NATIONAL ACADEMIES Sciences Engineering Medicine

Focus on Myopia – Pathogenesis and Rising Incidence

"Optical Visual Diet paper"

Susana Marcos, PhD

David R Williams Director, Center for visual Science

Nicholas George Professor of Optics, The Institute of Optics

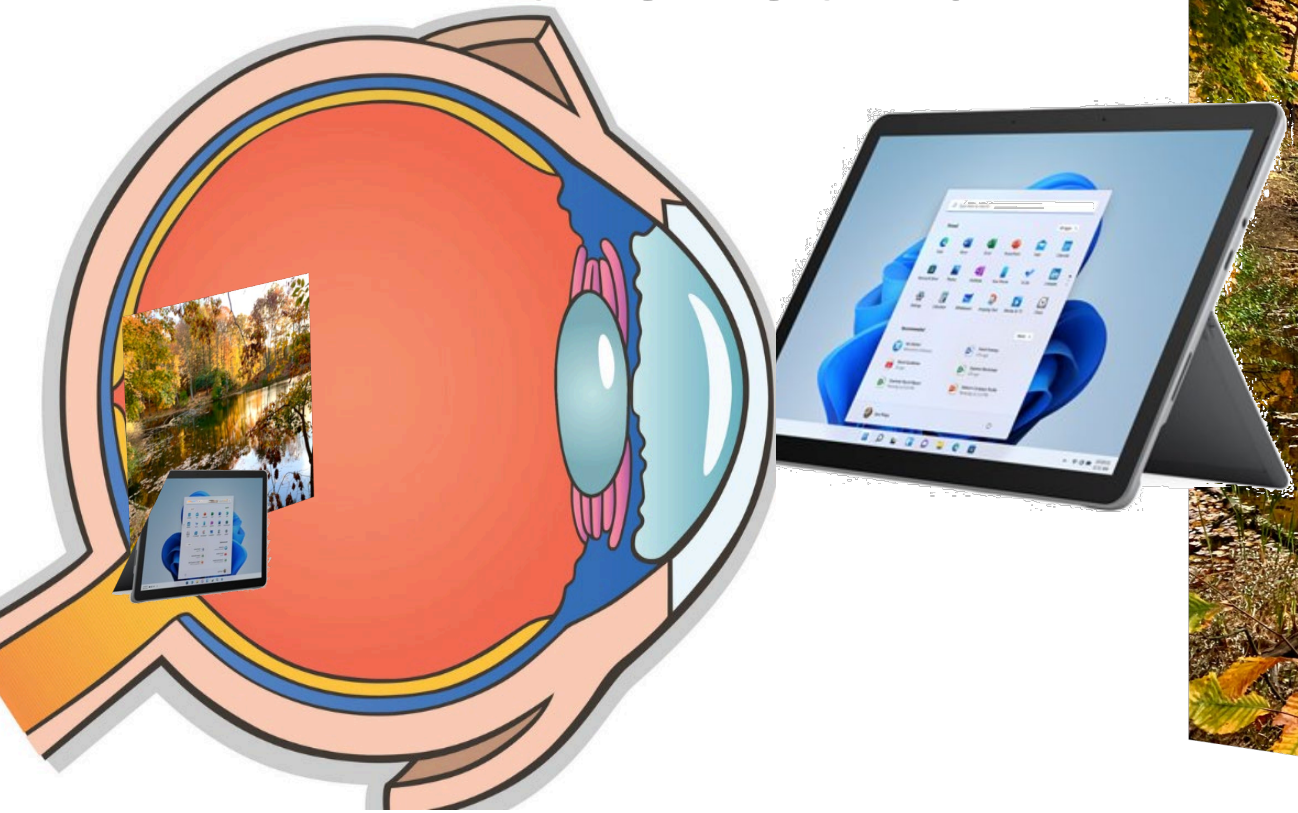
Professor of Ophthalmology, Flaum Eye Institute

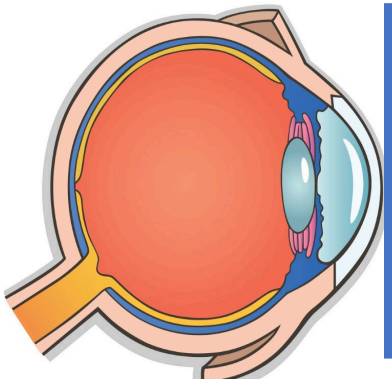
Center for Visual Science

UNIVERSITY of ROCHESTER

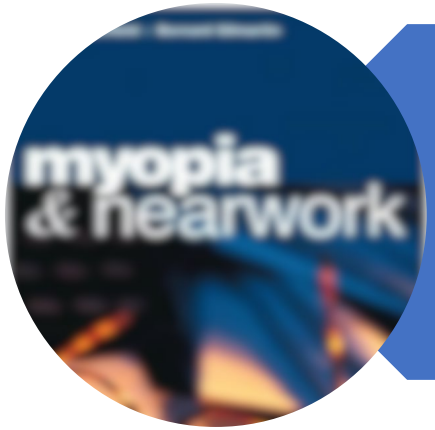
Visual Environment

Optical imaging on the retina





1.- Geometry and optics of the myopic eye



2.-Detecting blur sign and Optical Blur signal as a trigger for myopia

3.- Environment and myioia

The paper

✗ What it is not

- Meta-analysis paper
- Historical review
- Comprehensive review
- Tutorial

✓ What it means to be

- Concise state-of-the-art
- Identify the gaps
- Reflect on future directions and efforts

Section Structure

- **Facts**
  - State-of-the-art
  - Uncontested findings
  - Conflicting data

- **Open questions**
  - Gaps of technology/knowledge
  - Potential studies to address open questions
  - In which directions should the field advance

Methodology: Facts

- Personal knowledge
- Literature review
- Journal and institutional archives
- AI-powered databases and reference handling

NIH National Library of Medicine
National Center for Biotechnology Information
PubMed®

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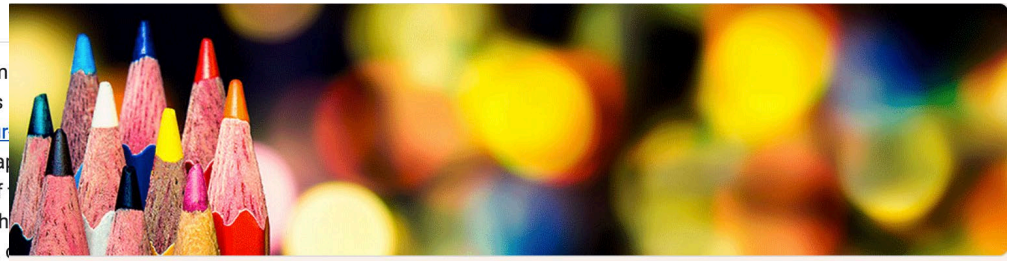
Petal

Methodology: Open questions

- Identified key open questions
- Developed survey
- Sent out to 30 recognized experts in the field

Questions on Myopia.- Optics of the Myopic Eye

Questions on Myopia.- Optical Blur as a Trigger for Myopia



Questions on Myopia.- Environment and Myopia

As you may know, The National Academies of Sciences, Engineering, and Medicine has launched a consensus study that will consider various aspects related to the global increase in myopia.
https://www.nationalacademies.org/our-work/focus-on-myopia-pathogenesis-and-rising-incidence
I have been commissioned to write a paper for the US National Academy of Sciences centered on the optics

1. Geometry and Optics of the Myopic Eye

- Dimensions of the myopic eye
- Emmetropization vs myopic changes in ocular geometry
- Accommodation in myopic eyes
- Optical aberrations in myopic eyes
- Chromatic aberrations
- Peripheral optics
- Cone mosaic and sensitivity
- State-of-the-art technologies for geometrical and optical characterization

2. Detecting blur sign and optical blur as a trigger of myopia

- Hyperopic defocus as a trigger for myopia
- Accommodative lag and near work
- Peripheral defocus with standard corrective optics
- Optical cues to detect the sign of defocus: chromatic cues, temporal microsacades

3. Environment and Myopia

- Environmental/epidemiological population studies linking myopia with:
  - Urban settings
  - Near work
  - Education
  - Indoor/outdoor activities
  - Geography
  - Visual displays
- Circadian rhythms and myopia
- Impact of light levels on pupil dynamics and accommodation

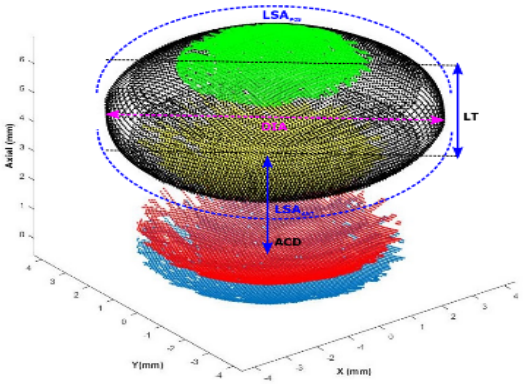
1. Geometry and Optics of the Myopic Eye I

OPEN QUESTIONS

*1.- The **crystalline lens** of the eye has probably not received the attention it merits as a agent in myopia development*

* What is in your view the role of the crystalline lens in emmetropization and myopia development?

* Would longitudinal studies help to determine if the lens has an active or passive role in myopia development?



Muradliharan et 2020

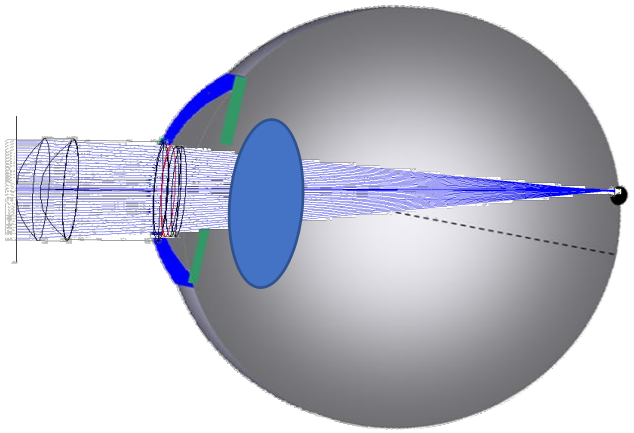
*2.- Building **computational myopic eye models** is of interest to predict the interactions of the eye's optics to the optics of correcting lenses, while age-dependent models would allow to evaluate the association between geometrical and optical changes with normal emmetropization, myopia development and myopia control. The eye models rely on accurate structural information of the eye, and can be informed by aberrometric measurement.*

* How can eye models based on population data will help advance the field?

* Will large intersubject variability in geometrical parameters be a limitation?

* What are current technical limitations of standard biometry techniques to generate reliable eye models (on axis and off-axis)? Where efforts should go in biometry that will help the field?

* How biometry and aberrometry can assess whether biometry and optical changes are a cause or consequence of myopia development?



1. Geometry and Optics of the Myopic Eye I

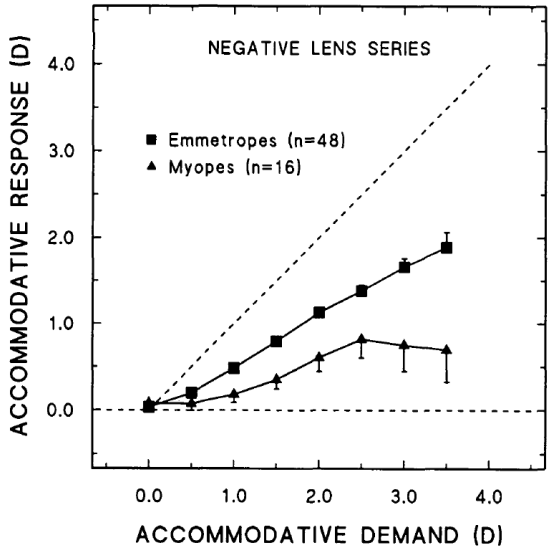
OPEN QUESTIONS

*3.- The role of **accommodation** in myopia has been a matter of debate.*

* Can we say that myopes are lousier accommodators?

* Has the study of accommodation in myopes been hampered by the limitations of existing methods to measure the accommodative lag?

* How should accommodation be properly measured? Will that technique allow to measure accommodation through multizone lenses?

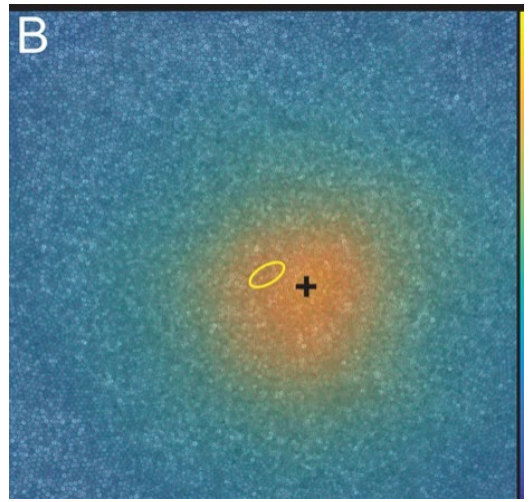


Gwiazda et al 1993

*4.- Adaptive Optics retinal imaging has allowed quantifying **cone spacing** in and outside of the fovea, and the differences between myopes and emmetropes have been investigated.*

* How can additional studies of retinal cone spacing shed light into the anatomical changes undergone by the eye as myopia develops?

* Could differences in observers cone mosaics (in particular S-cone mosaics) in the fovea and parafovea play a role in the detection of emmetropization (or myopia triggering) signals?



Wang et al 2019

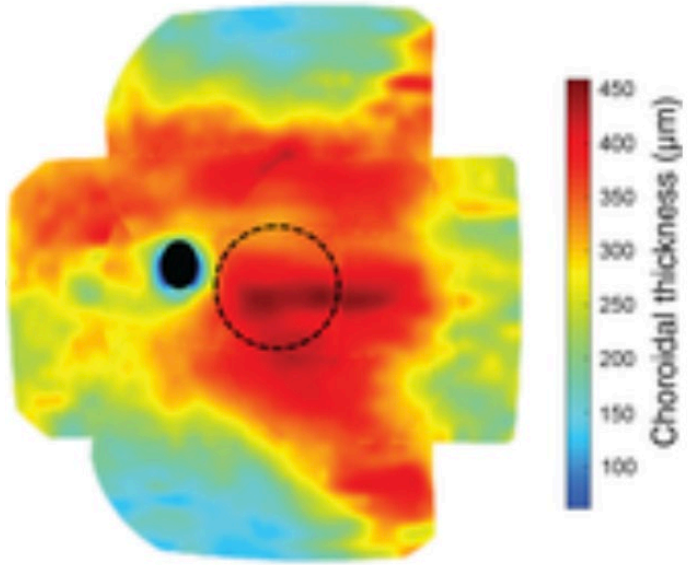
1. Geometry and Optics of the Myopic Eye III

OPEN QUESTIONS

5.- Axial biometry in the most distinct feature of myopia, and ***choroidal thickness*** *has been pointed as a potential immediate biomarker to longer-term axial elongation.*

* What physiological factors contribute to choroidal thickness and how is it modulated with defocus or optical manipulations?

* Most data in the literature have been obtained with off-the-shelf low coherence interferometry instruments, and in real time as the stimulus was presented? Besides, the magnitude of the reported thickness changes is close to the axial resolution of the optical coherence tomography technique. What technical advances would improve choroidal thickness measurements and the study of its implications in myopia?



Read et al 2018

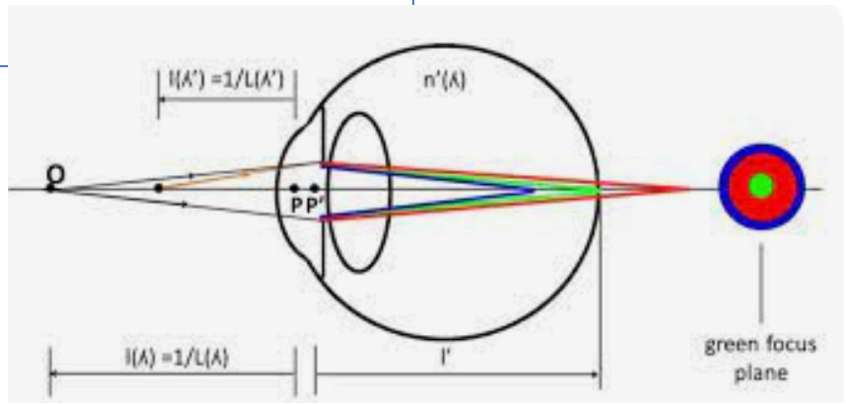
2. Detecting blur sign and optical blur as a trigger of myopia I

OPEN QUESTIONS

1.-Computer modeling, psychophysical experiments in humans presented with artificially blurred images, and experiments with animal models in chromatically manipulated background suggest that longitudinal ***chromatic aberration is a cue for emmetropization****, and emmetropes and myopes may respond differently to these chromatic cues.*

* What study could be designed that uncontestedly demonstrate the role of LCA on emmetropization?

* What open questions remain in understanding the role of LCA in detecting the sign of the focus (sparsity of S-cone mosaic versus higher density of L/M mosaics, others)? Is the mechanism driven by blur of red or blue?



2. Detecting blur sign and optical blur as a trigger of myopia II

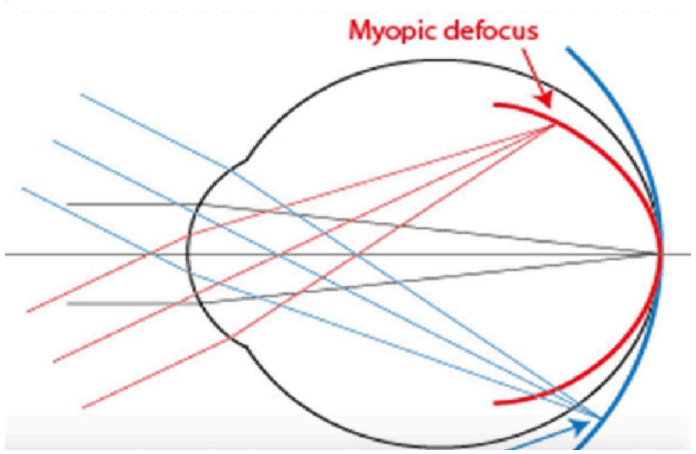
OPEN QUESTIONS

*2.- **Peripheral hyperopic defocus** has been attributed to be a primary trigger of myopia, and a primary target for optical intervention, but the peripheral cues for the detection of the sign of myopia are a matter of debate. Besides, intersubject variability in peripheral retinal shape and refractive error is large, and whether excessive peripheral hyperopic blur is a cause for myopia (even before this is corrected) or a consequence of axial elongation is unclear.*

* What mechanisms of action, specific to peripheral retina, would underlie the detection of the sign of defocus and what studies could be designed to elucidate those mechanisms?

* It appears that baseline peripheral refraction in isolation does not predict the onset or progression of myopia, and it is only the relative peripheral hyperopic defocus with respect to the fovea which exacerbates axial elongation. Peripheral hyperopic defocus is emphasized with spectacle and single vision contact lenses, prescribed once myopia has initiated. But what triggers myopia in the first place? If peripheral hyperopic defocus precedes axial elongation, what makes “to be myopic eyes” more myopic in the periphery? Is it retinal shape? Or the refractive elements (cornea and lens) peripheral optical quality?

* Peripheral defocus at near could be a crucial factor, resulting from thinner crystalline lens and distinct accommodative responses in (becoming?) myopes. However, results are inconclusive regarding peripheral aberrations and refraction as a function of accommodation. How could this be disentangled?



2. Detecting blur sign and optical blur as a trigger of myopia III

OPEN QUESTIONS

*3.- The ability of the retina to **detect the sign of defocus** appears to be key in most theories of myopia development. In some scenarios (i.e. presence of hyperopic defocus, the equivalent to lens-induced myopia) the retina would be capable to detect the sign of defocus and grow accordingly. In some other scenarios, the mechanism for blur sign detection would be impaired in myopes, work differently for imposed positive or negative defocus in different refractive groups, be dependent not only of the spatial but the spatio-temporal characteristics of the optical blur, which would be altered by differences fixational eye movement dynamics (apart from optics and retinal shape) in myopes.*

* There at least two distinctive forms of blur (non-signed form deprivation) and hyperopic blur (negative sign) that trigger myopia. What other specifics of the blurred stimulus should be investigated and taken into account in the studies? Which spatial frequency range? Spectral content? Visual angle? Temporal dynamics?

* Is understanding the mechanism for detection and encoding of the sign of defocus, and its potential impairment, key to understanding myopia development? If this is the case, where the efforts should be placed.

* Should the question be reformulated on the origin (and specifics -temporal, spatial, spectral-) of the blurred signal falling on the retina and how this influences axial growth?

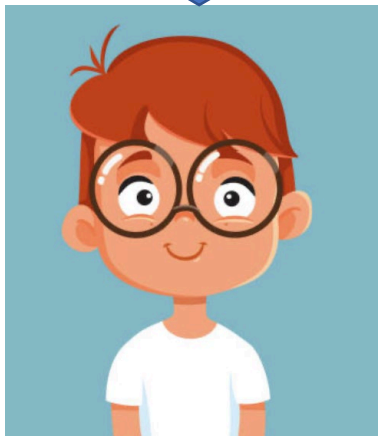
2. Detecting blur sign and optical blur as a trigger of myopia IV

OPEN QUESTIONS

*4.-**Animal models of myopia** are an extremely valuable source in myopia research, because they offer the possibility of optical, pharmacological and genetic manipulations, in a relatively fast timeframe. Despite some differences in response across species, the induction of myopia through form deprivation and through negative lenses, and eye shortening with positive lenses is fairly universal. Also, the response tends to be local in the retina. But, do they relate to the observations in humans?*

* Why simple undercorrection (positive lenses) has not functioned (in the majority of reports) as an inhibitory treatment for myopia in humans? Should this be revisited with new studies?

* In animal models, the retina responds locally (modulating axial growth) in the areas exposed to blur. Why is it expected modulating peripheral focus in humans controls axial growth in the retina.



3. Environment and Myopia

OPEN QUESTIONS

3.-· The relatively low prevalence of myopia reported in epidemiological studies in areas as diverse in latitude as Scandinavia, Australia or Tropical Brazil suggests that **outdoor light levels** may not be the predominant factor in myopia prevention, but probably other associated factors (lifestyle, lighting in classrooms, illumination during near work) are more important.

o Do you think comparative studies across different regions of the world using the same methodologies will shed light into the impact of sunlight on myopia?

4.- Evidence in animal models show that altered visual input induce changes in retinal/RPE and choroidal expression of **circadian rhythm**-related genes, while an association has been found between a disruption in the sleeping patterns (which alter circadian rhythms) and myopia.

o What studies could be designed to test the desynchronization of the endogenous circadian rhythms likely produced by unnatural lighting patterns and their effect on human myopia?

o Could behavioral or other strategies based on modifying circadian dysregulations be a potential avenue for myopia control?

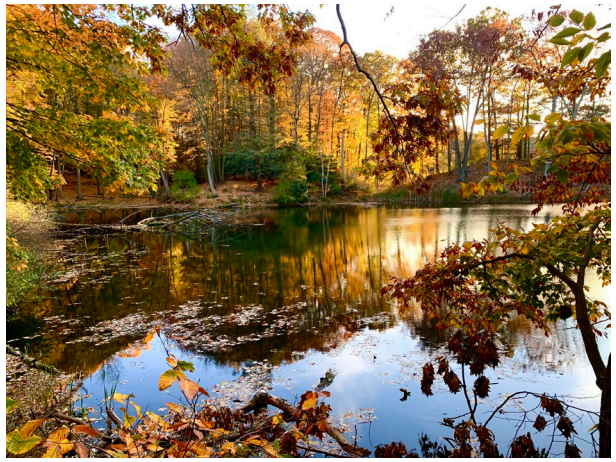
3. Environment and Myopia

OPEN QUESTIONS

· 1.- *Understanding which **attributes of the outdoor environment** are most relevant in preventing myopia development is crucial to unravel the causes for myopia and design interventional strategies. Those factors would include light levels, light spectrum, spatial frequency content, contrast, distance of gaze, pupil diameter or type of activity.*

o What studies can be designed to test the effects of individual factors on myopia control?

o Should those studies involve field tests in real environments, or could laboratory testing effectively shed insight to those questions?



·2.- *Conflicting results on the relationship between near work, indoor vs outdoor timing and myopia are likely connected to the lack of precise **objective measures** of far/near viewing behavior, and of objective characterization of the physical properties of the visual environment (i.e. light exposure, spectral properties, viewed stimulus content and viewing distance, and duration and intermittency of the exposure).*

o What (wearable?) recording devices are most suited for the continuous recording of real time interactions of test individuals with the visual environment.

o Which strategies (AI?) can be used to navigate potential massive data sets that integrate all that information?

1. Geometry and Optics of the Myopic Eye

OPEN QUESTIONS

David Atchison
QUT
Australia

Michel Collins
QUT
Australia

Stacey Choi
OSU
USA

Rhea Eskew
Northeastern U
USA

Arthur Ho
UNSW/Brian
Holden Instiute
Australia

Fabrice Manns
U Miiami
USA

Jos Rozema*
Antwerp U
Belgium

Austin Roorda
UC Berkeley
USA

Maciej Wojtowski *
ICTER
Poland

*TBC

2. Detecting blur sign and optical blur trigger

OPEN QUESTIONS

Pablo Artal
U Murcia
Spain

Linda Lundstrom *
KTK
Sweden

Sally McFadden
U Newcastle
Australia

Tom Norton
U Alabama
USA

Hema Radhakrishan*
Machester U
UK

Michele Rucci
U Rochester
USA

Frances Rucker
NECO
UK

Frank
Schaeffel
U Tubingen
/UMCO
Germany
Switzerland

David Troilo
SUNY Optometry
USA

Christine
Wildsoet
UC Berkely
USA

Geunyoung
Yoon
U Houston
USA

Len
Zheleznyak
ClerioVision
U Rochester
USA

*TBC

3. Environment and Myopia

OPEN QUESTIONS

Rigmor Baraas *
U South Eastern
Norway

Ranjay Chakraborty
Finders University
Australia

Ian Morgan
Australian National U
Australia

Mark Rea
NYU/Rensselaer
Polytecnique
USA

Lisa Ostrin
U Houston
USA

Richard Stone
U Penn
USA

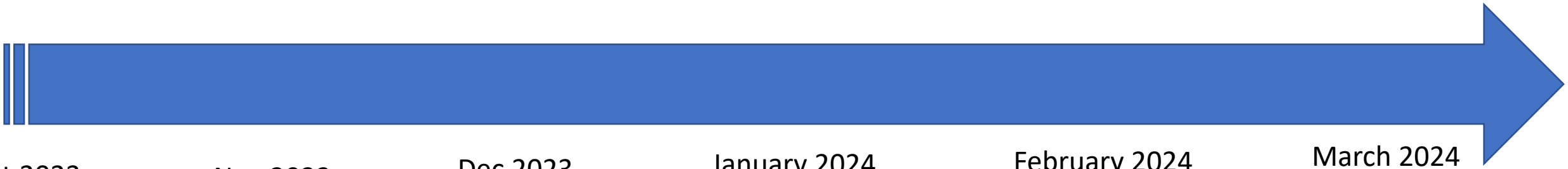
Fuensanta Vera-Diaz
NECO
USA

Pavan
Verkichala *
LV Prasad Eye
Institute
India

James Wolffsohn
Aston U
UK

*TBC

Timeline



Oct 2023
First Outline
Kick off meeting

Nov 2023
Revised Outline
Review kick off
Survey Kick off

Dec 2023
Survey Resposes
Complete review

January 2024
Survey compilation
Section 1 completed
First committee review

February 2024
Section 2 completed

March 2024
Section 3 completed
Completed draft
Committee Review