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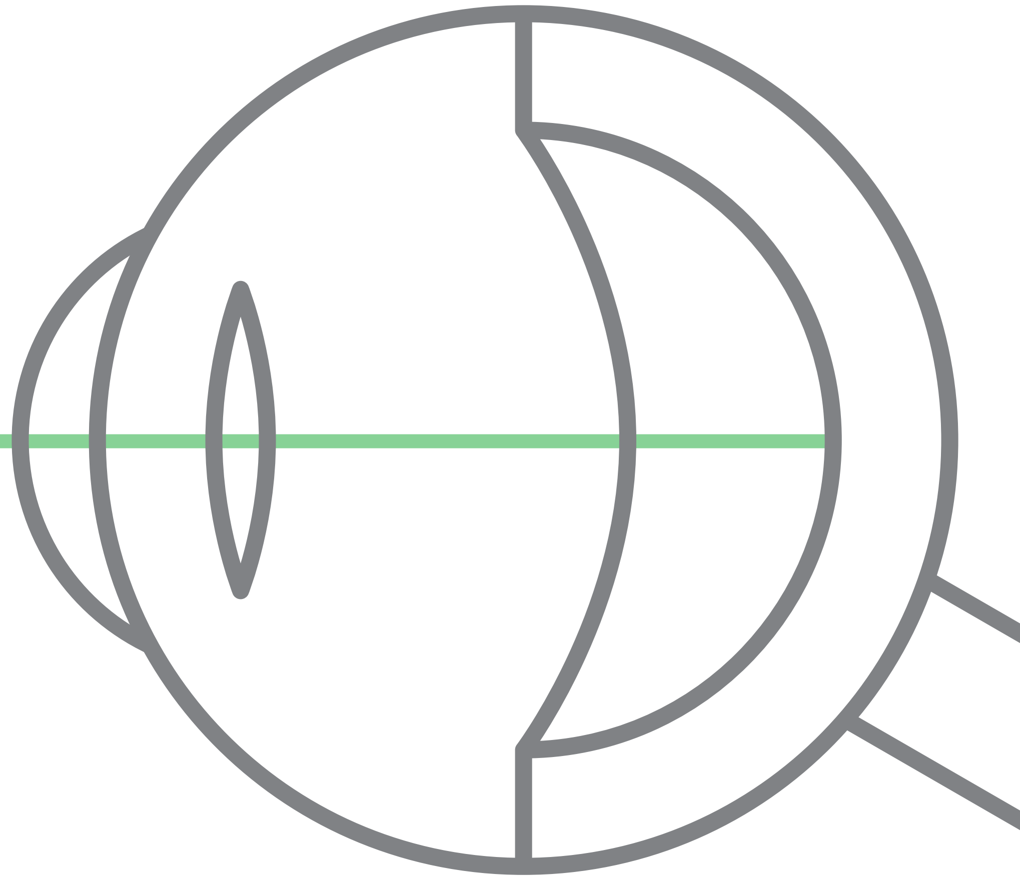

BEYOND STRUCTURE

Transforming Eye Care with Ocular Oximetry

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In the eye, the earliest sign of disease isn't the damage we can see,

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it's the metabolic changes that have remained beyond reach — until now.

WHAT'S INSIDE

Understanding the Metabolic Foundation of Eye Disease

Despite significant advances in ophthalmic imaging, a critical gap remains in our ability to assess the early functional changes that precede visible signs of disease. Traditional imaging techniques excel at detecting structural damage, but these manifestations typically appear only after substantial metabolic disruption has already occurred. This pattern of delayed detection is akin to seeing only the tip of an iceberg—while fundus photography, OCT, and OCT-A reveal structural abnormalities, the earliest metabolic shifts remain hidden.

These limitations create a crucial window of missed opportunity for early intervention. To move beyond reactive diagnostics and toward preventative care, we must expand our focus beyond structural assessment.

Functional biomarkers—signals of underlying metabolic activity and biochemical processes—offer the potential to reveal disease-associated changes before permanent damage takes hold.

Among these, blood oxygen saturation in the eye fundus—ocular oximetry—emerges as a particularly significant biomarker, offering direct insight into both metabolic demand and vascular health.

01 The Promise of Metabolic Imaging

Metabolic imaging offers a new perspective—one that shifts focus from documenting structural damage to investigating active changes at the metabolic level. The retina ranks among the most oxygen-demanding tissues in the body, requiring precise regulation between oxygen supply and consumption.

> Research suggests that even minor disruptions in this balance might trigger physiological changes associated with conditions such as glaucoma[1], diabetic retinopathy (DR)[2], and age-related macular degeneration (AMD)[3].

Understanding Ocular Oximetry

Ocular oximetry represents a non-invasive approach to measuring oxygen saturation in the tissues of the eye fundus, such as the optic nerve head and retinal microvasculature, enabling investigation of their metabolic state.

This technique, based on spectroscopy, analyzes the interaction between light and hemoglobin, the oxygen-carrying molecule in blood. By examining how light is absorbed and reflected from the back of the eye, it's possible to study the ratio of oxygen-rich to oxygen-poor blood, and assess the tissue's oxygen availability, which reflects the interplay between supply and cellular consumption.

02 Understanding Spectroscopy's Role in Medicine

To appreciate the potential of spectroscopic analysis in eye care, it's helpful to understand its broader applications in biomedical science. Spectroscopy functions as a sophisticated decoder of biological information carried by light. When light interacts with living tissue, it undergoes various changes based on the tissue's molecular composition and metabolic state. By analyzing these interactions, we can gain insights into biological processes without disrupting the tissue itself.

> The application of spectroscopy in medicine has already yielded significant advances across multiple fields.

In oncology, spectroscopic techniques help scientists study tissue composition non-invasively[4]. Cardiovascular researchers use similar principles to investigate arterial plaques[5], while cell biologists employ spectroscopy to observe metabolic processes in living cells[6]. Its ability to reveal subtle biochemical shifts makes it an invaluable tool for studying disease processes at a molecular level—a capability that is entirely new to eye care.

The Eye as a Window to Health

The eye's natural transparency makes it an ideal target for spectroscopic investigation, allowing light to pass through and return with valuable photonic information. This unique characteristic enables the study of both ocular and systemic health markers through the eye. The emerging field of "oculomics" builds on this principle, using ocular biomarkers to investigate broader physiological processes and systemic disease.

Assessing ocular oximetry provides valuable insight into retinal metabolism, but poses technical and physiological challenges. The eye is optimized to absorb light, not reflect it, and factors like pigmentation, scattering, and retinal structure complicate signal capture. Spectroscopy addresses these obstacles through advanced optics and computational models that extract meaningful data from complex light-tissue interactions—enabling more accurate, non-invasive assessment of ocular oxygenation.

03 Advancing Oxygen Saturation Measurement in the Eye

The journey to understand oxygen dynamics in the eye has been marked by both challenges and breakthroughs. Traditional approaches to measuring retinal oxygen saturation relied on two-wavelength oximetry, which provided relative estimates of oxygen saturation on the superficial and large blood vessels of the retina.

While this method offered useful insights, it faced significant limitations, mostly linked to blood vessel measurements not providing direct information on key microvascular changes that precede visible structural changes often observed in diseases.

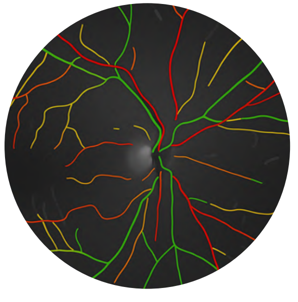
Moreover, various physiological and optical factors, including tissue pigmentation, vessel geometry, cataracts, and light scattering, complicated the acquisition of precise and reproducible measurements using these techniques.

The introduction of targeted spectroscopy, which relies on assessing diffuse reflectance patterns in the eye, represents a significant advance on how oxygen saturation can be measured. Unlike the limited two-wavelength approach, targeted spectroscopy analyzes a broad spectrum of light reflected from targeted areas of the eye fundus.

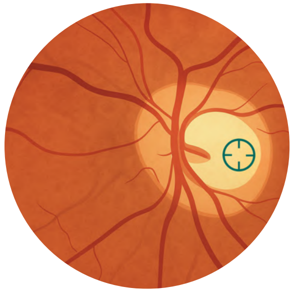
This comprehensive spectral analysis enables researchers to gather more detailed information about oxygen saturation in the tissues of the eye fundus.

The technology has been developed with careful attention to minimize the impact of confounding factors such as pigmentation and cataracts, aiming to offer more consistent measurements[7].

Two-wavelength oximetry
Relative estimates of oxygen saturation on the superficial large blood vessels of the retina.



Spectroscopy-based oximetry
Quantitative mesurement of oxygen saturation in targeted regions of the retina and optic nerve head.



The Scientific Rationale

Numerous studies have explored the link between oxygen regulation and eye diseases, uncovering several key patterns across many leading causes of vision loss.

Glaucoma

Glaucoma is no longer viewed solely as a disease caused by elevated intraocular pressure (IOP). Current understanding emphasizes its nature as a progressive optic neuropathy characterized by retinal ganglion cell loss, which can occur and worsen even at normal IOP levels.[8] Mounting evidence highlights the central role of vascular and metabolic dysfunction in glaucoma pathophysiology, particularly impaired retinal blood flow and altered oxygen metabolism.[9]

> Among these, abnormal retinal oxygen saturation has emerged as a key indicator, reinforcing the concept of vascular dysregulation as a fundamental mechanism driving disease onset and progression.[19]

DR

Diabetic retinopathy (DR) is marked by both vascular and neuronal alterations that drive inflammation, oxidative stress, and retinal ischemia, disrupting normal retinal function.[10] These pathological changes significantly impact the retina's metabolic demands and activity.

> In non-proliferative DR, oxygen saturation tends to rise with increasing disease severity.[11]

Moreover, several studies suggest that these changes in StO_2 may precede those detectable with other imaging modalities, thereby providing an earlier view of the metabolic imbalances associated with disease progression.[12]

AMD

Studies in AMD have investigated how reduced choroidal blood flow might affect retinal oxygenation[13], which may trigger different disease pathways: in wet AMD, research indicates hypoxia stimulates VEGF release[14]; in dry AMD, oxidative stress might affect retinal pigment epithelium (RPE) cells.[15]

Introducing Zilia Ocular™

Zilia Ocular* is an advanced platform designed to assess oxygen saturation within targeted regions of the eye's fundus tissue.

The product of state-of-the-art optical and computational advancements, Zilia's flagship technology enables unprecedented insight into the role of oxygen metabolism in ocular health and disease. The novel information provided by the Zilia Ocular is poised to transform our understanding of the mechanisms involved in ocular diseases and our approach to treating them.

*The Zilia Ocular is Health Canada approved. In other countries, it is available for investigational use only.

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04 How Zilia Ocular Measures Oxygen Saturation in the Eye

The Zilia Ocular is an investigational platform that combines advanced imaging and spectroscopy to analyze oxygen saturation in specific regions of the eye fundus tissue. During measurement, the device directs low intensity light into the eye, which passes through the transparent ocular media and reflects off the eye fundus. A portion of the returning light is captured for high-resolution imaging, while another portion—reflected from a selected target location in the eye fundus—undergoes spectral analysis to assess oxygenation levels. Zilia's proprietary software interprets the spectral patterns of hemoglobin, distinguishing between its oxygenated and deoxygenated states.

By isolating their respective spectral signatures, the system provides a real-time quantification of tissue oxygen saturation (StO_2) at the targeted site, offering researchers a novel way to explore metabolic activity and cellular function in the eye.

Validation of Ocular Oximetry

> The development of the Zilia Ocular has followed a rigorous validation pathway involving multiple phases of testing.

Initial computational modeling helped understand how light interacts with ocular tissues. These in silico studies, including work published in Scientific Reports[16], demonstrated how advanced analytical techniques like convolutional neural networks could improve measurement accuracy compared to traditional approaches. This foundational work established the theoretical framework for distinguishing between different hemoglobin states in ocular tissue.

Laboratory validation then moved to controlled experiments using eye phantoms and oxygenated blood samples.[7,17] These studies compared spectroscopic measurements against established reference standards, helping assess measurement precision under controlled conditions.

Finally, research involving over 1,000 participants examined how the technology performed in real-world settings. These studies found that oxygen saturation patterns aligned with known physiological and pathophysiological states, validating the utility of the technology for investigating metabolic and functional aspects of eye disease.

Applications in Eye Disease Research

Recent research has uncovered the role of oxygen saturation in DR and glaucoma, offering new possibilities for early detection and improved disease monitoring.

StO_2 as a Biomarker for DR

A study of 70 patients, including patients with DR and controls, found that as the disease progresses, oxygen saturation levels in the parafoveal region increase while vascular density declines.[18] These findings suggest that disease progression in diabetic retinopathy is associated with diminished metabolic activity, resulting in lower oxygen utilization in the affected regions.

> Tissue-based ocular oximetry holds great promise to aid in risk prediction, DR monitoring, and clinical decision-making.

StO_2 as a Biomarker for Glaucoma

A study published in the Journal of Glaucoma examined the connection between retinal oxygen saturation (StO_2) and visual field (VF) damage severity in glaucoma patients.[19] Researchers measured StO_2 at two peripapillary locations in 198 eyes from 131 patients, revealing a significant association between increased StO_2 and greater VF damage severity, suggesting that StO_2 could be a valuable biomarker in assessing glaucoma progression.

> This study highlights the potential of retinal oximetry in understanding and monitoring glaucoma.

User Perspective from the Field

The Zilia Ocular has added another potential retinal biomarker and functional tool into my research. It allows us to non-invasively explore local retinal oxygen saturation in ways that weren't possible before. In our studies on diabetic retinopathy and systemic factors influencing retinal oxygenation, its ability to provide real-time metabolic data has given us deeper insights into retinal health.

The local precision and versatility of this technology, in combination with other retinal functional testing, open exciting possibilities for early detection and monitoring of ocular and systemic diseases.

Wendy Harrison, OD, PhD, FAAO
Associate Professor, College of Optometry, University of Houston, Unites States

We have found that by comparing patients with retinal and choroidal diseases—such as diabetic retinopathy, retinal vein occlusion, age-related macular degeneration, retinal detachment, and glaucoma—with their fellow eyes and healthy individuals, it is possible to evaluate the impact of the disease on the oxygen saturation of the retinal tissue.

In the future, ocular oximetry will be useful for determining the severity of disease and the effectiveness of treatment, and it can be used to select the optimal treatment protocol for each individual patient.

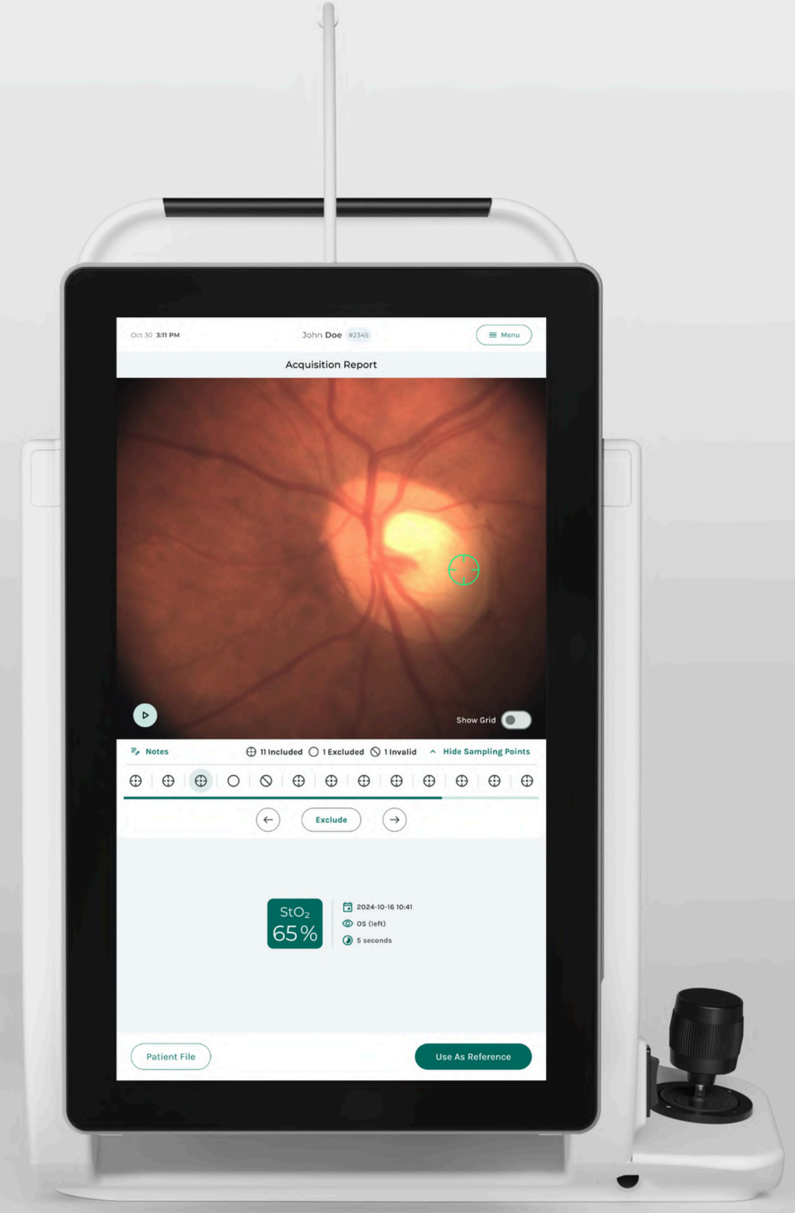
Pr. Kiyoshi Suzuma, MD, PhD
Professor & Chairman, Dept. of Ophthalmology, Faculty of Medicine, Kagawa University, Japan

05 Future Directions

Ocular oximetry is an evolving field that is unlocking new insights into eye health and disease. By detecting metabolic changes that often precede structural damage, it holds the potential to enhance early diagnostic strategies and transform how we detect and manage ocular conditions.

> As functional and metabolic biomarkers become more deeply embedded in research, these tools may significantly advance our understanding of ocular metabolism and its role in disease development.

Continued research will be essential to fully understand the potential applications of this technology. Areas of future investigation include longitudinal studies of disease progression, examination of treatment responses, and relationships between ocular metabolism and systemic health conditions.

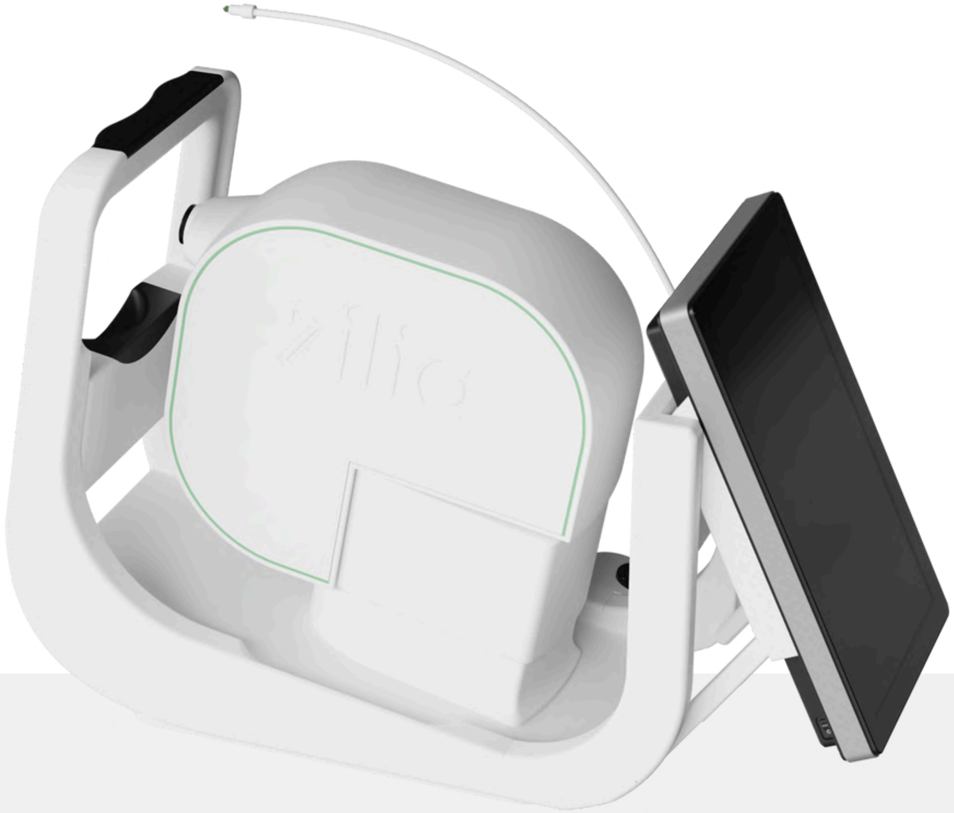


Would you Like to See a Demo?

Interested in exploring how ocular oximetry works?

Book a virtual demo with our team to see the Zilia Ocular in action and to discover potential applications.

Book a Demo



About Zilia

Zilia is a health technology company developing a groundbreaking platform to non-invasively measure biomarkers in the eye, with an initial focus on ocular oximetry. By integrating advanced photonics and artificial intelligence, Zilia's first-of-kind technology is intended to leverage the eye's optical properties and its direct connections to the vascular system and the brain, capturing critical information on ocular and overall health.

Follow us: zilia @ziliainc ziliahealth.com

Regulatory disclaimer: Zilia Ocular is approved for commercial use in Canada by Health Canada. It has not received clearance or approval from the U.S. Food and Drug Administration (FDA) or other international regulatory agencies.

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