Advocating for Improved Treatment and Outcomes for Diabetic Macular Edema in Canada

A report based on the Canadian National Multi-Stakeholder Expert Summit for Diabetic Macular Edema convened in Toronto, January 2015

The Angiogenesis Foundation

KEY POINTS

1. Diabetic macular edema (DME) is a significant — and growing — public health issue, both globally and in Canada. It's estimated that currently about 60,000 Canadians have DME-related vision impairment, making it a leading cause of vision loss in the country.

2. The number of Canadians living with diagnosed diabetes is expected to grow to at least 3.7 million by the year 2020. As a result, DME will become an ever-increasing health problem that will exact a severe socioeconomic burden on individuals, communities, and the nation's health system. Researchers have estimated, for example, that in 2014 DME-related healthcare expenditures per patient per year totaled CAD$4,184.

3. During the past decade, the development of VEGF-targeted drugs has produced a true paradigm shift in the treatment of DME. Patients now have an effective treatment option that not only stabilizes DME-related vision loss, but also, in many cases, helps to reverse it.

4. The rapid development of advances in the treatment of DME has led to new questions about how the diagnosis and long-term management of the disease is currently being addressed both globally and in individual countries — and how those care pathways can be improved.

5. There is a persistent concern that the majority of patients with DME, even in a country like Canada with a relatively well-liked and well-working health system, are not receiving the optimal evidence-based care that they need to maintain vision and prevent progressive vision loss.

6. All DME stakeholders in Canada — patients, caregivers, clinicians, patient-advocates, and government policymakers — need to work together to overcome current diagnostic and treatment gaps to create a continuum of care for people with DME that is efficient, effective, and compassionate.

CALLS TO ACTION

Educate DME Stakeholders
- Encourage national screening and awareness initiatives
- Empower care providers with evidence-based treatment information
- Prioritize diabetic eye care among all involved stakeholders

Improve the DME pathway of care
- Create meaningful resources for patients and providers
- Promote multi-disciplinary care teams and communication
- Advocate for greater treatment access and reimbursement

Gather — and disseminate — more data
- Support national data collection and dissemination efforts
- Identify and target high-risk patients
- Advocate for national databases and encourage future research

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What Is DME?

Diabetic macular edema (DME) is a consequence of diabetic retinopathy, an eye-related complication of both type 1 and type 2 diabetes. Diabetic retinopathy develops when chronically high levels of blood sugar (glucose) damage and block the tiny blood vessels (capillaries) in the retina of the eye. Cut off from oxygen, the hypoxic retinal tissue responds by increasing, or upregulating, the expression of a small glycoprotein called vascular endothelial growth factor (VEGF). As a result of the elevated levels of VEGF, the retinal capillaries become leaky, causing the macula to swell and thicken, distorting vision.[1] This is the condition known as DME.

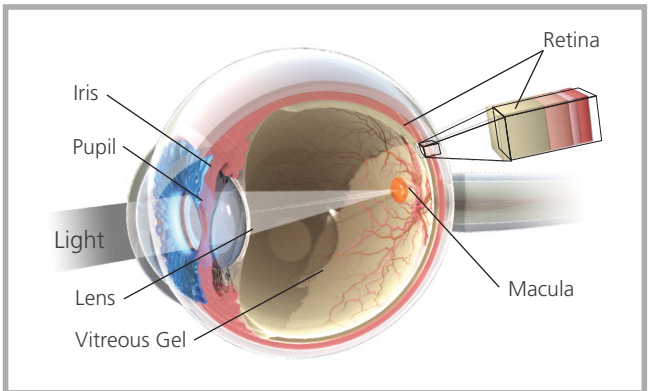

Figure 1. *Anatomy of the eye*

Defining DME

In many regions of the world, diabetic retinopathy is the leading cause of vision loss among working-age adults (20-74 years).[1] Furthermore, among people with diabetic retinopathy, the most frequent cause of vision loss is DME. One large epidemiological study found, for example, that 26% of patients with diabetic retinopathy have DME.[2] The International Diabetes Federation (IDF) estimates that among all people with diabetes, 11% have DME,[3] and that percentage increases to 29% among people who have lived with diabetes for 20 years or more.[4]

Given that an estimated 387 million people worldwide have diabetes, DME represents a significant public health issue.[5] It is also a growing public health concern, for the number of people with diabetes is expected to increase to almost 592 million by 2035 — or 10% of the world's adult population.[5]

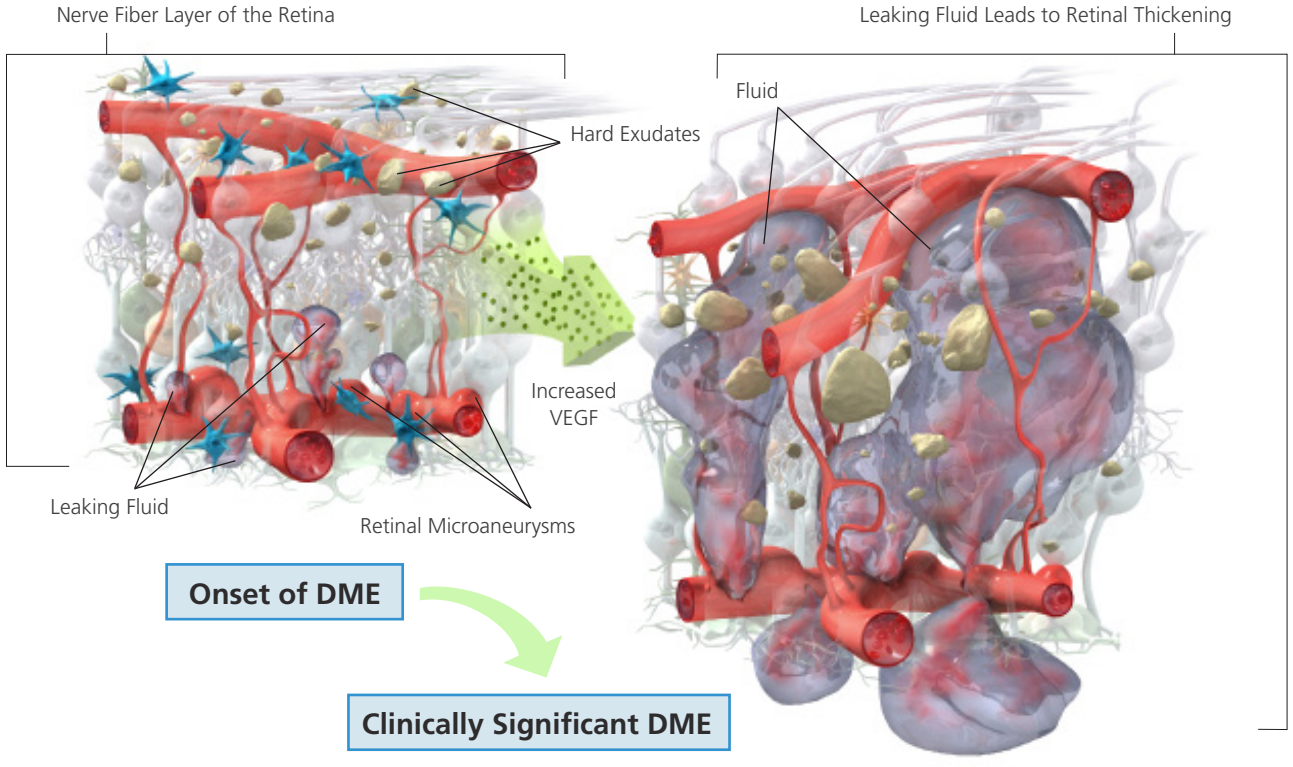

Figure 2. *3D representation of the development of DME*

Figure 3. *Comparison of normal vision to vision with DME*

DME in Canada

In Canada, an estimated 6.8% of children and adults — 2.4 million individuals — have diabetes, according to the Public Health Agency of Canada.[6] Little is known about the epidemiology of DME in Canada, but a 2012 study estimated the prevalence of DME among adults living with diabetes in Ottawa to be 15.7%, and the prevalence of vision loss due to DME among that same cohort to be 2.5%.[7] Those findings suggest that, nationally, about 60,000 Canadians have DME-related vision impairment, making it a leading cause of vision loss in the country.[8]

In addition to the personal, social, and economic burden that it imposes on individuals and their families, vision loss is also responsible for the highest direct healthcare costs and the fourth highest indirect costs (primarily lost productivity) of any major medical condition in Canada.[9] DME-related vision loss is a major contributor to those costs. In 2014, researchers estimated that DME-related healthcare expenditures per patient per year in Canada totaled CAD$4,184.[10] The DME-related economic burden to the country will only increase in the coming years, for the number of Canadians living with diagnosed diabetes is expected to grow by more than 50% to 3.7 million by 2018-2019.[6]

The structure of Canada's health system exacerbates the challenges of identifying and treating patients with DME. Through the Canada Health Act of 1984, the funding of core hospital and medical services occurs at the federal level, while the visioning and implementation of services is relegated to the provinces and territories. This approach has resulted in, essentially, 10 separate provincial (and three territorial) systems for which the government is the single payer. The effects of such a siloed system include fragmented care, inconsistencies in treatment and access, and variations in cost. While advances in treatments and public awareness have created an impetus for more coordinated, outcomes-based care in Canada, the lack of standardized policies across provinces remains a significant barrier.

Anti-VEGF Therapies for the Management of DME

When it became clear that VEGF performs a role in the development of DME, researchers went to work identifying and then evaluating the impact of anti-VEGF drugs — pegaptanib, ranibizumab, aflibercept, and bevacizumab (bevacizumab is used off-label, approved to treat a variety of solid tumors) — on the clinical management of the disease. All four drugs have been shown to be effective, but only two — ranibizumab and aflibercept — have received regulatory approval in Canada for the treatment of DME.

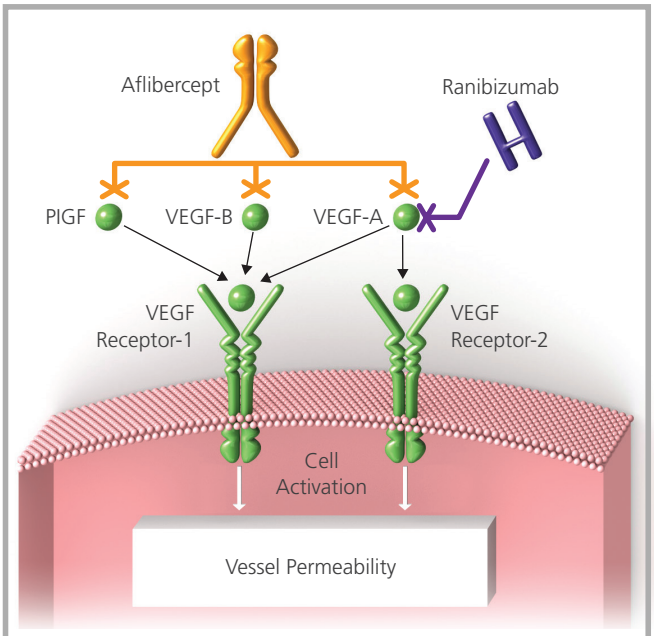

Figure 4. *FDA-approved anti-VEGF treatments for DME*

Ranibizumab

Ranibizumab received regulatory approval for the treatment of DME by the European Union's Committee for Medicinal Products for Human Use in 2010. Other country-specific approvals soon followed, including by Health Canada in 2011[11] and by the U.S. Food and Drug Administration (FDA) in 2012.[12] Most countries had previously approved ranibizumab for the treatment of wet age-related macular degeneration (wet AMD) and for macular edema following retinal vein occlusion (RVO).

Ranibizumab's efficacy and safety for the treatment of DME were first established in the RISE and RIDE studies, two randomized clinical trials involving 759 patients who were treated and followed for three years.[13] The studies found that between 34% and 45% of patients treated with monthly ranibizumab intravitreal injections of 0.3 or 0.5 milligrams (mg) gained at least three lines of vision on a standardized vision chart compared with 12% to 18% of patients who received sham (placebo) injections. The most common side effects observed were intraocular pressure, bleeding in the membrane (conjunctiva) that lines the inside of the eyelids, eye pain, and vitreous floaters (shadowy specks or strings of material that float across the field of vision). Based on these clinical trials, the FDA approved a monthly ranibizumab dose of 0.3 mg for the treatment of DME because the studies found no additional benefit for the higher dose of 0.5 mg. The approval of ranibizumab for the treatment of DME in Canada was based on the RESTORE study, which involved 345 patients at 73 retina clinics in Canada, Australia, and Europe.[14] The patients were randomly assigned to one of three treatment groups: ranibizumab injections (0.5 mg) plus sham laser therapy, ranibizumab injections plus laser therapy, or sham ranibizumab injections plus laser therapy. The study found that after 12 months, the patients who had received ranibizumab alone or in combination with laser had significantly better visual acuity scores, on average, than the patients who received standard laser therapy alone.

Aflibercept

In 2014, aflibercept received governmental approved for the treatment of DME in Canada, the United States and the European Union.[15] All three had previously approved aflibercept for the treatment of wet AMD and for macular edema following central retinal vein occlusion (CRVO). The approval of aflibercept for the treatment of DME was based on the results of the VIVID and VISTA trials, two clinical trials involving 872 patients.[16] These studies found that, after 52 weeks, patients treated monthly with 2.0 mg of aflibercept for five months and then every two months afterwards gained, on average, two additional lines on a standardized vision chart compared to patients treated with laser therapy. The most common side effects observed in the studies were conjunctival bleeding, cataracts, eye pain, and vitreous floaters.

With the advent of anti-VEGF drugs, clinicians could offer their patients with DME the opportunity to not only stop vision loss, but, in many cases, to reverse that loss. These drugs have several drawbacks, most notably the burden that receiving multiple injections over many months places on patients and caregivers.

Expert Summit: Identifying and Meeting a Need

By early 2014, it had become clear that rapid advances in anti-VEGF therapies were revolutionizing the treatment of DME — and the field of ophthalmology. Recognizing the clinically transformative nature of these remarkable therapies, the Angiogenesis Foundation decided to bring together the DME stakeholder community to review the impact that the new drugs are having on the treatment of DME; the challenges that such treatments present to patients, clinicians, advocates, and policymakers; and the questions that still need to be answered to ensure the very best outcomes for patients with the disease.

As a scientific nonprofit organization with expertise in how anti-VEGF therapies are used across many different indications, the Angiogenesis Foundation was well positioned to play the role of the neutral facilitator of such a review. The Foundation hosted a global summit comprised of a group of international leaders in DME treatment and translational science — a summit similar to successful ones the Foundation has hosted on other angiogenesis-related diseases, including wet AMD and metastatic colorectal cancer (mCRC). The International Expert Summit on Advocating for Improved Treatment and Outcomes for Diabetic Macular Edema, was convened in Paris, France, on June 22, 2014. It was clear from that global summit that different countries and regions of the world face their own specific challenges regarding DME prevention, diagnosis, and treatment.

To assist in identifying regional and country-specific solutions for these challenges, the Angiogenesis Foundation has begun to work in collaboration with DME stakeholders across the globe to organize a series of regional summits. The first of these, the Canadian National Multi-Stakeholder Expert Summit for Diabetic Macular Edema, was convened in Toronto on January 17, 2015. Dr. William Li, president, medical director, and

co-founder of the Angiogenesis Foundation, was the chair of the event.

The Canadian summit, like the global one in Paris, was not a traditional scientific meeting, but rather an interactive, professionally moderated set of roundtable discussions that aimed to establish a dialog and agreement among the participants. The summit opened with three short presentations. The first presentation outlined the scope of the burden from DME-related vision loss and its public health implications; the second offered an overview of the disease's etiology, diagnosis, treatment options, and long-term management; and the third provided a state-of-the-art review of anti-VEGF therapies. Under the direction of a moderator, the 17 assembled experts then engaged in a discussion that defined and prioritized the greatest concerns that different DME stakeholders — patients with diabetes, caregivers, and physicians and other clinicians — have regarding the potential for vision loss both before and after the patient is diagnosed with DME. A graphic facilitator captured key points of this and all other discussions via live illustration during the meeting, enabling the participants to visually review the content of their conversations as they worked through the tasks at hand.

Once the key stakeholder values were identified, the summit's experts focused on mapping current care pathways for the treatment of DME, starting with awareness and screening and moving through diagnosis, referral, treatment, and follow-up. Next, the participants turned their focus to identifying the gaps between those care pathways and the vision-related concerns of various DME stakeholders. The meeting ended with the experts compiling a list of recommended "action steps" for Canada's DME stakeholders — patients, caregivers, clinicians, patient-advocacy groups, and policymakers — to undertake. This white paper is a result of the open, comprehensive, and lively discussions that took place during the summit. It offers detailed summaries of the key points raised during the meeting.

The Role of The Angiogenesis Foundation

Founded in 1994 and headquartered in Cambridge, Massachusetts, the Angiogenesis Foundation is the world's first 501(c)(3) nonprofit organization dedicated to conquering disease with approaches based on angiogenesis, the growth of new blood vessels in the body. Its global mission is to help people benefit from the full promise of angiogenesis-based medicine, and to make life-, limb-, and vision-saving treatments available to everyone in need.

Figure 5. *Canadian National DME Expert Summit, Toronto, January 2015*

As a scientific organization, the Angiogenesis Foundation is independent of any individual, institution, or commercial entity, and, as such, it takes a unique approach to achieving its mission to help people lead longer, better, and healthier lives. It has helped propel innovative research involving both angiogenesis inhibitors and stimulators. Although much of this research has been pharmacological, promising studies involving nutrition and biomarkers are also being actively pursued. In addition, the Angiogenesis Foundation is constantly looking for ways to innovate new and more effective prevention and care pathways.

Angiogenesis-related research is being conducted across a remarkably wide variety of disease states. In recent years, for example, profound angiogenesis-treatment breakthroughs have been discovered in oncology, wound care, and cardiovascular disease, as well as in ophthalmology. The Angiogenesis Foundation recognizes the challenges of optimizing patient care and outcomes with such paradigm-shifting discoveries as anti-VEGF treatments for DME. It also deeply understands that to meet the goal of improving global health through angiogenesis-based medicine, the complex needs of all the stakeholder groups involved, including patients, caregivers, patient-support organizations, physicians, researchers, scientists, industry leaders, regulators, policymakers, and funders, must be aligned and met. The Angiogenesis Foundation is committed to helping these groups work together to ensure that all people benefit from current and future advances in angiogenesis-based medicine.

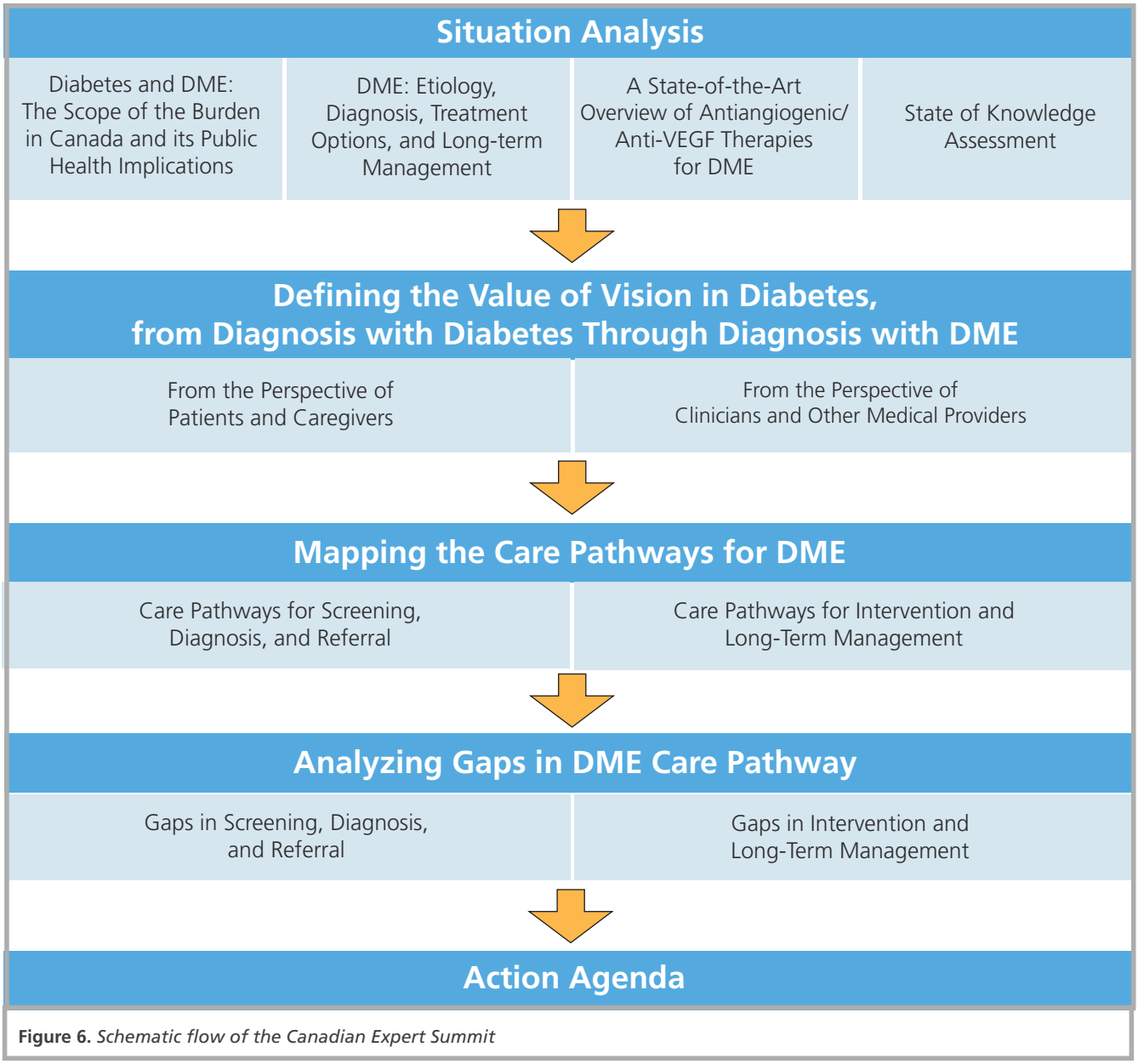

Figure 6. *Schematic flow of the Canadian Expert Summit*

The Canadian National Multi-Stakeholder Expert Summit for Diabetic Macular Edema opened with welcoming remarks from **Dr. William Li**. He explained the origins and purpose of the current summit. Dr. Li's remarks were followed by brief presentations by three DME experts. **Dr. Alice Cheng** of the University of Toronto described the scope of the burden from vision loss in Canada and its public health implications. **Dr. Deepa Yoganathan** of the Toronto Retina Institute provided an overview of the diagnosis, treatment options, and long-term management for DME. **Dr. David T. Wong** of St. Michael's Hospital in Toronto ended the presentations with a review of the state-of-the-field of anti-VEGF therapies for DME.

Diabetes and DME: The Scope of the Burden in Canada and Its Public Health Implications

The proportion of Canadians with diabetes has been steadily rising over the past two decades. An estimated 6.8% of Canadian children and adults — 2.4 million individuals — had diabetes in 2008-2009, according to a report by the Public Health Agency of Canada.[6] That rate was up from 3.3% in 1998-1999. The prevalence rate would be much higher, however, if only adults were included. Prevalence increases with age, with the sharpest increase occurring after age 40. It's estimated that about one-quarter of Canadian adults aged 70 to 84 have diabetes.

The prevalence rate of diabetes in Canada varies by province and territory. The lowest rates in 2008/2009 were in Nunavut (4.4%), Alberta (4.9%), and Quebec (5.1%), while the highest rates were in Newfoundland/Labrador (6.5%), Ontario (6.0%), and Nova Scotia (5.9%). First Nations Canadians had a two- to threefold higher rate of diabetes than non-aboriginal Canadians. The rate was particularly high (17.2%) for those living on Indian reserves. First Nations people also tend to develop diabetes at a younger age and have earlier and more severe disease complications.

If the incidence rates remain at 2008/2009 levels, the number of Canadians living with diagnosed diabetes will reach 3.7 million by 2018/19 — an increase of 56 percent. This will pose a major challenge for the country's health services. According to the public Health Agency of Canada, Canadians with diabetes are 5.9 times more likely to be hospitalized with kidney disease, 12 times more likely to be hospitalized with end stage renal disease, and 20 times more likely to be hospitalized with non-traumatic lower limb amputations that those who do not have diabetes.[6] In 2008-2009, about 12 percent of deaths in the Canadian adult population were attributable to diabetes. Working adults with diabetes — those aged 20 to 64 years — have a life expectancy that is 5 to 10 years shorter than adults of the same age without diabetes.[6]

Fifteen years ago, it was generally believed that almost all people with type 1 diabetes and about 60 percent of people with type 2 diabetes would develop some form of diabetic retinopathy during the first two decades after their diagnosis. That view of the course of the disease is probably not true anymore, due to improvements in the treatment and management of both types of diabetes. The Diabetes Control and Complications Trial (DCCT)[17] and its follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) trial,[18] reported, for example, that intensive glycemic control lowered the relative risk of the onset of DME by 46% and 58%, respectively.

No major population-level eye health studies have been conducted in Canada, but DME with visual impairment is assumed to affect about 3% of the country's patients with diabetes.[19] The prevalence of retinopathy among First Nations populations is particularly high — more than 24%.[9] DME-related vision loss places an enormous and often devastating personal and economic burden on individuals and their caregivers, but the economic burden to Canada's economy is also quite significant, given that DME is a leading cause of vision loss in the country. Researchers estimate that in 2007 the annual financial cost to Canada of vision loss resulting from all causes was CAD$15.8 billion, including CAD$8.6 billion in direct health care expenditures and CAD$7.2 billion in productivity losses and other non health-related costs.[9] These numbers underscore the urgent need for preventive programs and policies.

DME: Diagnosis, Treatment Options, and Long-term Management

Most data on the demographics of DME come from research conducted on populations in the United States. A 2014 study found that 3.8% of the U.S. population — or about 750,000 individuals — have DME.[20] That study also suggested that the disease is more prevalent among certain groups, particularly non-Hispanic blacks, smokers, people with high levels of hemoglobin A1c, and people who have had diabetes for more than 10 years. Another recent U.S. study found that only one-quarter of that country's Medicare beneficiaries who had been diagnosed with DME or other frequently occurring eye diseases had received a follow-up eye exam within 5

years of diagnosis, despite being advised to do so by their healthcare provider.[21] Men, people with limited physical and cognitive function, and those who lived a greater distance (more than 20 miles) from an ophthalmologist were especially at risk of falling into this follow-up gap; health insurance coverage was not a factor.

Other landmark trials include the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, which reported in 2014 that both intensive glycemic control and cholesterol lowering drugs added to statin therapy reduced the progression of diabetic retinopathy.[22] A much earlier trial, published in 1985 by the Early Treatment Diabetic Retinopathy Study Research (ETDRS) Group, established many of the diagnostic and disease-management tools still in use today, including the ETDRS vision chart, the clinical diagnosis of macular edema, and the effectiveness of laser treatment on reducing vision loss.[23] Those tools remained the standard of care for several decades. Then, in 2009, the Diabetic Retinopathy Clinical Research Network published the 3-year follow-up results of a randomized clinical trial that compared laser treatment (focal/grid photocoagulation) to steroid injections (intravitreal triamcinolone).[24] Not only did the study find laser to be more beneficial long term, it also changed the way that macular edema was diagnosed. The Network established a standard definition of macular edema that involved the use of optical coherence tomography (OCT) — an "optical biopsy" of the retina — and the thickness of the retina (250 µm or greater in the central subfield).

OCT technology has made it possible to recognize many different types of abnormalities in patients with DME, including diffuse versus focal edema, subretinal as well as inner and outer fluid, cysts, thickening (in microns), and exudate (lipid residues that have escaped from damage capillaries). Various other imaging techniques, such as scanning laser ophthalmoscopy, are now available to help with diagnosing additional DME-related abnormalities, such as microaneurysms, flame and dot blot hemorrhages, cotton wool spots, arteriolar attenuation, and petaloid patterns of cystoid macular edema. In addition, 3D cube imaging is now used to look at the traction between the vitreous and the fovea. These imaging tools also make it possible to observe the immediate effect of a treatment intervention.

Diagnostic technology is thus constantly challenging the management of DME, particularly since so many different treatment strategies are now available. For example, if a small amount of fluid is identified in the central macula, laser options include focal, grid, micropulse, and subthreshhold. If the periphery of the macular is being treated, the options include performing a full pan retinal photocoagulation laser or targeting only the ischemic areas; other considerations include the duration and wavelength of the laser. If there is significant fluid, and anti-VEGF treatment is indicated, treatment options include different anti-VEGF medications, perhaps in combination with laser or steroids. Decisions must also be made about the frequency of the anti-VEGF treatments: Should they be administered only when fluid is present, or at regular intervals as often suggested by on-label instructions? Another important issue is that retina specialists, who are very busy in Canada, may not be able to see each of their patients monthly for treatment. Retina specialists need to give strong consideration to co-managing their DME patients with general ophthalmologists and optometrists.

A State-of-the-Art Overview of Antiangiogenic/Anti-VEGF Therapies for DME

Bevacizumab (Avastin), a recombinant humanized antibody, works against all isoforms of VEGF-A. In the BOLT (Bevacizumab or Laser Therapy in the Management of DME) study, repeated intravitreal bevacizumab injections were compared with modified laser photocoagulation in 80 patients with persistent DME.[25] Among the patients in the bevacizumab arm, 31% gained 10 or more ETDRS letters after one year compared to 7.9% of those in the laser arm. The thickness of the central macula also decreased more in the bevacizumab arm than in the laser arm.

Ranibizumab (Lucentis), a smaller fragment of the same recombinant humanized antibody, also works against all isoforms of VEGF-A. The RISE and RIDE clinical trials randomized patients with DME to either monthly ranibizumab or sham injections for 36 months.[26] The ranibizumab treatment group experienced strong visual acuity gains and reductions in the thickness of the macula's central fovea; these improvements were sustained through month 36 of the study. Patients in the sham group who were crossed over to ranibizumab treatment after 24 months experienced lower gains in visual acuity, a finding that underscores the need for early treatment. The RESTORE study, which randomized 345 patients to either ranibizumab injections plus sham laser therapy, ranibizumab injections plus laser therapy, or sham ranibizumab injections plus laser therapy, demonstrated similar benefits for ranibizumab therapy.[14] Patients treated with ranibizumab, whether or not they also received laser therapy, showed greater visual acuity after 12 months than those treated with laser therapy alone.

Aflibercept (Eylea) is a slightly different molecule than

bevacizumab or ranibizumab. It binds not only to VEGF-A, but also to another member of the VEGF family, placental growth factor (PIGF). In a pair of phase III clinical trials, VISTA and VIVID, treatment with aflibercept injections was compared with laser photocoagulation treatments.[28] After 52 weeks, patients in the aflibercept arms of the trials were found to have experienced significantly greater improvement in visual acuity from baseline than those in the laser photocoagulation arms.

The Diabetic Retinopathy Clinical Research Network has completed a 1-year head-to-head comparison trial of ranibizumab, bevacizumab, and aflibercept. The results of the Protocol T study, though not published in time for this summit, demonstrated that aflibercept, bevacizumab, and ranibizumab are all effective and relatively safe treatments for DME, with little difference between the drugs with baseline visual acuity 20/40 or better. The data did show, however, that at a baseline visual acuity of 20/50 or worse, aflibercept is the more effective treatment at improving vision.[29] As the study noted, "at worse initial levels of vision, aflibercept had a clinically meaningful advantage; for example, an improvement in the visual-acuity letter score of at least 15 (3 snellen lines) was observed in 63% more aflibercept-treated eyes than bevacizumab-treated eyes (67% vs. 41%) and in 34% more aflibercept-treated eyes than ranibizumab-treated eyes (67% vs. 50%)." The mean change in central subfield thickness (CST) from baseline was greater with aflibercept compared to the other agents, regardless of baseline visual acuity, and the reductions in CST with aflibercept were significantly greater compared to bevacizumab. On average, subfield thickness decreased by 169 µm with aflibercept, 101 µm with bevacizumab, and 147 µm with ranibizumab. Laser photocoagulation was performed in fewer aflibercept-treated eyes compared to eyes treated with the other agents, which may reflect the greater proportion of aflibercept-treated patients with resolution of central-subfield involved diabetic macular edema.[29]

Other notable findings include:

- Patients in the aflibercept arm of the study gained an average of 2 more ETDRS letters at the end of 52 weeks.
- Rates of most eye-related and other systemic adverse events were similar across all three groups.
- Rates of thromboembolic events (strokes, heart attacks, and vascular deaths) were 2% in the aflibercept group, 4% in the bevacizumab group, and 5% in the ranibizumab group.

In Protocol T, almost all patients were given a loading period of monthly doses for the first 6 months, and this study population had extremely encouraging results in terms of improvement in visual acuity. The impression among the professional community based on the initial Protocol T results and the previously published Protocol I is that aggressive treatment in the first year results in better outcomes and, in the case of Protocol I, in fewer injections needed later on regardless of which treatment was used.

Many ongoing questions about anti-VEGF treatments remain to be answered: How many treatments are needed? What are the long-term effects of VEGF suppression, both locally (in the eye) and systemically (particularly in the kidneys and heart)? What is the current role of macular laser in the treatment of DME? Finally, now that we seem to be reducing the curve of proliferative diabetic retinopathy, what does that mean for how we treat the disease in the future?

State of Knowledge Assessment

After the opening presentations, the summit's experts were asked to assess how well the material that was presented is understood by seven key DME stakeholders: patients/caregivers, diabetologists, general ophthalmologists, retina specialists, diabetes advocacy leaders, and health authorities. It was clear from the experts' assessments that much more work needs to be done to educate stakeholders about DME. As the summit's opening presentations made clear, DME is a leading cause of vision loss in Canada, as it is around the world. Recent advances in anti-VEGF therapies promise to dramatically improve how DME is treated and managed, but the disease's social and economic burdens are predicted to remain high and, indeed, to significantly grow in the coming years as populations age and the incidence of diabetes increases. Still, DME is just one of many serious health complications, including heart disease, kidney disease, and nerve damage (neuropathy), for which people with diabetes are at risk. The question then arises: What value do the stakeholders in diabetes, especially patients, caregivers, clinicians, and other healthcare providers, put on preventing and restoring vision loss?

The moderator opened this segment of the summit by asking the meeting's participants to discuss that question from two perspectives: patients/caregivers and providers/clinicians. They were also asked to consider the questions from various points in the course of the disease, starting with the diagnosis of diabetes and continuing through and after the diagnosis with DME. Key points raised during that discussion are summarized below.

From the Perspective of Patients and Caregivers

Canadians diagnosed with diabetes want their normal daily activities to continue without any major disruptions from the disease. They want to be able to return to work, to travel, to drive, and to spend time with family and friends, including (or especially) grandchildren. Above all, they want to retain their independence. The specific lifestyle activities that are most important to each person with the disease varies. One of the jobs of the healthcare provider is to help ensure that the management of each patient's disease supports that patient's particular values, which may differ from those of the provider.

Patients newly diagnosed with diabetes — and their caregivers — want clear, consistent, and complete communication from their healthcare providers about the disease. They want to be informed about all potential complications, including vision loss. Often, however, the education of patients with diabetes by healthcare providers tends to focus primarily on preventing complications involving the kidney and the heart. Patients may not become immediately aware that vision loss is also another major potential complication — and one that is, perhaps, the greatest diabetes-related threat to their independence.

Often, patients with diabetes fail to make an immediate emotional connection to why they must take care of themselves. They may also simplify the messages they hear about their disease. Many start out believing, for example, that they can ignore their blood sugar levels as long as they just watch what they eat. Others recognize that they must get their blood sugar levels down, but then mistakenly believe that taking that action is all they need to do to manage their disease. Still others fail to approach the management of their disease with any sense of urgency because of the "normalization of diabetes" — the perception that "everybody has it" and, therefore, it can't be that serious an illness. This latter attitude is particularly widespread among Canadians aged 60 and older, an age group in which the prevalence of diabetes is currently well over 20%.[6]

As patients learn more about their diabetes — and live with it longer — they want to not just avoid complications, but also reverse them. Those with other illnesses also value that their healthcare providers take a holistic approach to their medical care — one that helps them address all their health issues, and not just their diabetes. Some patients may feel a sense of failure and helplessness about their diabetes, particularly since the message often promoted in the media is that people who develop type 2 diabetes have only themselves to blame (for becoming overweight). Healthcare providers need to understand and address these complicated emotions to avoid having them interfere with successful management of the patient's disease.

After patients are diagnosed with DME, they tend to value retaining their normal daily activities even more, because they recognize how their loss of vision is impacting their lives. They may no longer be able to read or drive. They may also worry about becoming a burden to their families. Younger adults in particular worry about not being able to continue to work and provide for their families.

Patients diagnosed with DME are thus eager to reverse their vision loss or, at least, to stabilize it. But they want clarity about the care pathway, and they want to be offered effective — and affordable — treatments that provide hope for their future. Patients also want to feel that they are part of a care team and that all members of their team welcome and respect their participation in discussions about treatment and other disease-management issues. Patients also want their time — and that of their caregivers — to be valued. They don't want to be sent to many different sites and clinicians for treatment and follow-up. Most patients, therefore, find it very helpful to have a treatment "coach" on their team who efficiently coordinates their care.

Patient/Caregiver Perspective
Impact vs. Ease: Stakeholder Dot-Voting

Summit participants were provided green and red voting stickers to assign to the categories within the patient/caregiver value chain. Green dots represented "impact," or those values that the participants believed would have the greatest effect, if instituted, on patients and their caregivers pre-diagnosis. Red dots signified the "ease" of instituting these values. A few of the values received more red or green dots and are thus worth an expanded discussion.

	Value (from the patient/caregiver perspective)	Impact	Ease	Rating
Pre-Diagnosis	Retaining "normal" daily activities	●●●●●		Low
	Understanding how diabetes affects overall health/knowing what actions to take to improve health	●●●	●●●●●●	Medium
	Receiving sensitive and effective communication from doctor	●	●●	Low
	Avoiding complications and recognizing early signs of them	●●●		Low-Medium
	Being able to affect or control vision impairment		●●	Low
	Understanding the emotional "hook" of why they should care	●		Low-Medium
Post-Diagnosis	Maintaining hope	●●●●●●●	●●●●●●●●●●	High
	Retaining independence	●●●●●●●●●●●●	●●	Medium
	Saving the second eye	●●		Low
	Reversing vision loss	●●●●		Low-Medium
	Continuing to provide for family	●●●		Low
	Receiving timely, coordinated, and clearly communicated care	●●●●●	●●●●●●●●●●●●●●	High
	Having patient input valued and listened to	●	●	Low
	Receiving affordable treatment (with timely reimbursement)	●●●●●●	●	Low-Medium
	Understanding the disease process	●●●●	●●●●	Low-Medium
	Being seen as a whole person and held accountable for adherence	●●●	●●	Low

Figure 7. *Representation of the stakeholders' dot-voting on DME issues from the perspective of patients and caregivers*

Pre-Diagnosis

The ability to retain "normal" daily activities was rated by participants as the most impactful value for patients and caregivers. This category was not, however, regarded as easy to accomplish. As disease progresses, patients are likely to develop symptoms that will affect their daily living. So, although the ability to retain normal daily activities, such as working and driving, is of great value to patients, it is currently a challenging goal to achieve.

A value less impactful but easier to initiate is helping patients understand their overall health and how their diabetes affects it, as reported by the summit participants. This goal could be accomplished, for example, by improving communication (between the patient and his or her clinicians, and between all members of the patient's clinical team), as well as by setting up better processes for educating patients about diabetes, including its potential effects on vision and the importance of adhering to treatments and medical appointments.

Post-Diagnosis

The post-diagnosis value that received both a high impact and a high ease rating from the summit's participants was "maintaining hope." Patients want to see distinguishable improvement in their vision as a result of treatment. Furthermore, patients/caregivers want to be guided and empowered by their physician to take control of their own health. This value underscores the importance of incorporating the physician/clinician as a partner in care.

Similarly, patients value retaining independence despite their disease. Unfortunately, DME-related vision impairment or loss affects many aspects of this value, including daily activities such as reading and driving. Therefore, while this value has significant impact and importance to patients and caregivers, it is not easily accomplished, especially as the disease progresses.

From the Perspective of Clinicians and Other Healthcare Providers

Clinicians and other healthcare providers want to know that they are making a difference in their patients' lives. Thus, when patients are diagnosed with diabetes, clinicians value being able to provide the care that will prevent major complications, including vision loss. Clinicians would also like to see the eye "elevated" to a higher position within the diabetes care pathway. Currently, concerns about vision loss are often not directly addressed until the patient's diabetes has significantly progressed. Clinicians also value having patients who are well informed about their disease, so that the patients are active in their own care and fully aware of the importance of following their individual treatment plan.

To help patients with diabetes retain their vision, clinicians value simple, universal, and easily accessible methods of screening patients for DME, as well as access to all state-of-the-art monitoring and surveillance tools so that they can catch changes in their patients' eyes early, when treatment is most effective. Clinicians also want more DME research so that both the disease and its treatment pathway can be better understood. In addition, they want an improved and more efficient method of referring patients to retina specialists for treatment.

After DME is diagnosed in their patients, clinicians value safe, effective, and affordable treatments for their patients — treatments that will reverse as well as stabilize vision loss. In addition, they want those treatment options to be patient-specific and universally agreed upon by the medical community. Clinicians also value state-of-the-art technology for diagnosing and monitoring DME, as well as better access to teleophthalmology, which delivers eye care through digital medical equipment and telecommunications technology. Teleophthalmology is especially important for diagnosing and following patients living in Canada's rural areas.[30]

Canada's clinicians also value a healthcare system that enables them to deliver DME treatments and other diabetes-related care with some level of autonomy. Retina specialists, for example, do not want to be just a technician who delivers injections. Finally, all clinicians want a strong and trusting physician-patient relationship, one that enables them to have control over the quality of care that they deliver.

Clinicians/Other Healthcare Provider Perspective Impact vs. Ease: Stakeholder Dot-Voting

As they did with the values they identified as being of importance to patients and caregivers, the summit participants gave "impact" and "ease" ratings to the values they considered imperative to clinicians and other healthcare providers (see figure 9). Again, some of the values received more red or green dots and are thus worth an expanded discussion.

Figure 8. *Moderated discussion at the Expert Summit*

Pre-Diagnosis

The value of "unified clarity" — assisting patients in navigating the entire care pathway — was a particularly popular category among the summit's participants. They pointed out that many gaps in communication and other processes exist within the current care pathway, causing patients to "slip through the cracks." Prioritizing this value would be relatively easy to implement, they agreed, and would have a very high impact on patient care.

Another value that the experts said would be relatively easy to implement while having a high impact is "offering patients a referral to a single place where they can get all the information they need." This value includes an easy and simple screen for patients that would identify further follow-up, catching those patients at risk for further complications. As a tool and process, participants highlighted this screen as a value with significant impact in which they recommend investing.

Post-Diagnosis

"Building a trusting relationship with patients" was one of the key post-diagnosis values from the clinician perspective identified during the summit. The patient-clinician relationship is particularly important during the post-diagnosis period, a time when patients must navigate a changing and sometimes unpredictable care pathway. The summit participants agreed that building stronger patient-clinician relationships is one high-impact aspect of the DME care pathway that would be relatively easy to improve.

Similarly, clinicians and other healthcare providers value a system that reduces barriers that affect care, such as financial burdens and drug-access limitations. The summit's participants voted to give this value a high impact designation, although they also acknowledged that ending such barriers would not be easy. This value represents the ongoing struggle that healthcare systems face when trying to match healthcare policies with the day-to-day realities of patient care. Clinicians want to practice medicine at the highest level, but policies, such as those regarding drug access and reimbursement, often interfere with their ability to do so. Reducing some of these barriers, therefore, would have significant impact on the DME care pathway, but that action is often not possible without significant policy changes.

	Value (from the perspective of clinicians and other healthcare providers)	Impact	Ease	Rating
Pre-Diagnosis	Providing "unified clarity" (an easy-to-navigate treatment pathway for the patient)	●●●●●●●●●●●●	●●●●●●●●	High
	Maintaining patient's hope		●●●●●●●●●	Medium
	Empowering patients with information	●●●●●●	●●●●●●●●●●●●	High
	Delivering ongoing monitoring and surveillance	●●●	●●	Low
	Offering patients a referral to a single place where they can get all the information they need	●●●●●●●●●	●●●●●●●●	High
	Being able to screen patients with a simple but effective technology	●●●●●●●●		Medium
	Having better access to teleophthalmology technology	●●●	●●●●●	Low-Medium
	Developing a better understanding of the treatment pathway (through better research)	●●	●●●●	Medium
	Making a difference in patients' lives	●●●●●●●●	●●●●●●●	High
	Identifying the diabetic patient	●	●●●●	Low
	Having an effective, standardized care system	●	●●	Low
	Being able to triage patients and their care more effectively	●●●	●●	Low
Post-Diagnosis	Building a trusting relationship with patients	●●●●●	●●●●●●●●●	High
	Eliminating systemic barriers	●●●●●●●●●●●●	●●●●	High
	Accessing technology that closes gaps in care	●●	●●	Low
	Building more efficiency into the care process	●●●	●●●●●	Medium
	Avoiding treatment risks and misdiagnoses (qualified professionals only)	●●●	●●●●	Low-Medium
	Educating patients	●●●●●●	●●●●●●●●●●●	High

Figure 9. *Representation of the stakeholders' dot-voting on DME issues from the perspective of clinicians and healthcare providers*

Mapping the Care Pathways for DME

After identifying what patients, caregivers, clinicians and healthcare providers most value and want before and after DME is diagnosed, the summit's participants turned their focus to care pathways. The discussion focused on two specific points along that continuum: 1) screening, diagnosis and referral, and 2) intervention and long-term management. Key points raised during those discussions are summarized below.

Care Pathways for Screening, Diagnosis, and Referral

The conversation began with the experts answering this question posed to them by the meeting's moderator: Who makes the initial diagnosis of DME, and does the answer to that question differ among Canada's provinces? The experts noted that, in Canada, optometrists often make the first, preliminary diagnosis of DME during a routine fundus exam, which may or may not involve dilating the pupil. Almost all optometrists have a fundus camera on site. Standard medical care mandates that optometrists perform the fundus exam on all patients with diabetes and that they dilate the eyes for the exam when patients exhibit any symptoms. General ophthalmologists also frequently make the initial DME diagnosis, as do some family practitioners and endocrinologists, who may see the exudate (the mass of cells and fluid that has seeped out of the capillaries in the retina) while examining a patient's eyes with an ophthalmoscope. In remote areas, particularly in northern provinces, the original finding of DME is often made by nurse practitioners with special training in fundus examinations.

The gold standard for an official diagnosis of DME is, however, the optical coherence tomography (OCT) exam. The fundus exam is a somewhat subjective method of diagnosis, whereas the OCT exam is entirely objective. The summit experts stressed that the OCT should be used only when DME is suspected; it is not a screening tool. In Canada, OCT exams are almost always performed by general ophthalmologists or retina specialists, yet primary care providers – whether optometrists, family practitioners, or nurse practitioners – do not always know to whom they should refer patients for the OCT exam. Furthermore, follow-up communication should occur between primary care providers and vision specialists.

Although the Canadian National Health Insurance Program (Medicare) covers the cost of routine eye exams, it does not always pay for fundus photography and OCT imaging. The specifics regarding what is covered and what isn't varies from province to province, for although Canadian health care is federally funded, it is provincially administered. Most Canadians are unaware of these limitations to their insurance, and thus are often surprised when they receive the bill for the imaging part of their eye exam. The out-of-pocket charge for these tests can be as much as CAD$200. When some patients do become aware of those costs, they sometimes decline the test, an action that puts their vision at risk.

Care Pathways for Intervention and Long-term Management

The conversation then shifted to the second part of the DME care pathway: intervention and long-term management. The moderator opened the discussion by asking the experts the following question: What services and interventions are patients able to access once they have been diagnosed with DME? The experts acknowledged that treatment for DME is often disconnected from other aspects of the patient's diabetes care due to a lack of coordination among the patient's various healthcare providers. Although glycemic control plays an important role in the success of DME treatment, ophthalmologists/retina specialists often do not communicate effectively — if at all — with their patients' general practitioners and/or diabetologists and endocrinologists. In comparison, when patients with diabetes develop foot pain or ulcers, integrative care is almost always implemented because the patient's entire medical team recognizes that treatment will require more than just caring for the foot. A similar comprehensive and integrated approach is needed when DME develops, the summit experts stressed.

Canadians diagnosed with DME have many intervention options: laser therapies, steroid treatments, surgery, anti-VEGF therapies, and general diabetes-related medical care aimed at glycemic control. Patients also have access to low-vision rehabilitation. In Canada, physicians have no financial incentive to offer one treatment over another to their patients — a situation that the experts agreed is desirable and commendable. Treatment guidelines for DME exist, but they are "a moving target" because technology and treatments are always improving. Modern lasers, for example, leave much less scarring of the retina than earlier versions of the technology. As some of the summit experts pointed out, multi-modality therapies may work best for many DME patients, and any decision about treatment should reflect each individual patient's medical profile.

Among the three anti-VEGF drugs available for the treatment of DME, two have been approved by Health Canada: ranibizumab and aflibercept. The cost of aflibercept and ranibizumab are covered under several provincial health plans, although only for people age 65 and older. Younger patients must rely on private insurance or pay for these drugs out of pocket, usually

on an income-based sliding scale. The exact method by which payment is determined varies among the provinces, a variation highlighted as a concern by experts at the summit. In January 2015, when the summit was convened, reimbursement was not available for aflibercept anywhere in Canada, but that situation has since changed. A handful of provinces also reimburse for bevacizumab, but with a warning that such use of the drug is off label for the treatment of DME. In Newfoundland, for example, most DME patients are started on bevacizumab, primarily because of its much lower cost. Indeed, bevacizumab is so commonly prescribed in some areas of Canada, that its off-label designation is not always communicated to patients. The summit experts agreed that the various ways that DME drugs are reimbursed in Canada is confusing to patients and physicians alike. They also expressed strong agreement that younger people with DME should have more affordable access to these drugs. Most also supported the statement that if each of the anti-VEGF drugs cost only one dollar, they would probably treat their DME patients with aflibercept because it required fewer injections. The experts concluded this section of the discussion by emphasizing that it was the responsibility of the medical community and public health officials to figure out the best evidence-based way to treat DME, as well as the most efficient and affordable way to deliver that treatment to patients.

Figure 10. *Graphical representation of the DME care pathways*

Analyzing Gaps in the DME Care Pathway

After mapping the various current DME care pathways in Canada, the summit's experts engaged in a quick review of their earlier discussion about the various priority values of DME stakeholders. They then turned their attention to identifying the gaps between the values with the highest priority and the current pathways for DME. They focused their discussion on the following gaps that, if closed, would lead to significant improvements in those pathways.

Gaps in Screening, Diagnosis, and Referral

- Family physicians often lack knowledge of the importance of identifying damage to the retina early, when treatment is most effective. Nephrologists have done a good job of educating family physicians about the need to regularly test the kidney function of their patients with diabetes; ophthalmologists should be equally proactive about encouraging family physicians (and other primary healthcare providers) to regularly look for retinal damage.

- When it comes to the treatment of patients with diabetes, the medical community often fails to take a holistic approach. Communication among the patient's healthcare providers is fragmented or even nonexistent. Nor does anybody step up to be the "quarterback" to oversee all of the patient's care. As a result, many patients with diabetes are not being screened for DME in a regular or timely manner.

- In general, Canadians are poorly informed about diabetes, particularly about how to prevent type 2 diabetes by adopting more healthful lifestyle behaviors. Once people have diabetes, they often remain poorly educated about the disease and about how to prevent its complications, especially vision loss.

- Not enough diabetes patient-educators are embedded within the offices and clinics of primary care providers — or within the offices of retina specialists. Nor do all provinces equally encourage the efforts of diabetes educators; some provinces will not reimburse healthcare providers for using their services.

- The onus is often on the patient to locate an optometrist/ophthalmologist, both for screening and for diagnosis.

- Access to screening and diagnostic technology is not equitably distributed across Canada. The largest gaps in access are in rural areas of the country. Screening and diagnostic technology is also not equitably available to economically and socially marginalized populations with a high risk for diabetes and low access to services.

- Optometrists and ophthalmologists sometimes engage in turf wars that can result in unnecessary confusion for patients about where they should go for screening and diagnosis.

Gaps in Interventions and Long-term Management

- Treatment guidelines for DME exist, but they quickly become outdated due to new technological and pharmaceutical advances. In addition, several different forms of treatment are available, including the choice between various anti-VEGF agents. As a result, DME treatment decisions are often quite complex for healthcare providers and patients alike.

- Canada's provinces reimburse for DME therapies in different and often confusing ways, further complicating individual treatment decisions.

- Canada has no national registry that captures real-world treatment outcomes for DME.

- DME treatments are often unaffordable for patients, particularly for those under the age of 65.

- Access to treatments for DME is not equitably distributed across Canada. As with access to diagnostic technology, the largest gaps in care are found in rural areas of the country. Often, retina specialists must be flown into these areas to deliver care. Access to treatment is also not equitably available to economically and socially marginalized populations.

- Evidence-based epidemiologic and treatment-outcomes research about DME in Canada is lacking. Funding for that research is also lacking.

Action Agenda

In the final session of the summit, the experts proposed game-changing actions that could bridge the gaps previously identified and lead to significant improvement in outcomes for Canadians with DME.

Educate DME stakeholders

- Create more effective public service announcements about DME, including videos of patients describing how DME-related vision loss has affected their lives; the messages need to be balanced, however, to include patients who have experienced good outcomes as the result of early treatment.
- Empower primary care providers to be the "ambassadors" of diabetes information — including information about DME — to patients with the disease. Use the task force to expand communication with ophthalmologists and other clinicians who treat people with diabetes to persuade them of the importance of placing a greater emphasis on the diagnosis and treatment of DME.
- Add diabetic eye care (screening, diagnosis, treatment, ongoing management) to the continuing medical education (CME) requirements of family physicians and other primary care providers. (The Canadian National Institute of the Blind (CNIB) has already created materials as a foundation for this effort.)
- Create Canadian Diabetes Association (CDA) modules for healthcare providers that explain the rationale behind current DME treatment choices.

Improve the DME pathway of care

- Create easily accessible, geographically organized website listings of optometrists, ophthalmologists, and retina specialists.
- Encourage the development of multi-disciplinary care teams for people diagnosed with DME. Assign each team a "quarterback," a healthcare provider who takes on the responsibility of coordinating the patient's care.
- Embed more diabetes patient educators within the offices and clinics of primary care providers and retina specialists; advocate for full insurance coverage of these services.
- Connect family practitioners to specific eye specialists so that the patient is not obliged to find a specialist and make the appointment themselves.
- Create a secure and comprehensive online treatment registry — a "diabetes dashboard" of medical records — for each patient with diabetes to enable the patient's healthcare providers to easily follow all aspects of the patient's care and quickly identify any gaps in treatment.
- Create a resource (perhaps through a patient-advocacy group) that describes the treatment care pathways on a province-by-province basis.
- Advocate for full national health insurance coverage for all evidence-based DME screening and treatments. In addition, advocate for extending that coverage to people with DME who are under the age of 65.
- Advocate for making anti-VEGF treatments for DME more affordable.

Gather — and disseminate — more data

- Support Statistics Canada's effort, which will start in January 2016, to collect data on vision loss, including DME-related vision loss.
- Make sure that collected data is effectively disseminated throughout the medical community and throughout all population groups, with a special emphasis on reaching economically and socially marginalized populations that are at high risk for developing DME.
- Embed more diabetes patient educators within the offices and clinics of primary care providers and retina specialists so that they can disseminate the data.
- Advocate for the creation of a national registry that captures real-world treatment outcomes for DME.
- Encourage more funding for DME-related research in Canada.

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