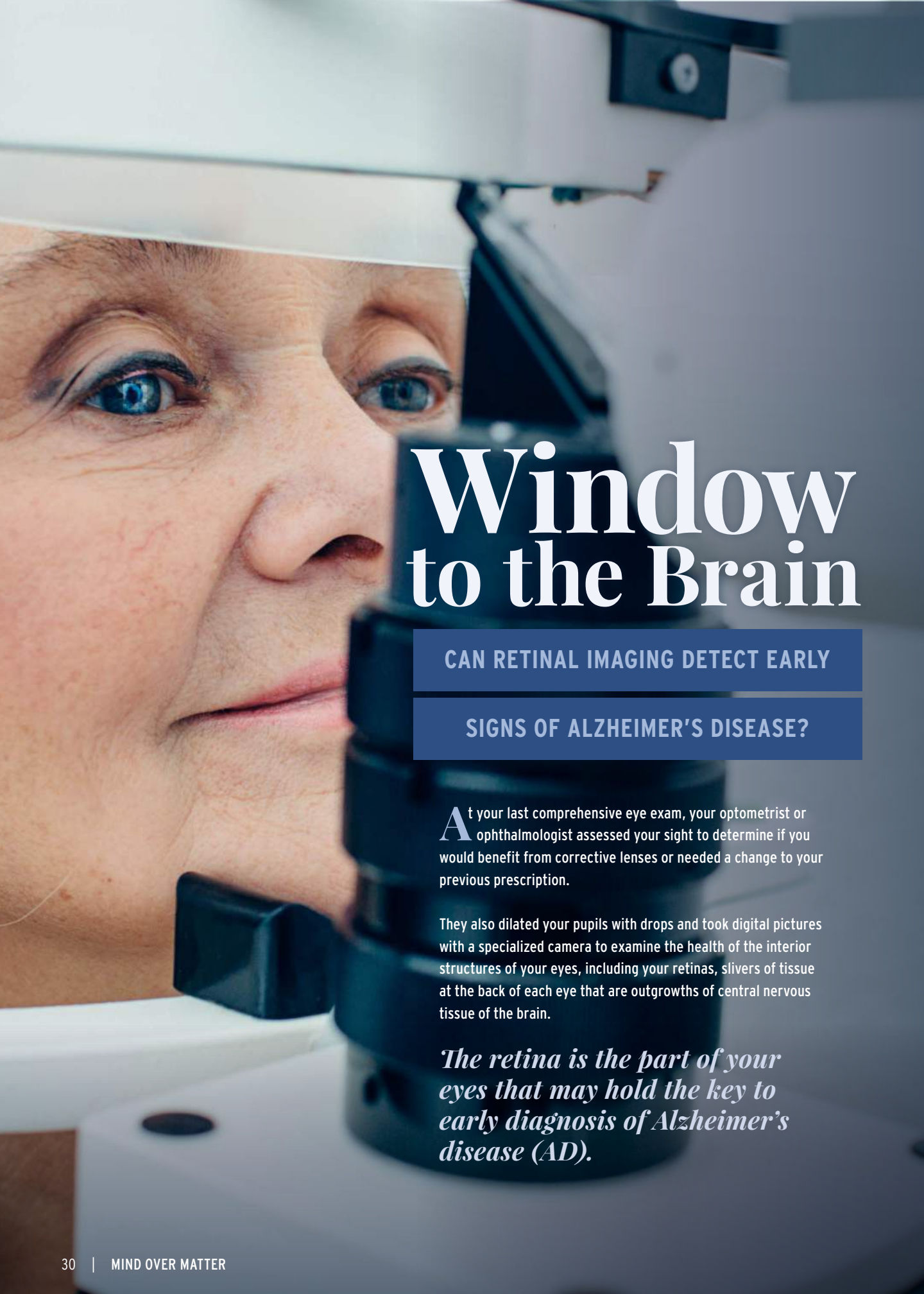


Window to the Brain

CAN RETINAL IMAGING DETECT EARLY SIGNS OF ALZHEIMER'S DISEASE?

At your last comprehensive eye exam, your optometrist or ophthalmologist assessed your sight to determine if you would benefit from corrective lenses or needed a change to your previous prescription.

They also dilated your pupils with drops and took digital pictures with a specialized camera to examine the health of the interior structures of your eyes, including your retinas, slivers of tissue at the back of each eye that are outgrowths of central nervous tissue of the brain.

The retina is the part of your eyes that may hold the key to early diagnosis of Alzheimer's disease (AD).

A fundus camera is a low-power microscope attached to a camera used to take images of the interior of your eye.

Neurologists typically diagnose AD through a full clinical workup, including patient history, blood work, and magnetic resonance imaging. They may also assess biomarkers of AD using positron emission tomography (PET) imaging or cerebrospinal fluid (CSF).

These tests are sensitive enough to detect early signs of amyloid accumulation in the brain decades before symptoms appear. However, they are typically expensive, difficult to access, and invasive: PET imaging involves an injection of a radioactive tracer into the blood, and CSF is collected through a needle placed between vertebrae in the spine in a procedure called a lumbar puncture.

Now, an innovative imaging technology called hyperspectral retinal imaging can detect accumulating amyloid in the retina long before symptoms of cognitive decline occur.

If clinical research continues to show positive results, individuals with memory concerns may soon be able to access a five-minute screening test for early signs of AD as part of a comprehensive eye exam at their local optometry clinic.

HYPERSPECTRAL RETINAL IMAGING

Drs. Robert Vince, Swati More, and James Beach, three researchers at the University of Minnesota's Center for Drug Design, needed a way to measure whether an AD drug they were developing in 2014 worked in preclinical mouse models. They created a specialized hyperspectral camera that attached to standard fundus imaging equipment.

"The drug didn't work out, but the hyperspectral imaging concept became the foundation for our retinal imaging technology," said Dr. Catherine Bornbaum, Chief Business Officer at RetiSpec, the Canadian company that licensed the technology and was the first worldwide to use it to test for the detection of early signs of AD in optometry clinics.

Hyperspectral imaging looks for a change in spectral light in regions of the eye. "When amyloid beta proteins begin to aggregate as toxic oligomers, they reflect light differently in a characteristic pattern called the Rayleigh scatter effect. These changes in the retina are not noticeable to the individual and cannot be detected with a standard fundus camera," said Dr. Bornbaum.

RetiSpec is currently conducting clinical trials at multiple optometry clinics in Canada and the United States. At Victoria Village Optometry in Toronto, one of the clinical trial sites, optometrist Dr. Negar Sohbati asks patients over age 55 if they have memory concerns and, if so, offers them an opportunity to participate in the study.

"Patients fall into three categories: they have no memory issues personally and are happy to see this research is taking place; they have noticed memory issues and are interested in a screening test, especially if they have a family history of the disease; or they have noticed some memory lapses but are fearful about finding out their test results," said Dr. Sohbati.

"For the latter group, I tell them participation is voluntary, and there are new treatment options for delaying disease progression in people with early-stage symptoms. Some take time to consider their decision and return for a test at another appointment."

Different from a standard fundus camera that captures red, green, and blue colours, the hyperspectral camera captures more than 100 wavelengths of colour at a very high resolution. Patients see a brief flash of light, the same as any standard fundus camera, as the camera captures the data.

THE DATA IS ANALYZED USING RETISPEC'S ARTIFICIAL INTELLIGENCE ALGORITHMS THAT COMPARE AN INDIVIDUAL'S RESULTS WITH THOSE WHO WERE DIAGNOSED WITH AD USING PET IMAGING OR CSF.

When clinically available, individuals will learn about their test results from their primary care physician or a nurse practitioner. Those with concerning signs of retinal amyloid deposits are referred to a neurologist for memory testing. Dr. Sohbati noted that while many of her patients have indicated they'd like to know their imaging results on the spot, she doesn't have access. RetiSpec's proprietary artificial intelligence algorithms assess the data and generate patient reports.

PRELIMINARY RESEARCH RESULTS

Preliminary findings from clinical trials of RetiSpec presented at a conference in November 2021 included 108 patients with mild cognitive impairment or preclinical AD. Researchers compared the advanced retinal screening test results with PET and CSF results. RetiSpec correctly identified individuals with brain amyloid 86% of the time and correctly identified those without brain amyloid 80% of the time.

While these results were strong, RetiSpec is collecting more clinical trial evidence before applying to Health Canada and the U.S. Food and Drug Administration for approval. Dr. Bornbaum anticipates approvals for everyday use in optometry clinics in early 2025. →

VISION IMPAIRMENT AND DEMENTIA: A TWO-WAY STREET

Vision impairment is common as we age. For many of us, that means losing the ability to see things up close, having trouble distinguishing colours, like black from blue, or needing more time to adjust to changing light levels. Eye diseases and conditions such as age-related macular degeneration, diabetic retinopathy, cataracts, and glaucoma may also reduce our ability to see well as we age.

Despite having healthy eyes, people with dementia may experience vision problems if dementia affects the part of their brain that handles processing visual information, according to the U.K. Alzheimer's Society. For example, one of the characteristic symptoms of progressive supranuclear palsy, a rare neurodegenerative disorder that otherwise mimics Parkinson's disease, is an inability to focus the eyes.

Even though it may be challenging to separate the signs of sight loss from those of dementia because they can overlap, it's essential to ensure individuals with dementia have eye exams because trouble seeing may increase confusion, the U.K. Alzheimer's Society advises.

A person with dementia can have a sight test, despite the common belief to the contrary.

The test can be adapted for people with dementia by allowing more time, asking questions that only have a yes or no answer or don't require a subjective response, and having a care partner accompany them.

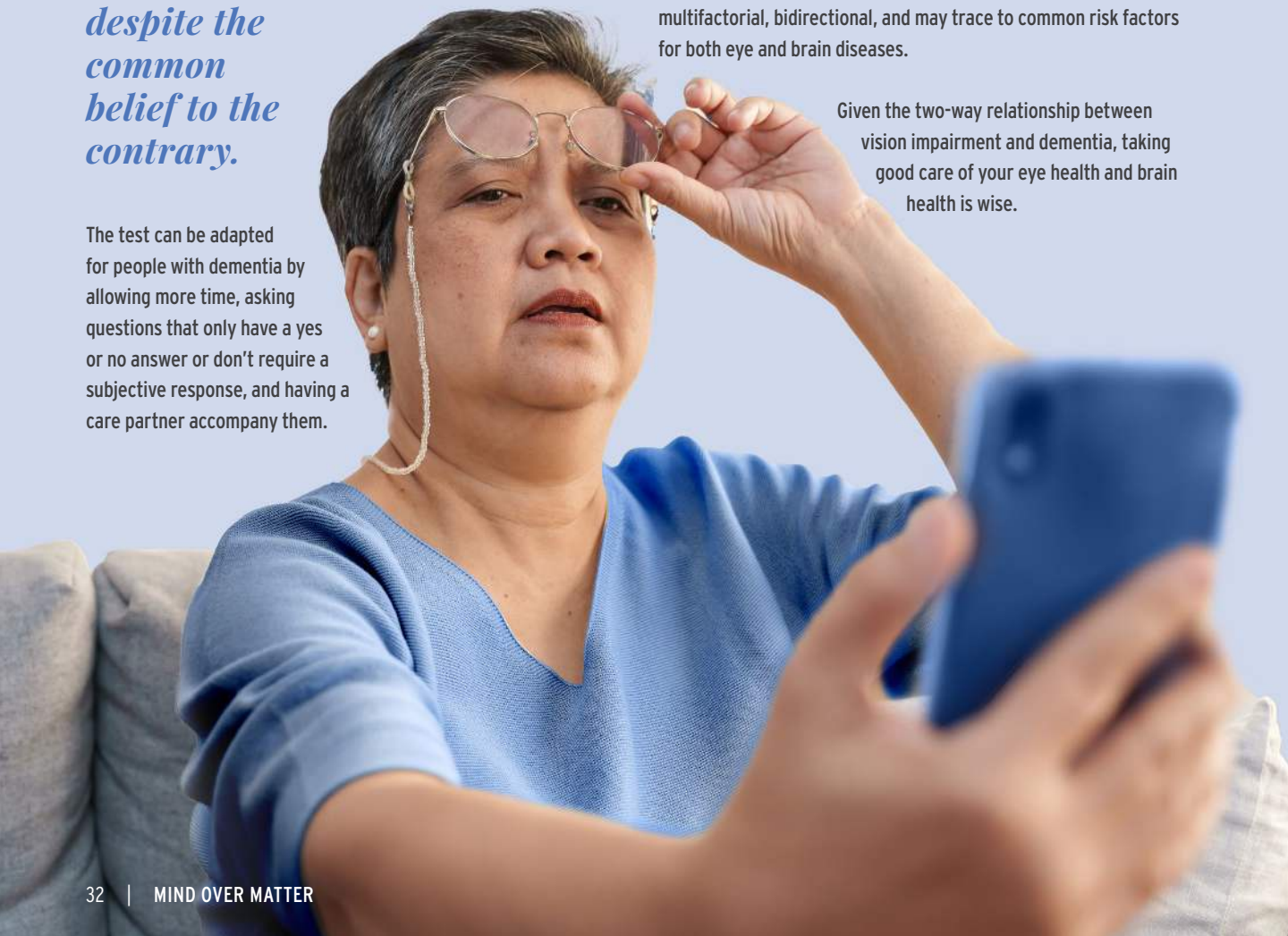
It's easy to see how dementias damaging neurons in the brain can cause vision impairment, but the relationship works in the other direction, too. Vision impairment is a risk factor for dementia and accelerating cognitive decline, according to a systematic review and meta-analysis led by researchers at the University of Hamburg, Hamburg, Germany, published in *Journal of Alzheimer's Disease* in 2021.

After pooling evidence from 30 studies, their analysis found a 38% increased risk for all-cause dementia in people with visual impairment. The investigators also identified that diabetic retinopathy and cataract were associated with a 34% and 17% increased risk of dementia, respectively. They did not find an association between glaucoma or age-related macular degeneration and the risk of dementia.

A retrospective study published in the journal *Ophthalmology* in 2021 explored the relationship between vision impairment and dementia in adults over age 65. Researchers analyzed data for more than 10,000 participants in the U.S. National Health and Aging Trends Study collected from 2011 to 2018.

The investigators found that self-reported vision impairment was associated with a 2.3 times greater likelihood of dementia, and dementia was associated with a 2.5 times greater chance of vision impairment over time. They concluded these associations are likely multifactorial, bidirectional, and may trace to common risk factors for both eye and brain diseases.

Given the two-way relationship between vision impairment and dementia, taking good care of your eye health and brain health is wise.



EARLY DETECTION MATTERS

Diagnosing early signs of AD is essential for making lifestyle changes for slowing cognitive decline and speeding access to the latest treatment options. Moreover, newly approved disease-modifying drugs such as lecanemab (Leqembi®), which was approved by the U.S. Food and Drug Administration in July 2023, are indicated only for individuals with early-stage Alzheimer's disease or mild cognitive impairment.

Current wait times to see a neurologist can be long. One study published in *Alzheimer's & Dementia* in 2021 estimated a 50-month wait time for a referral to see a neurologist based on a brief cognitive test, but when accompanied by a confirmatory biomarker test, the wait time would shorten to 12 months. According to Dr. Sohbati,

> **SCREENING FOR AD AT OPTOMETRY CLINICS USING HYPERSPECTRAL RETINAL IMAGING COULD HELP STREAMLINE PATIENTS REFERRED TO NEUROLOGISTS ON FASTER TIMELINES AND POTENTIALLY ELIMINATE UNNECESSARY REFERRALS.**

"In future clinical research, hyperspectral retinal imaging could also be used as a faster, more accessible, and less invasive way to measure responses to new AD treatments, potentially speeding the time to approval compared to using standard PET and CSF tests," said Dr. Bornbaum.

STAY TUNED

Optina Diagnostics, in Montreal, and NeuroVision Imaging, Inc., in Sacramento, California, are two other companies currently conducting clinical research into hyperspectral retinal imaging for early AD detection.

"While there is still work ahead for validation and approval purposes, the science behind hyperspectral imaging is very strong," said Dr. Bornbaum. "We were in this space before any of the new disease-modifying drugs were available, and we're in good company with others that took the leap to build a new future with more accessible, less invasive, and less expensive testing for detecting early signs of Alzheimer's disease."

COMPREHENSIVE EYE EXAMS CAN DETECT SIGNS OF:

- cardiovascular diseases
- diabetes
- hypertension
- some cancers
- brain injuries
- neurological conditions

COMMON EYE PROBLEMS IN AGING ADULTS

- Presbyopia: loss of the ability to focus on close objects that happens over time as we age. It can cause blurry vision, headaches, sore eyes, and the need for more light.
- Cataracts: the lens becomes cloudy over time, causing blurry or distorted vision. Treatment includes surgical removal or getting an updated lens prescription.
- Diabetic retinopathy: signs of bleeding or the growth of abnormal blood vessels in the retina and retinal swelling due to uncontrolled blood sugar levels. Your eye specialist will refer you to your general practitioner for a blood test.
- Age-related macular degeneration: degeneration of the macula, the part of the eye that enables sharp central vision, leads to a loss of central vision, making it difficult to recognize faces, read, or drive. It is the leading cause of vision loss in older adults.
- Glaucoma: damage to the optic nerve at the back of the eye increases pressure, leading to vision loss and blindness.

BIOMARKERS BEYOND RETINAL AMYLOID

RetiSpec plans to add additional biomarkers to their screening algorithm in the future, including tau tangles and neurofilament light, other proteins known to aggregate abnormally in AD and other neurodegenerative diseases.

"Alzheimer's is our core focus for now, but we are also exploring biomarkers for Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), and chronic traumatic encephalopathy," Dr. Bornbaum said. "Ultimately, we'd like to build a tool that screens for different proteins associated with various neurodegenerative diseases and provide results in one report."