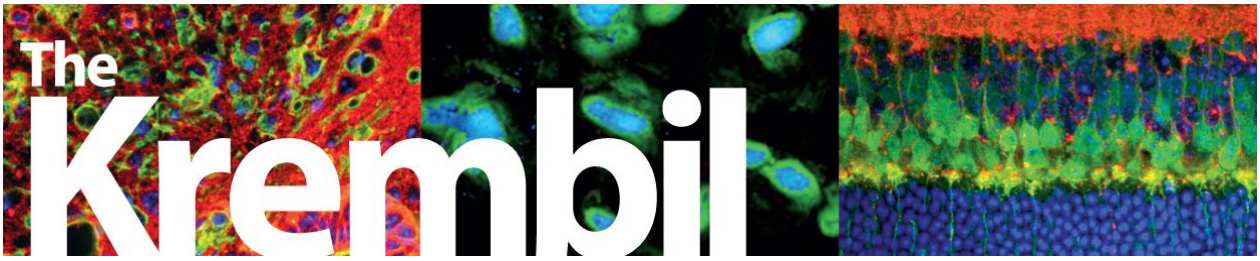


October 2022

The Krembil is the official newsletter of the Krembil Research Institute. It informs the Toronto Western Hospital community, external stakeholders and interested community members about the exciting news and innovative research happening at the Krembil Research Institute.

Stories in this month's issue:

News

Krembil Welcomes New Director

Neuroscientist Dr. Jaideep Bains will take the reins at Krembil.

Following an extensive international search, neuroscientist Dr. Jaideep Bains has been named the new Director of the Krembil Research Institute.

Dr. Bains joins UHN from the University of Calgary, where he served as the Scientific Director of the Hotchkiss Brain Institute, a centre of excellence in brain and mental health research and education. In this role, he chaired the Institute's Strategic Research and Innovation Committee, establishing short- and long-term research priorities and managing a multimillion-dollar annual budget.

Dr. Bains is a highly respected neuroscientist who has spent the last two decades characterizing how the neural circuits that regulate our internal states store information in response to challenges such as stress. His discoveries have advanced our understanding of the roles of particular neuron populations in stress and how animals communicate stress through social interaction and chemical signals. He has an exceptional record of publications and funding acquisition and is a sought-after speaker worldwide.

This appointment follows the nine-year directorship of Dr. Donald Weaver, who will remain at the Krembil as a Senior Scientist researching Alzheimer disease.

“When I began my tenure as Director almost a decade ago, my goal was to foster a team-based approach to research and clinical care that would help to translate discoveries from bench to bedside,” says Dr. Weaver. “Today, I am incredibly pleased with what we have achieved.”

Dr. Bains brings a wealth of experience to the role, not only in scientific research but also in institute management and advocacy. He was selected because of his ability to foster cultures of diversity, collaboration and innovation, and to transform research organizations.

“The Krembil Research Institute is in an excellent position to become a research power internationally,” says Dr. Bains. “We will do this by building a diverse and inclusive culture of excellence, supporting individual investigators while also creating a rich environment where synergy can occur.”

“Our international search attracted a pool of exceptional candidates from around the world,” says Dr. Bradly Wouters, Executive Vice-President of Science and Research at UHN. “The interest in this position is a testament to UHN’s outstanding global reputation for research excellence, and we are extremely excited to attract someone the caliber of Dr. Bains.”

Congratulations, Dr. Bains!

We Are Krembil: 2022 Annual Report

Read the latest report to learn how we are working together to improve lives.

The 2022 report features recent discoveries from Krembil's three research institutes: the Krembil Brain Institute, the Donald K. Johnson Eye Institute and the Schroeder Arthritis Institute.

Science is a team sport.

Every discovery and clinical breakthrough that comes out of the Krembil is a direct result of teamwork.

We attribute our success to many people with unique ideas, perspectives and skills coming together with a shared goal of improving lives.

In the 2022 Krembil Annual Report, we want to introduce you to some of the people who make our Institute what it is—from our dedicated staff who support research and patient care, to our passionate patient partners who inspire us to keep going.

This report highlights a selection of the research achievements that we have made together over the past year, including:

- developing a model for early-stage Parkinson disease with the potential to accelerate drug discovery;

- optimizing an innovative tool for testing drugs to treat eye diseases such as glaucoma; and
- discovering a possible treatment target for a severe form of arthritis

The report also highlights some of Krembil's recent outreach events and initiatives, including a new podcast geared towards making science accessible and engaging to everyone.

Click here to read the report.

Research

Improving Health for All

Researchers identify the main causes of neurotrauma burden in Indigenous populations of Canada.

Indigenous communities in Canada experience high rates of brain and spinal cord injury. Improving health and well-being in these communities requires an understanding of the factors that increase injury risk and improving access to high-quality, culturally sensitive care.

Researchers at the Krembil Brain Institute have identified key factors that contribute to high rates of brain and spinal cord injury in Indigenous populations of Canada, as well as strategies to address this health care issue around the world.

Across Canada, Indigenous peoples tend to have poorer health status compared with the non-Indigenous population, and injury rates are much higher in these groups than in the rest of the country.

“Neurotrauma—including traumatic brain and spinal cord injuries—annually accounts for over 24,000 hospitalizations in Canada, and Indigenous peoples are disproportionately

affected," says Dr. Michael Fehlings, a Senior Scientist at the Krembil Brain Institute and the senior author of the study.

To explore the major factors that contribute to neurotrauma in Indigenous populations, Dr. Fehlings' team reviewed the results of 17 published studies about the causes and management of neurotrauma.

Factors contributing to the burden of neurotrauma in Indigenous populations fell into three themes:

1. inadequate resources leading to compromised safety and limited access to health care;
2. social issues within Indigenous communities leading to increased risk of injury; and
3. challenges within the health care system leading to a lower standard of care received by Indigenous people.

Specific factors found to increase the risk of neurotrauma among Indigenous peoples included unsafe housing, workplace and road conditions, community violence, and inadequate education on brain and spinal cord injuries. Factors that increased the burden of neurotrauma included barriers to receiving patient-centered care and limited access to rehabilitation services and assistive devices such as wheelchairs.

The researchers next explored strategies to address neurotrauma in Indigenous communities. Proposed strategies included changes to the health care system, such as increasing access to translators, increasing education for health care workers so they can provide culturally sensitive care, incorporating traditional healing approaches and increasing the supports available to patients once they leave the hospital. There was also an emphasis on increasing funding to reduce costs of transportation to receive medical care and to enable elders and traditional healers to travel with families during the treatment process to provide spiritual guidance.

The evidence generated from this study will help health care workers and the government develop strategies to prevent and manage neurotrauma in Indigenous populations.

The next steps for this research include determining the leading causes of neurotrauma in individual Indigenous communities, particularly those in the territories and Atlantic provinces, which the team did not assess in this study. It will also be crucial to work with Indigenous partners to gain a holistic understanding of how neurotrauma affects their communities.

"Canada has more than 630 distinct Indigenous communities, each with unique cultural and social factors that can influence the rates and experience of brain and spinal cord injury," explains Zaid Salaheen, a medical student at the University of Toronto and the first author of the study. "Identifying community-specific factors that influence injury

rates and burden is critical for developing tailored, culturally appropriate strategies to address this serious health issue."

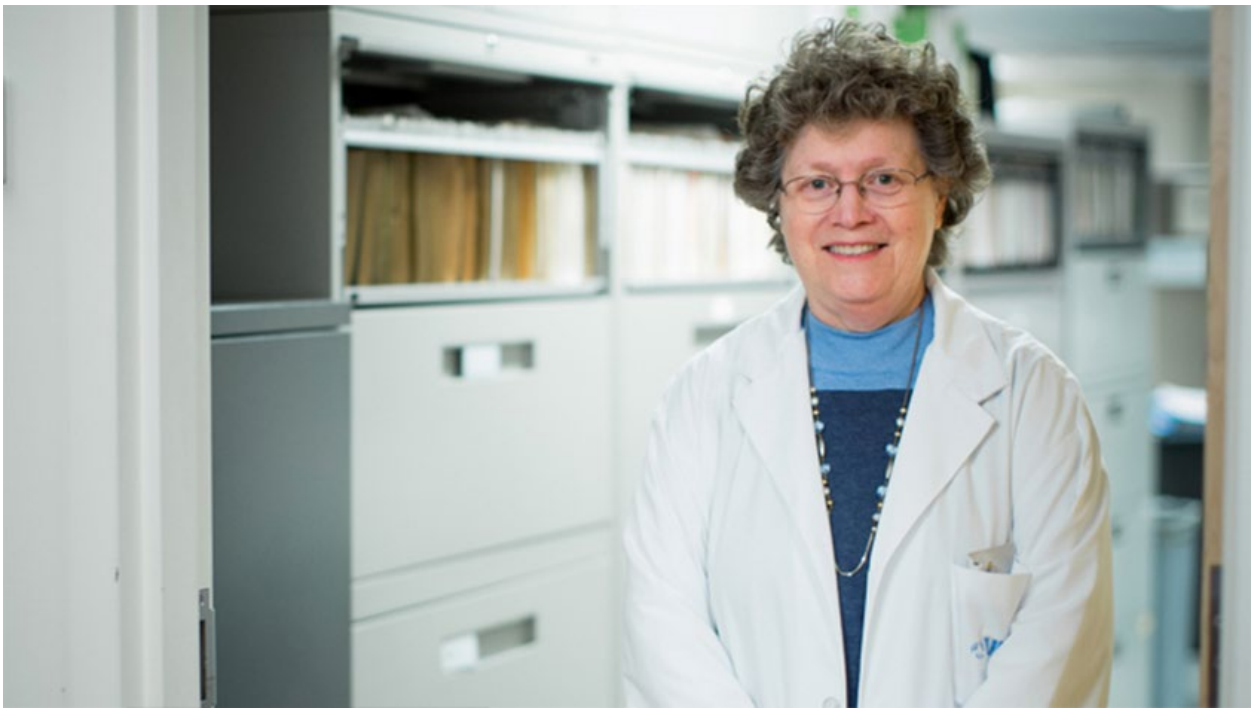
This work was supported by the UHN Foundation. Dr. Michael Fehlings is a Professor of Neurosurgery at the University of Toronto and the Robert Campeau Family Foundation/Dr. C.H. Tator Chair in Brain and Spinal Cord Research at University Health Network.

Salaheen Z, Moghaddamjou A, Fehlings M. Neurotrauma in Indigenous Populations of Canada - Challenges and Opportunities at a Global Level: A Scoping Review. World Neurosurg. 2022 Aug 1. doi: 10.1016/j.wneu.2022.07.108.

Zaid Salaheen (left) is a medical student at the University of Toronto and a student in Dr. Fehlings' lab. Dr. Michael Fehlings (right) is Senior Scientist at the Krembil Brain Institute and Head of the Spinal Program at the Toronto Western Hospital.

Patiently Waiting

Study identifies key causes of long wait times for rheumatology consults in Toronto.



Dr. Dafna Gladman is a Senior Scientist at the Schroeder Arthritis Institute and the Director of the Psoriatic Arthritis Program at the Toronto Western Hospital (Photo: The Globe and Mail).

Researchers at the Schroeder Arthritis Institute have uncovered key reasons why patients are often unable to see a rheumatologist at the Toronto Western Hospital Psoriatic Arthritis Clinic within the recommended time from their referral.

Psoriatic arthritis is a severe form of arthritis that is linked to psoriasis, a chronic inflammatory skin disease. The Canadian Rheumatology Association and the Spondyloarthritis Research Consortium of Canada recommend that individuals with symptoms of psoriatic arthritis be assessed by a rheumatologist within six weeks of their referral.

“Even short delays in diagnosing psoriatic arthritis can lead to worse outcomes for patients, including the development of irreversible joint damage,” explains Dr. Dafna Gladman, a Senior Scientist at the Schroeder Arthritis Institute and the senior author of the study. “Patients regularly face long wait times to see specialists in Toronto, and this is a major issue for the Toronto Western Hospital Psoriatic Arthritis Clinic. We wanted to get a clear picture of the percentage of our patients that are seen within the recommended time frame and identify reasons for delays.”

The team reviewed medical records and referral letters for 168 patients who were seen at the clinic between January 2013 and May 2019. “Using these data, we dug deep to examine what happens from the time that a referral is received at the Clinic to when the patient first sees a rheumatologist,” explains Dr. Gladman.

The team discovered that the average time from referral to rheumatologist consult was approximately 11 weeks. Only one quarter of patients were seen within the recommended six-week period.

The team determined that the primary cause of delays was a lack of spots at the clinic, suggesting a lack of resources and availability of clinicians who specialize in psoriatic arthritis.

The researchers also found that there was a disparity in wait times related to the location of referring physicians. Patients whose physician worked closer to the hospital were more likely to see a rheumatologist within six weeks from their referral than those whose physicians worked farther away. One reason for this might be because, if a patient lives further away, they may have less flexibility in terms of when they can make a scheduled appointment. This finding highlights the inequities and barriers to accessing care faced by individuals in rural communities.

“The Psoriatic Arthritis Clinic is a leader in arthritis care in Canada, but we need to do better to ensure that patients can access our services in a timely fashion,” says Dr. Gladman. “Our findings support the value of ongoing efforts to reduce wait times, such as implementing alternative models of care including specialized physiotherapy assessment, telehealth or establishing early arthritis clinics as intermediate points of care.”

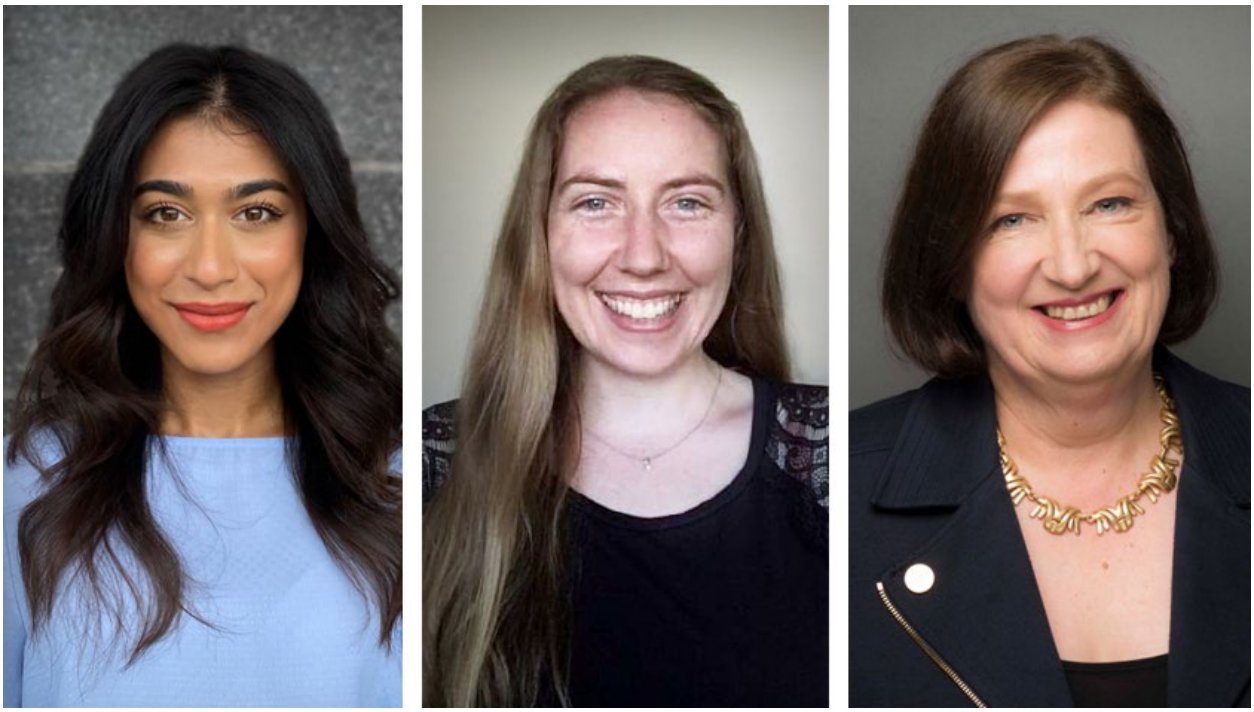
This work was supported by the Canadian Institutes of Health Research, the Krembil Foundation and the UHN Foundation. Dr. Dafna Gladman is a Professor in the Faculty of Medicine at the University of Toronto. She is also the Director of the Psoriatic Arthritis Program, Co-Director of the Lupus Clinic and Deputy Director of the Centre for Prognosis Studies in Rheumatic Diseases at the Toronto Western Hospital.

Park S, Silverberg OM, Moez E, Chandran V, Gladman DD. Investigation into the wait time for consultation in the psoriatic arthritis program. Clin Rheumatol. 2022 Jul 22. doi: 10.1007/s10067-022-06288-8.

Patients regularly face long wait times for rheumatology specialists in Toronto, which must be addressed to improve health outcomes.

Maintaining Immune Balance

A cellular balancing act keeps people with antinuclear antibodies from developing autoimmunity.



L-R: Co-first authors Rashi Gupta and Emma Vanlieshout, and senior author Dr. Joan Wither.

Researchers at the Schroeder Arthritis Institute have identified immune system factors that prevent and promote the development of systemic autoimmune rheumatic diseases (SARDs).

SARDs are rare inflammatory conditions, including lupus and Sjögren's disease, that are associated with the production of high levels of antinuclear antibodies (ANAs)—antibodies that attack the body's own tissues.

A positive ANA test—meaning that ANAs have been detected in a patient's blood—typically indicates the presence of an autoimmune disease; however, healthy individuals can also have positive ANA tests and ANAs can be detected years before the onset of autoimmune symptoms.

"It is largely unknown what immunological changes promote symptom development in SARDs and what factors prevent autoimmunity in asymptomatic individuals who have a positive ANA test," explains Dr. Joan Wither, a Senior Scientist at the Schroeder Arthritis Institute and the senior author of the study. "A better understanding of these

factors can help clinicians identify patients who are at risk of developing symptoms in the near future."

To determine the factors that promote or prevent SARD symptoms, Dr. Wither's team characterized the amount and activity of immune cells in the blood of individuals with and without symptoms that took an ANA test. Twenty of the individuals with no symptoms at the time of their ANA test went on to develop a SARD over the two-year study period, providing an opportunity to identify critical differences that may point to the risk of SARDs.

The team discovered that people with a positive ANA test had high levels of particular immune cells, such as antibody-producing B cells and T helper cells, compared to individuals who had a negative ANA test. People with symptoms had higher levels of pro-inflammatory cells than those without symptoms. In those who progressed to develop SARD symptoms, the researchers identified higher levels of particular inflammatory and regulatory immune cells.

These findings suggest that the key difference between symptomatic and asymptomatic individuals with positive ANA tests lies in the balance between pro-inflammatory and regulatory immune cell activity. This delicate balance is disrupted in SARDs in a way that favours inflammation.

"Our discovery of immune system features that contribute to the development of SARD symptoms can guide the development of improved tests to diagnose SARDs and predict symptom progression," says Rashi Gupta, a master's student in Dr. Wither's lab and co-first author of the study. "We may also be able to eventually target these features to slow or prevent symptom progression."

"SARDs affects about 0.5% of Canadian adults and the symptoms can be debilitating," adds Emma Vanlieshout, a PhD student in Dr. Wither's lab and co-first author of the study. "If we can diagnose these conditions early, before symptom onset, we have a better chance of treating them and improving patients' quality of life."

This work was supported by the Canadian Institutes of Health Research, the University of Toronto Pfizer Chair Research Award, the Arthritis Centre of Excellence, Arthritis Society Canada, the Schroeder Arthritis Institute and the UHN Foundation. Dr. Linda Hiraki holds a Tier 2 Canada Research Chair in Genetics of Rare Systemic Inflammatory Diseases. Dr. Joan Wither is a Professor of Medicine at the University of Toronto.

Gupta R, Vanlieshout E, Manion K, Bonilla D, Kim M, Muñoz-Grajales C, Nassar C, Johnson SR, Hiraki LT, Ahmad Z, Touma Z, Bookman A, Wither JE. Altered Balance of Pro-Inflammatory Immune Cells to T Regulatory Cells Differentiates Symptomatic From Asymptomatic Individuals With Anti-Nuclear Antibodies. Front Immunol. 2022 Jun 30. doi: 10.3389/fimmu.2022.886442.

Autoimmune diseases are often likened to a war being waged internally. Rather than producing antibodies to target invading bacteria and viruses, the body makes autoantibodies that target healthy tissue.

The Other Eye

Researchers discover that NAION vision loss can go unnoticed until it affects both eyes.

It is not uncommon for a NAION episode to go undetected, remaining 'in the dark' until a second episode affects the other eye and causes significant visual changes.

A research team led by Dr. Edward Margolin, a Clinician Investigator at the Krembil Research Institute, has found that a particular form of vision loss known as NAION occasionally occurs in both eyes, despite seeming to affect only one.

NAION (nonarteritic anterior ischemic optic neuropathy) occurs when blood flow to the nerve that connects the eyes to the brain becomes reduced, specifically at the point where the nerve meets with one of the eyes. The loss of blood flow causes nerve damage that typically results in a sudden but painless loss of vision in the affected eye.

Although NAION episodes only affect one eye, approximately 15% of individuals who experience one episode will experience a second that affects their other eye within five years. Intriguingly, when doctors assess patients after a single NAION episode, they often detect minor vision changes in the unaffected eye that the patients had not noticed.

"We wanted to determine whether a substantial portion of the NAION cases that we see in the clinic could be second episodes, with a previous episode having already affected the other eye but going unrecognized," says Dr. Margolin.

To explore this idea, the research team reviewed nearly 140 past cases of NAION diagnosed in Toronto. In each case, the team reassessed previous eye exams, and medical images and records.

The team found that 10% of these patients had experienced unrecognized episodes in the other eye, accounting for almost 60% of unnoticed vision defects. Interestingly, all the unrecognized episodes had caused defects in the patients' fields of view that overlapped with those that were later successfully diagnosed.

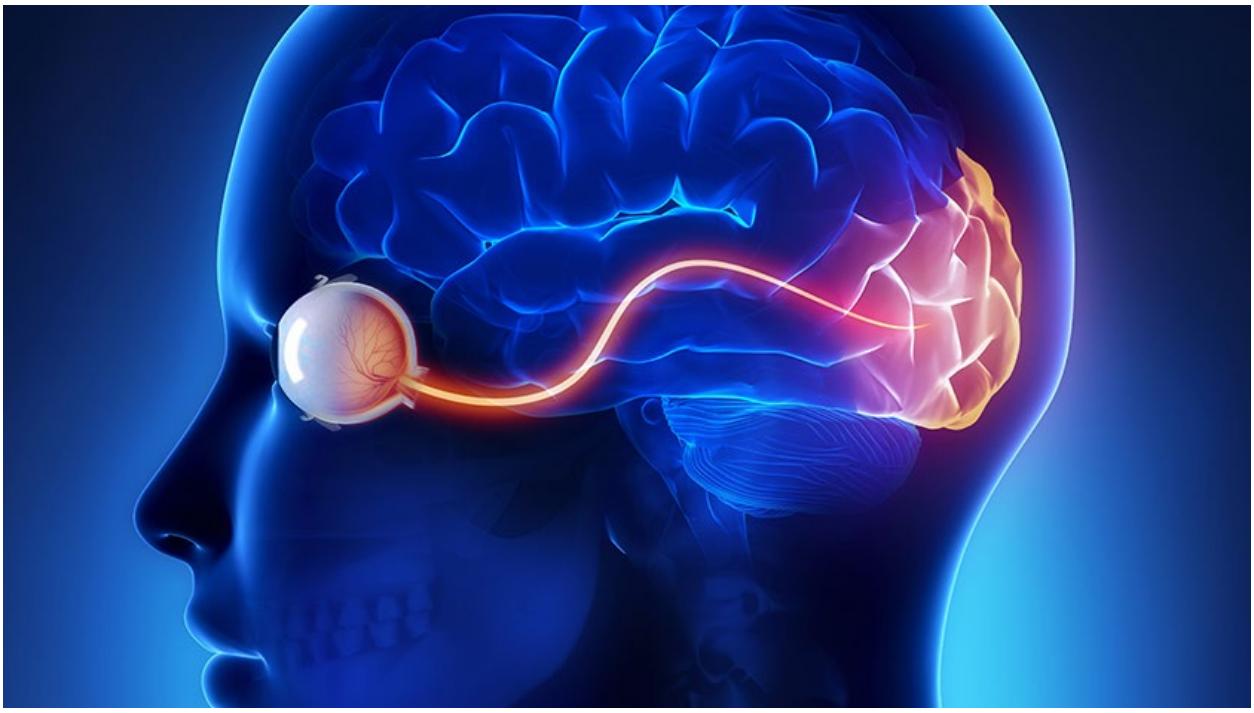
"Redundancy in our vision could explain why patients often do not notice a problem until NAION episodes affect both eyes," says Dr. Margolin. "There is considerable overlap in what each eye sees."

Repeat episodes in the same eye are rare, so knowing whether the other eye has already undergone a NAION episode is important for deciding whether significant preventative action should be taken.

"Our study highlights the importance of carefully examining each eye after a NAION episode," says Dr. Natalie Brossard Barbosa, a former clinical fellow of Dr. Margolin and the first author of the study. "Modifiable factors such as a history of smoking, diabetes, high blood pressure and sleep apnea elevate the risk for NAION, so lifestyle changes or medications can be used to minimize a patient's risk of experiencing additional episodes."

This work was supported by the UHN Foundation. Edward Margolin is a Professor of Ophthalmology and Vision Sciences at the University of Toronto.

Brossard Barbosa N, Donaldson L, Margolin E. Asymptomatic Fellow Eye Involvement in Nonarteritic Anterior Ischemic Optic Neuropathy. J Neuroophthalmol. 2022 Jun 23. doi: 10.1097/WNO.0000000000001644.



Information collected from the eyes is carried to the brain through the optic nerve, creating the sensation of sight. Each eye connects to this nerve at a point called the optic disc, a small region at the back of the eye where NAION can occur.