US20150036102A1, assignee Queensland University of Technology) (P). Cylite Pty Ltd. (F)
Hidemasa Torii MD, PhD
(P)

**IMI – Industry Guidelines and Ethical Considerations for Myopia Control**

Lyndon Jones
Consultant for Alcon, CooperVision, J&J Vision, Novartis and Ophtecs (C)
Honoraria and/or travel reimbursement from Alcon, CooperVision, J&J Vision, Novartis and Ophtecs. ( R )

Bjorn Drobe
Employee of Essilor which sells myopia control lenses. ( E)
Holds patents in myopia control (P)

Donald Tan
Santen (F); Santen and Eye-Lens ( C); patents in atropine (P); Santen (R)
Lyle Gray ( N)

Jacinto Santodomingo-Rubido
Employee of Menicon Company Ltd (E)

Jason J. Nichols
Alcon (C) ; Alcon (R)

José Manuel González Méijome

Alcon, CooperVision, Essilor, J&J Vision, Menicon, Paragon Vision Science and Procornea. (F); Alcon, Bausch+Lomb, CooperVision, Procornea (C); Alcon, Bausch+Lomb, CooperVision, Procornea (R)

Kah-Ooi Tan
Brien Holden Vision Institute (E)

Arne Ohlendorf
Carl Zeiss Vision International GmbH, University of Tuebingen (F); Carl Zeiss Vision International GmbH (E)

Stephanie Ramdass
Bausch + Lomb, Contamac, Euclid, Paragon Vision Sciences, Specialeyes and SynergEyes.(F); Bausch and Lomb (C); Paragon and Wink Production Inc. (R)
Stephen Newman
Menicon Co Pty Ltd (E); myopia control (P)

Fuensanta Vera-Diaz (N)

Yee Ling Wong
Essilor International R and D (E)

Katrina Schmid
IMI – Myopia Genetics report
Milly S. Tedja N
Annechien E.G. Haarman N
Magda A. Meester-Smoor N
Jaakko Kaprio N
David A. Mackey N
Jeremy A. Guggenheim N
Christopher J. Hammond N
Virginie J.M. Verhoeven N
Caroline C.W. Klaver
Topcon (F); C: Thea Pharma (C)

IMI – Experimental Models of Emmetropization and Myopia
David Troilo P
C Johnson & Johnson Vision

Earl L. Smith III P
F Brien Holden Vision Institute
C Tree House Eyes, SightGlass Vision
Regan Ashby P
Debora Nickla N
Andrei Tkatchenko P
Lisa A. Ostrin N
Tim Gawne N
Machelle Pardue N
Jody Summers P
Chea-su Kee N
Falk Schroedl N
Seigfried Wahl Carl Zeiss Vision International (E)

Lyndon Jones* Alcon, Allergan, Contamac, CooperVision, Essilor, GL Chemtec, Inflamax Research, Johnson & Johnson Vision, Menicon, Nature’s Way, Novartis, Safilens, Santen, Shire, SightGlass, TearLab, TearScience, Visioneering (F); Alcon, CooperVision, Johnson & Johnson Vision, Novartis, Ophtecs (C); Alcon, CooperVision, Johnson & Johnson Vision, Novartis, Ophtecs (R)

**IMI – Clinical Management Guidelines report**

Kate L Gifford
Myopia Profile Pty Ltd (I), CooperVision, Menicon (C), Alcon, CooperVision, Menicon, Visioneering Technologies(R)

Kathryn Richdale
Alcon Euclid (F); Novartis (C)

Pauline Kang
CooperVision USA, CooperVision Australia, Paragon Vision Sciences USA, Bausch + Lomb Australia (F)

Thomas A Aller
Specialeyes, LLC; Visioneering Technologies, Inc (F)
Treehouse Eyes, LLC; Reopia, LLC; Johnson & Johnson (I)
Visioneering Technologies, Inc., Reopia, LLC (C)
Vision CRC, BHVI (P)
R: Visioneering Technologies, Inc.; Pentavision; Nevakar (R)
Carly S Lam
Hoya Corporation and Johnson & Johnson (F), (P)
Y Maria Liu
Paragon (F), Paragon (C)

Langis Michaud
Johnson, Cooper, Blanchard Labs (F); Patent of a medical device for myopia control (P); Bausch & Lomb, Cooper Vision, Shire, Blanchard Labs, Allergan (R)

Jeroen Mulder (N)
Janis B Orr (N)
Kathryn A Rose (N)
Kathryn J Saunders (N)
Dirk Seidel (N)
J Willem Tideman (N)
Padmaja Sankaridurg
Brien Holden Vision Institute (E); (P)

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