



Advocating for Improved Treatment and Outcomes for Diabetic Macular Edema

A Report Based on an International Expert Summit
Convened in Paris, June 2014

Acknowledgements

This publication was supported by unconditional grants from the Boston Foundation, Significance Foundation, Henry Mellon, and Bayer Pharma AG, who had no influence on the scope or content of the document.

KEY POINTS

1. Diabetic macular edema (DME) is a leading cause of vision loss in the world, particularly among working-age adults (20-74 years).
2. Because the number of people living with diabetes is expected to almost double globally by 2035, DME is projected to become an ever-increasing health problem that will exact a severe socioeconomic burden on individuals, communities, health systems, and governments around the world.
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 globally — and how those care pathways can be improved.
5. There is a persistent concern that the majority of patients with DME are not receiving the optimal evidence-based care that they need to maintain vision and prevent progressive vision loss.
6. All DME stakeholders — patients, caregivers, clinicians, patient-advocates, insurers, drug companies, and 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.

Table of Contents

| | |
|--------------------------------------------------------------------------------------------------|-----------|
| Acknowledgements | 2 |
| Key Points | 3 |
| Introduction | 5 |
| • What is DME? | 5 |
| • Anti-VEGF Therapies for the Management of DME | 5 |
| • Expert Summit: Identifying and Meeting a Need | 6 |
| • The Role of the Angiogenesis Foundation | 7 |
| | |
| Situation Analysis | 8 |
| • Diabetes: The Burden of Vision Loss and Its Public Health Implications | 8 |
| • DME: Overview of Etiology, Diagnosis, and Treatment Options | 8 |
| • State-of-the-Art Overview of Anti-VEGF Therapies | 11 |
| • State of Knowledge Assessment | 12 |
| | |
| Defining the Value of Vision in Diabetes, from Pre-Diagnosis Through Treatment of DME | 13 |
| • From the Perspective of Patients and Caregivers | 13 |
| • From the Perspective of Clinicians and Other Medical Providers | 13 |
| • From the Perspective of the Diabetes Community, Including Its Associations and Advocacy Groups | 14 |
| | |
| Mapping the Care Pathway for DME | 15 |
| • Screening, Diagnosis, and Referral | 15 |
| • Access, Intervention, and Long-Term Management | 16 |
| | |
| Analyzing Gaps in the DME Care Pathway | 18 |
| | |
| Action Agenda | 20 |
| | |
| References | 22 |
| | |
| Participants | 23 |

Introduction

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 needed 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.

In many regions of the world, diabetic retinopathy is the leading cause of vision loss among working-age adults (20-74 years),¹ and among people with diabetic retinopathy, the most frequent cause of vision loss is DME. One large epidemiological study found, for example, that 26% of people 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 382 million people worldwide have diabetes, DME presents a significant public health issue⁵ that is growing as 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

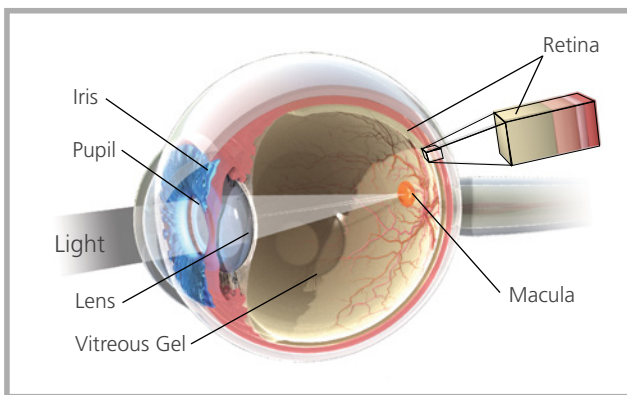


Figure 1. Anatomy of the eye

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 four

Normal Vision

Vision with DME



Figure 2. Comparison of normal vision to vision with DME

anti-VEGF drugs — pegaptanib, ranibizumab, bevacizumab, and aflibercept — 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 for the specific treatment of DME.

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 U.S. regulation in 2011⁶ and Japanese regulation in 2014.⁷ 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 established in two randomized clinical trials involving 759 patients who were treated and followed for three years.⁸ The studies found that between 34% and 45% of patients treated with monthly ranibizumab intravitreal injections of 0.3 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). The results of those two studies have been supported by later data from the Diabetic Retinopathy Clinical Research Network, which followed 854 patients for two years.⁹

In 2014, aflibercept was approved by the U.S. Food and Drug Administration (FDA) and the European Commission for the treatment of DME. Aflibercept had been previously approved 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 two clinical trials involving 872 patients.¹⁰ 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, however, 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 that it was an opportune time 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 recognized that it was well positioned to play the role of the neutral facilitator of such a review. Thus, it decided to host a



Figure 3. International DME Expert Summit, Paris, June 2014

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. **Dr. William Li**, President, Medical Director, and Co-Founder of the Angiogenesis Foundation was the Chair of the event, along with regional Co-Chairs **Dr. Francisco Rodriguez** (representing Latin America), **Dr. Ramin Tadayoni** (Europe), and **Dr. Tien Yin Wong** (Asia-Pacific). This event was not a traditional scientific meeting, but rather an interactive, professionally moderated set of short presentations and roundtable discussions that aimed to establish a dialogue 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 and its global public health implications; the second offered an overview of the etiology, diagnosis, and treatment options for DME; and the third provided a state-of-the-art review of anti-VEGF therapies. Under the direction of the moderator, the assembled experts, who represented 13 different countries, then engaged in a discussion that defined and prioritized what DME stakeholders — patients, caregivers, clinicians, advocates, and policymakers — value most about DME care. A graphic recorder captured key points of this and all other discussions 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. Differences in care pathways among countries and regions of the world were noted and discussed. Next, the participants turned their focus to identifying the gaps between those care pathways and the vision-related values of various DME stakeholders. The meeting ended with the experts proposing that a global task force be organized to advocate for improved treatments and outcomes for people with DME. The experts also compiled a list of recommended "action steps" for the task force to undertake.

This white paper is a result of the open, comprehensive, and often provocative 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.

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 ophthalmology, wound care, and cardiovascular disease, as well as in oncology. 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.

Situation Analysis

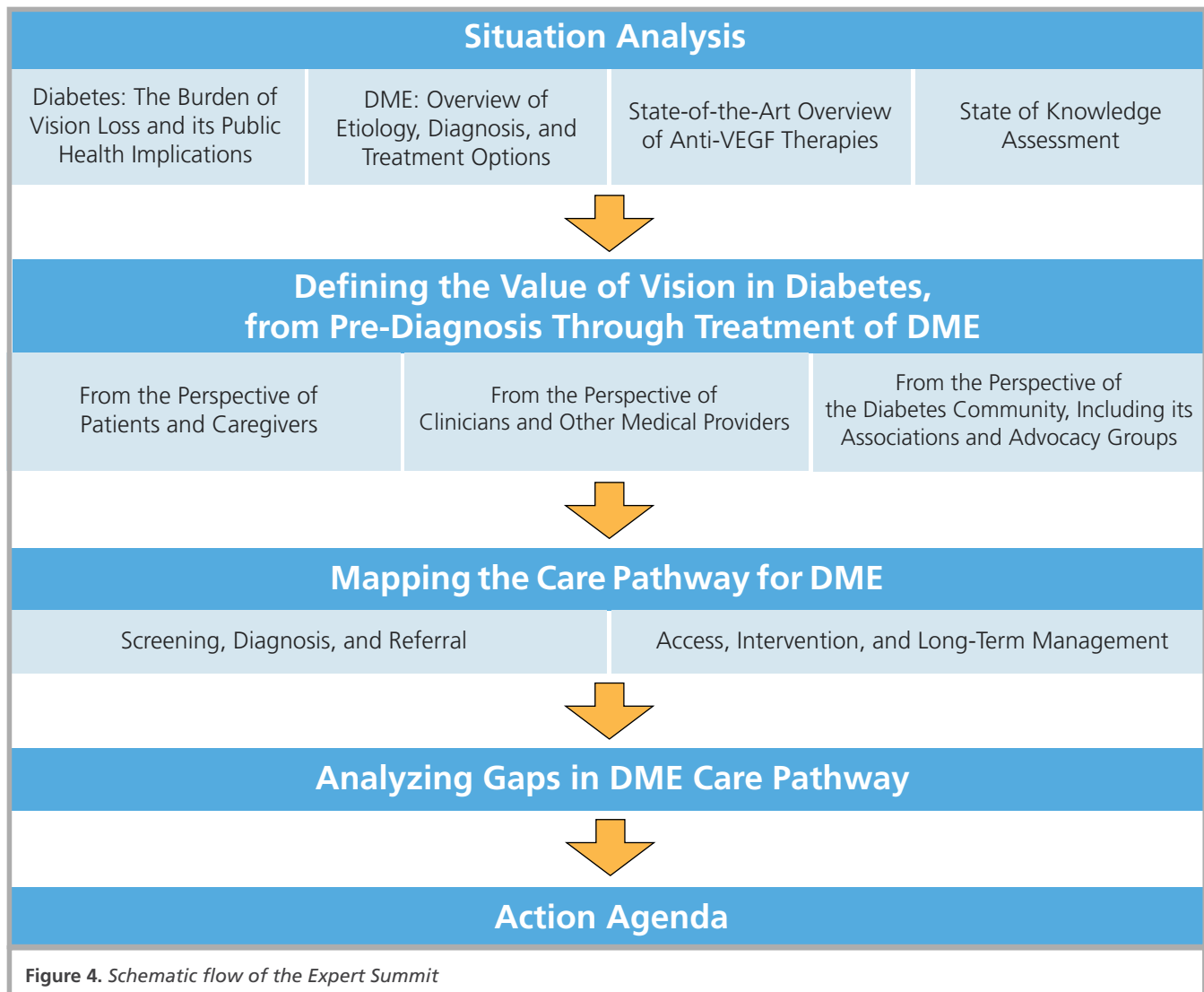


Figure 4. Schematic flow of the Expert Summit

The International DME Summit 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. **Lydia Makaroff** of the Belgium-based International Diabetes Federation described the global burden of diabetes-related vision loss and its public health implications. **Dr. Patricio Schlottman** of the Organización Médica de Investigación in Argentina provided an overview of the etiology, diagnosis, and current treatment options for DME. **Dr. Tien Yin Wong** of the Singapore Eye Research Institute ended the presentations with a review of the state-of-the-field of anti-angiogenic therapies for DME.

Diabetes: The Burden of Vision Loss and Its Public Health Implications

Worldwide, an estimated 382 million people are living with diabetes. That number is expected to grow to 592 million by 2035.⁵ Almost half (46%) of the people who currently have diabetes are undiagnosed. In some areas of the world, the rate of undiagnosed diabetes is extremely high — 76% in sub-Saharan Africa, for example. Most people with diabetes — 80% — live in low- and middle-income countries.⁵ Of the 10 countries with the highest prevalence of the disease, three are in the Middle East and North Africa (Kuwait, Saudi Arabia, Qatar) and seven are in the Western Pacific (Federated States of Micronesia, Marshall Islands, Kiribati, Tokelau, Nauru, Vanuatu, Cook Islands). But diabetes affects significant numbers of people elsewhere as well: 24 million in Central and South America, for example, 37 million in North America and the Caribbean,

56 million in Europe, and 138 million in Southeast Asia and the Western Pacific. Those numbers impose a significant financial cost on governments and societies. In 2013, annual diabetes-related expenditures totaled US\$263 billion in North America and the Caribbean, US\$147 billion in Europe, US\$88 billion in Southeast Asia and the Western Pacific, US\$26 billion in Central and South America, US\$14 billion in the Middle East and North Africa, US\$6 billion in the Indian subcontinent, and US\$6 billion in Africa.⁵

Diabetes is a serious disease, with co-morbidities that can severely affect a person's quality of life. One of these complications is vision loss. Diabetes is a leading cause of blindness. Worldwide, 93 million people have diabetic retinopathy (DR), including 21 million with DME; another 300 million people are at risk.¹¹ On average, one third of people with diabetes have retinopathy, although in some countries, such as China, Malaysia, and South Africa, the rate is closer to one half. Unfortunately, statistics on the rate of DME in individual countries are difficult to obtain due to a lack of country-specific epidemiological research. Worldwide, the economic cost of all forms of visual impairment was US\$2.95 trillion in 2010.¹² More than 80% of those costs were in direct medical and other expenditures. By 2020, that cost is expected to climb to US\$3.56 trillion. When considering these costs, it's important to note that 85% of global visual impairment is avoidable.

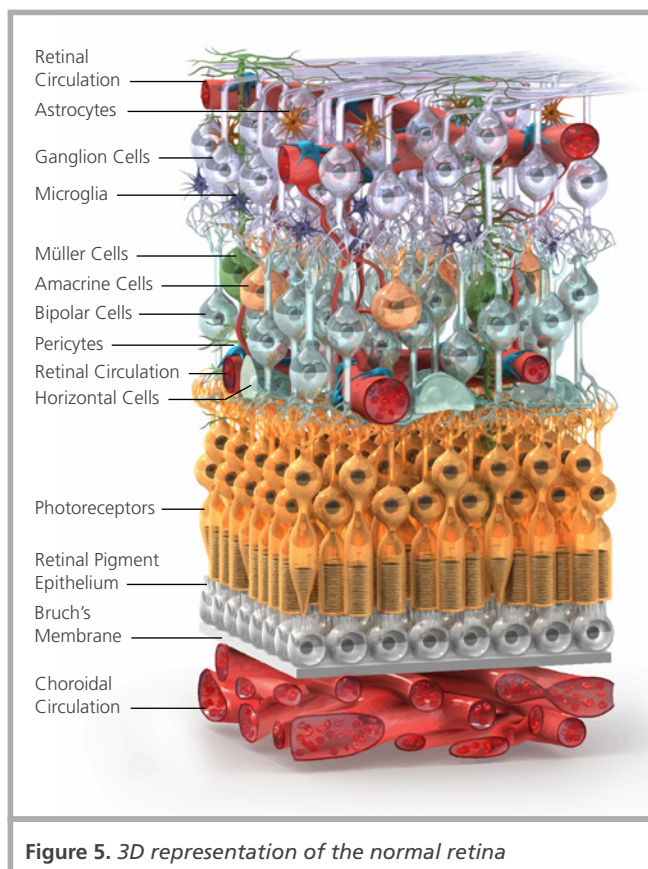


Figure 5. 3D representation of the normal retina

The International Diabetes Federation, along with the International Federation on Ageing, the International Agency for the Prevention of Blindness, and the New York Academy of Medicine, are currently collecting and analyzing data from around the world on diabetes-related vision loss. The data is being incorporated into a new and exciting global initiative, which will be launched in 2015.

DME: Overview of Etiology, Diagnosis, and Treatment Options

The biological path to decreased vision due to diabetic retinopathy and DME begins with chronically elevated blood glucose levels. Over time, poor glycemic control damages the vascular tissue, in particular the endothelial cells and the pericytes (perivascular cells), resulting in vascular dysfunction, inflammation, and hypoxia. Hypoxia, in turn, causes increased VEGF levels in retinal tissue, leading to increased vascular permeability and an accumulation of fluid.

All people with diabetes are at risk of developing DR and DME. The onset of DME is usually insidious and asymptomatic, so patients have no warning signs that the DME is occurring until they notice a blurring of their central vision. The severity of the condition can range from mild — a loss of just one line of vision on a standardized eye chart — to blindness.¹³

Defining DME

In broad terms, DME is defined as a thickening within an area of the retina that is equal to two disc diameters (3 millimeters) of the foveal center. The edema is classified as either focal or diffuse, according to the distribution of the fluid.¹⁴ Clinically significant macular edema (CSME) has a more precise definition; classification is based on the presence of thickening or hard exudates (yellow flecks) within pre-specified areas of the retina.¹⁵ Other definitions exist as well. In addition, a "severity scale," which identifies the severity (mild, moderate, or severe) of DME based on the distance of retinal thickening and/or lipid from the fovea, has been developed.¹⁶

It's not clear, however, that any of these current definitions for DME, which are based on very old clinical trials, are helpful with treating and managing DME in patients today. One important factor not included in the current definitions is the presence of ischemic maculopathy, which often occurs in conjunction with DME.¹⁷ It is characterized by a narrowing or blockage of capillaries in the macula, thus expanding the capillary-free area of the retina known as the foveal avascular zone. Ischemic maculopathy is a very severe prognostic factor for the vision of DME patients, and one that often responds to timely treatment.

Diagnosing DME

Current methods of diagnosing DME have significant limitations. Retinal thickening can be assessed with biomicroscopy, but that assessment is dependent on the observer's experience, and the results do not offer a reproducible measurement of the change in volume.¹⁸ Color stereo fundus photographs can document the presence, size, and location of hard exudates, but to be clinically useful, sequential images must be taken at every follow-up visit. In addition, the thickness of the retina and the presence of cysts and sub-retinal fluid cannot be objectively measured with this technique. The only clinical indication for fluorescein angiography is

the identification of lesions and areas of the retina that require treatment once the decision to treat has been made on clinical grounds.

Optical coherence tomography (OCT) is currently considered the most effective tool for diagnosing DME. It can pinpoint structural changes in the retina caused by DME, often at a stage difficult to assess by other imaging methods, and thus considerably enhances the ability to diagnose and follow macular edema over time.

OCT can be particularly important to identify vitreomacular traction, which may produce cystic changes and macular thickening unrelated to leaking vessels. When OCT is used, fluorescein angiography is probably not needed as well, for the correlation between the two technologies' results is fairly good.¹⁹

Treating DME

One element of the standard of treatment for DME has been glycemic control. This recommendation is based primarily on findings from the Diabetes Control and Complications Trial (DCCT)²⁰ and its follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) trial.²¹ Those studies found that intensive glycemic control lowered the relative risk of the

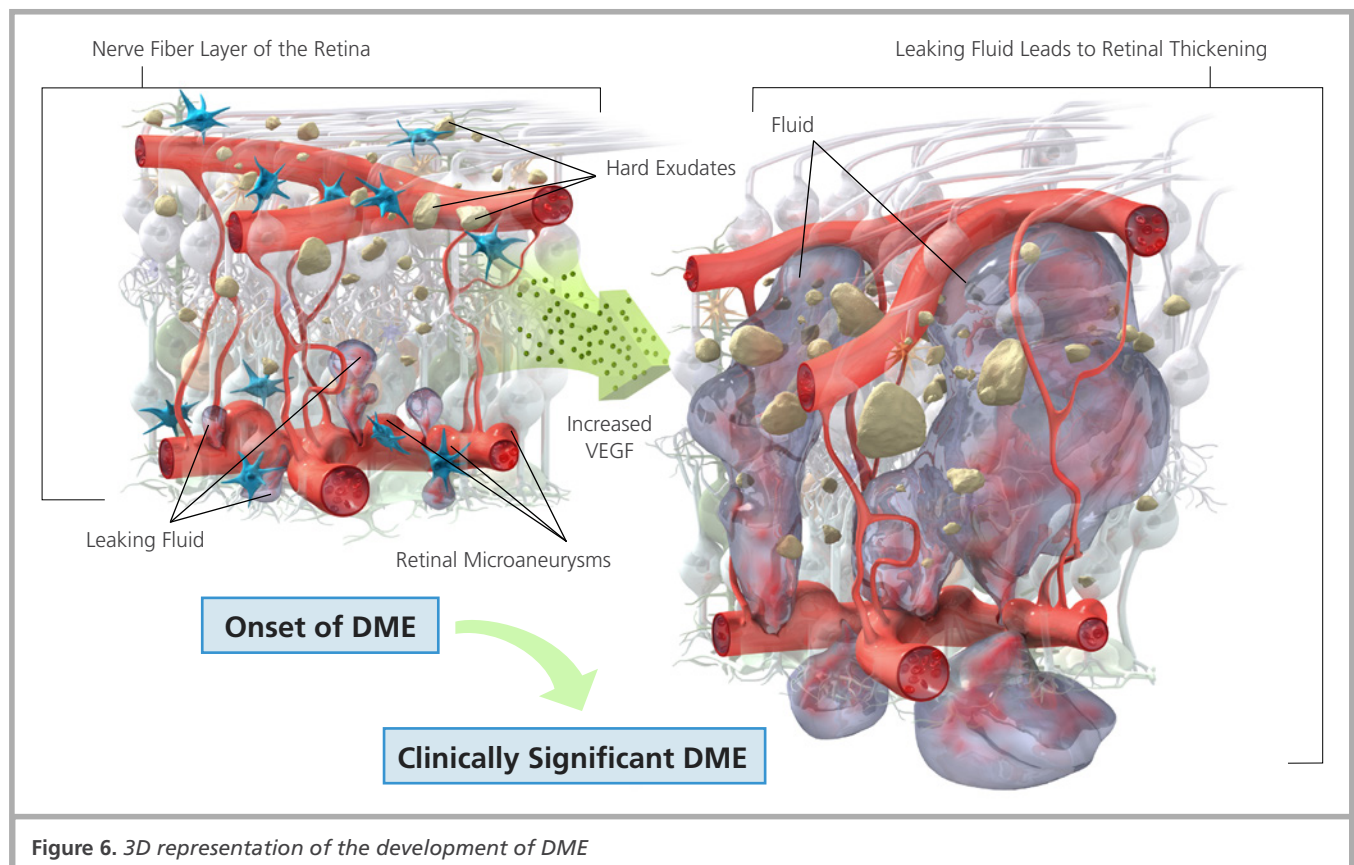


Figure 6. 3D representation of the development of DME

onset of DME by 46% and 58%, respectively. In terms of absolute risk, however, the results were less impressive: only 3% and 10%, respectively. In addition, the studies were looking only at the effect that intensive glycemic control has on the onset of DME; they did not investigate its effect on established disease. More recently, intensive glycemic control has been found to be associated with an increased risk of mortality.²²

Corticosteroids, including intravitreal injections of triamcinolone acetonide, have been used to treat DME but the treatment can accelerate the development of cataracts and cause an elevation of intraocular pressure that may damage the optic nerve and lead to glaucoma.²³ A dexamethasone intravitreal implant has recently been approved by the FDA for adults with DME who have an artificial lens implant (pseudophakic) or who are scheduled for cataract surgery (phakic).²⁴

Laser photocoagulation has also been used to treat DME, often in conjunction with corticosteroids. One study reported that laser treatment reduced the relative risk of moderate visual loss from DME by 50%; but in absolute terms, the risk was a more modest 12%.¹⁵ Potential side effects from laser therapy include a loss of peripheral vision and the development of blind spots in central vision. Vitrectomy is another treatment option. After this surgical procedure is performed, retinal thickening is reduced in most eyes, and research has shown that between 28% and 49% of patients are likely to experience an improvement of visual acuity. Unfortunately, 13% to 31% of the patients have a worsening of their visual acuity.²⁵

The real game-changer in the treatment of DME has been the introduction of various anti-VEGF therapies. They have revolutionized the treatment and management of the disease.

State-of-the-Art Overview of Anti-VEGF Therapies

Anti-VEGF therapies for DME were developed when it became clear that although laser treatments were often able to stabilize vision and prevent further vision loss, they were not helping patients regain lost vision. Treating DME with anti-VEGF drugs, on the other hand, has been found in many different randomized clinical trials to be effective in not just stopping the progression of the disease, but also in improving vision. Furthermore, the improvements are maintained over time.

Recent research has revealed other important findings regarding anti-VEGF therapies and DME, including the following:

1. DME does not progress rapidly, in comparison to a condition like wet AMD. Thus, clinicians and patients have much more time to plan and implement an effective course of treatment with DME. The fact that DME is more of a chronic rather than an acute disease also means that anti-VEGF treatments do not need to begin with three loading doses (ones with higher amounts of the anti-VEGF drug than the maintenance doses that will be given later), as is the case in the treatment of wet AMD.
2. Anti-VEGF therapies are superior to laser therapy for the treatment of DME, and adding laser to anti-VEGF therapies offers no further benefits.²⁶ In fact, deferring laser treatments may actually result in better visual acuity outcomes. Thus, anti-VEGF drugs appear to be a better choice as a first-line therapy for DME.
3. Unlike the anti-VEGF dosing regimen for wet AMD, the regimen for DME involves progressively fewer injections: an average of 9 injections in the first year of treatment followed by an average of 2-3 injections in the second year and 1-2 injections in the third year.
4. Anti-VEGF treatments appear to work even in eyes with chronic DME that have been previously treated with laser therapy.
5. No racial or ethnic differences in the effectiveness of anti-VEGF treatments have been found.²⁷

Although anti-VEGF therapies have been demonstrated to be effective in the treatment of DME, many questions remain unanswered about their clinical application, including the following:

- When should we start anti-VEGF treatment? For example, do we treat an eye with a vision of 20/30 (6/9)? Or when there are extensive exudates with little edema? Or when there is evidence of macular ischemia with edema?
- When should we stop treatment? Furthermore, how do we decide when a treatment has been “successful” — or when it has “failed?”
- What are appropriate injection intervals?
- What is the best approach to manage concurrent proliferative diabetic retinopathy and DME?
- Which anti-VEGF agent is better? Head-to-head trials of different agents have not yet been conducted.
- Is there a role for “sequential” treatments with different agents?
- How does the clinician manage the disease when both eyes are affected?
- Are anti-VEGF agents safe over the long term?

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 six key DME stakeholders: patients/caregivers, diabetologists, general ophthalmologists, retinal specialists, diabetes advocacy leaders, and health authorities. That assessment is reflected in the chart below. It was clear from the experts’ assessments that much more work needs to be done to educate stakeholders about DME.

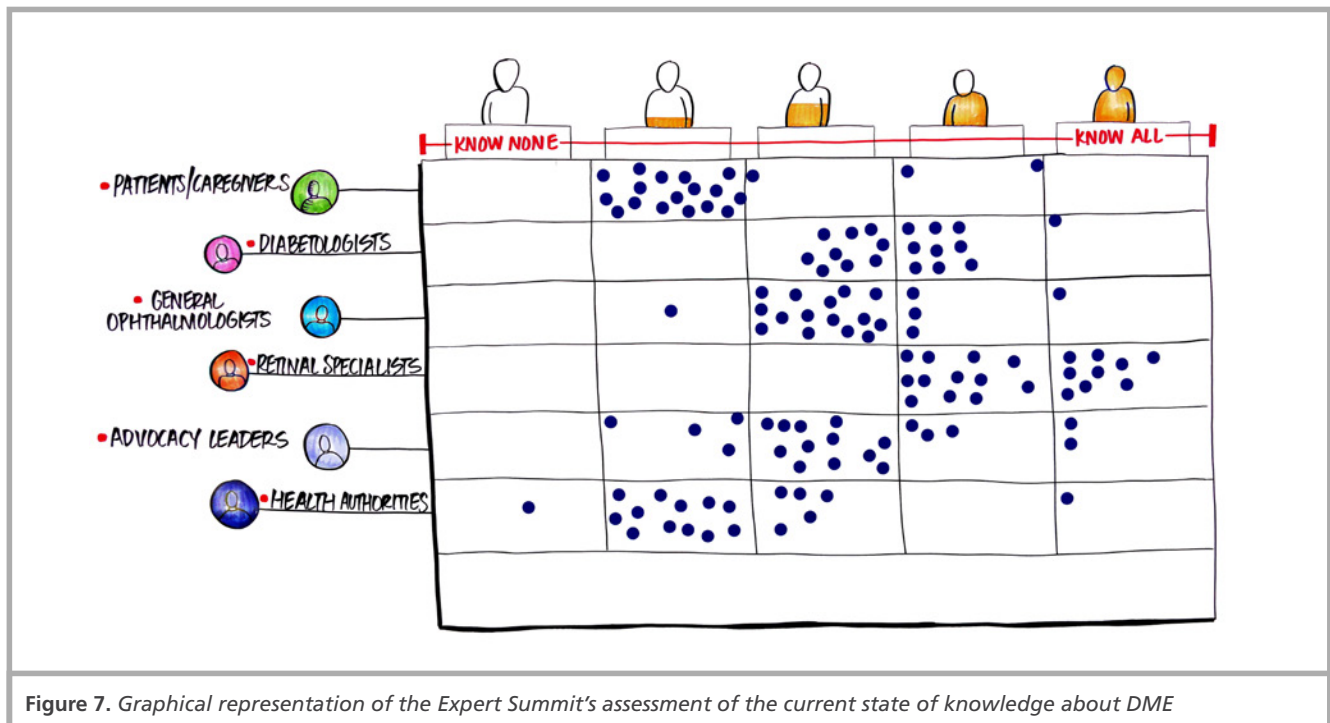


Figure 7. Graphical representation of the Expert Summit's assessment of the current state of knowledge about DME

Defining the Value of Vision in Diabetes, From Pre-Diagnosis Through Treatment of DME

As the summit's opening presentations made clear, DME is a leading cause of vision loss 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, in fact, 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 diabetes advocacy groups, 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 the perspective of the various stakeholder groups. Key points raised during that discussion are summarized below.

From the perspective of patients and caregivers:

Pre-diagnosis (Prevention):

- Most people with diabetes want to be informed and educated about potential complications, including vision loss.
- Individuals with diabetes want to retain their physical independence; vision loss is perhaps the greatest diabetes-related threat to that independence.
- People with diabetes also want to retain their financial independence. Many worry about how vision loss will affect their ability to make a living and support their family.
- Individuals with diabetes value knowledge about their disease because it gives them the confidence that they can do something to reduce the risk of complications, including vision loss.
- Immediately after being diagnosed with diabetes, many people are highly motivated to take steps to reduce their risk of diabetes-related complications, including vision loss. They may lose some of that motivation, however, as time passes. That's because living with the disease requires daily self-monitoring and lifestyle changes that may begin to feel onerous to the patient and because the development of diabetes-related complications, including vision loss, tend to be "silent" until their symptoms appear.

- The aspects of their disease that a person with diabetes focuses on often change over time. Preventing vision loss, therefore, may not always be on a patient's "radar screen."
- Many people with diabetes do not understand how DME will affect their lives and their independence until they lose their driver's license. Often, that is when they seek care.
- Asking people to focus on reducing their risk of diabetes-related complications means asking them to put themselves first in their lives. But people with diabetes often have other responsibilities, particularly involving their families, that they consider more pressing.

Post-diagnosis (Addressing vision loss):

- Individuals who have been diagnosed with DME want their vision returned to normal, not just stabilized.
- After being diagnosed with DME, people tend to develop a deeper understanding of how better management of their diabetes can help them lower their risk of vision loss and other complications. Still, because DME is a slowly progressing disease, not all individuals feel an urgency to begin treatment.
- People with DME would prefer that treatments not involve injections, which many of them fear.
- Individuals tend to want big changes in their vision with as little effort as possible. They particularly want treatments that require few trips to a medical facility.
- People with DME want access to state-of-the-art DME-related diagnosis equipment and treatments.
- Individuals with diabetes would find great value in an imaging biomarker that could clarify their personal risk of vision loss and identify the most effective therapy for their particular medical situation.

From the perspective of clinicians and other medical providers:

Pre-diagnosis (Prevention):

- Clinicians want to help empower their patients to be responsible for their own health.
- Having a full — and easily accessible — medical history of a patient with DME is very valuable to clinicians as they develop a treatment plan for that individual.
- Conducting routine annual eye screenings of people with diabetes is one of the most significant actions the medical community could

take toward increasing the early diagnosis and treatment of DME. Such annual screening already occurs in the United Kingdom.

Technicians in separate diabetic centers do the screening; if the screening reveals a potential problem, the individuals are referred to specialists.

- Screening needs to be proactive rather than reactive. For example, sending letters to people with diabetes to remind them that they are due for an eye check-up is very effective.

Post-diagnosis (Addressing vision loss):

- Clinicians want all their patients with DME to have full access to timely, affordable treatment options.
- The most valuable treatment approach is one in which a patient's clinicians are working together. The success of this "silo-breaking" approach requires close communication and cooperation among the clinicians.
- Having one clinician — perhaps the patient's primary care physician or diabetologist — overseeing all the patient's care can help ensure that the patient's treatment plan is effectively executed. Ideally, the care would occur in a clinic specifically dedicated to people with diabetes.
- Post-diagnostic care should include a psychologist or psychiatrist to help people with DME adjust to living with condition and to making the subsequent lifestyle changes necessary for maintaining health — and good vision.

From the perspective of the diabetes community, including its associations and advocacy groups:

Pre-diagnosis (Prevention):

- The diabetes community places a high value on evidence-based research. It wants good, solid data that it can take to national and international health organizations to ask for more resources. Resources are needed not just to educate people about diabetes, but also for diabetes-related screening and medication. This includes screening and medication specific to diabetes-related eye conditions, such as DME, which are major causes of vision loss around the world.

- The diabetes community values prevention. Thus, it recognizes the urgent need for more awareness and educational efforts aimed at reaching the large (and growing) numbers of people with undiagnosed diabetes.
- Creative use of the media, including social media, is key to any educational campaign.
- Awareness efforts must also be aimed at healthcare practitioners so that the disease can be caught early, before serious complications develop.
- The diabetes community also values educational efforts aimed at helping policymakers understand the growing societal and financial burden of diabetes and the cost-effectiveness of early diagnosis and treatment.
- Any large diabetes-screening program should recognize and accommodate the differential risk across ethnic groups.

Post-diagnosis (Addressing vision loss):

- Educational efforts must help people with diabetes understand the course of the disease and how it can be systematically controlled. The effects of diabetes on the eye need to be emphasized and carefully explained, especially as many people do not understand the basics of how vision works.
- Educational efforts must also be updated frequently to include state-of-the-art diagnostic techniques and treatments, including those for the diagnosis and treatment of DME.
- The diabetes community recognizes that it can learn from the HIV/AIDS community about peer-to-peer patient education. Videos in which patients talk about their experiences with diabetes-related vision loss, including DME, and its treatment can be very effective.
- Stronger advocacy efforts to help get anti-VEGF drugs licensed for the treatment of DME are needed.
- The diabetes community encourages efforts to develop DME-related treatments that are longer lasting and that have fewer required interventions.
- The diabetes community wants a greater emphasis placed on vision and DME in the primary management of diabetes.
- The diabetes community would like to see an organized group of advocates develop around the issue of DME. Glaucoma has such advocates, as does wet AMD.

Mapping the Care Pathway for DME

After identifying what DME stakeholders most value and want regarding the prevention, diagnosis, and treatment of the disease, the summit's participants turned their focus to care pathways. The discussion was in two parts. It began with a conversation about screening, diagnosis, and referral, and then moved on to one about treatment and ongoing care. Key points raised during those discussions are summarized below.

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? The experts noted that in many countries the clinicians most likely to diagnose DME are general ophthalmologists. They tend to have the OCT equipment and training to make a reliable diagnosis. But other types of clinicians are also diagnosing DME, and who those clinicians are varies from country to country. In the United Kingdom, for example, most patients are diagnosed through the National Health Service's Diabetes Eye Screening Programme. Spain has a less comprehensive screening program that also helps identify people with DME. In Japan, major employers sponsor yearly eye screenings; if any maculopathy is observed, the employee is referred to an ophthalmologist for further testing. In Spain, Germany, Italy, Singapore, and Turkey, a general ophthalmologist is most likely to make the initial diagnosis, although in

some areas of these countries, retinal specialists are also diagnosing the disease. The same is true in Columbia and Argentina, where general ophthalmologists who suspect that a patient has DME usually refer that patient to a retinal specialist for confirmation of the diagnosis. In the United States, optometrists are often making the initial diagnosis, primarily because those are the clinicians that people tend to go to first when they have eye problems. Optometrists tend not to have the necessary technology to make a reliable diagnosis, however.

The experts expressed concern about a DME diagnosis that relies on digital retinography (fundus photography) results alone. It was emphasized that OCT is the gold standard for diagnosing the disease. In the United Kingdom, individuals with a suspicious digital retinography result are referred to an OCT screening by either an ophthalmologist or retinal specialist. In most other countries, however, the referral process to OCT screening is more fragmented. In some countries, access to OCT screening depends on where you live. In Argentina, for example, people living in major cities have access to OCT, but such access is much more problematic in the country's rural areas.

The next question posed to the summit's experts was this: To whom are people diagnosed with DME referred for treatment? Again, the answers varied from country



Figure 8. Moderated discussion at the Expert Summit

to country. In France, for example, general ophthalmologists often treat the “easy” cases of DME, but when anti-VEGF injections are needed, the patients are usually sent to a retinal specialist. In Italy, general ophthalmologists also treat patients with minor diabetes-related eye problems, but more severe cases are referred to hospitals, where patients can see a retinal specialist. In the United Kingdom, patients diagnosed with DME are sent to an ophthalmologist or, perhaps, to a retinal specialist. Seeing a retinal specialist in the U.K. sometimes involves a long wait for patients with DME because preference is given to patients with wet AMD, which is a more acute disease and requires more timely treatment. In Columbia, only retinal specialists can treat patients with anti-VEGF injections and/or laser therapy. Not all countries, however, make a clear-cut medical-certification distinction between an ophthalmologist and a retinal specialist.

The summit’s experts also pointed out that people with DME are often referred to ophthalmologists or retinal specialists for diagnosis and treatment by clinicians who are involved in the patient’s general health or in specific, non-eye-related aspects of the patient’s diabetes. These clinicians include nephrologists, diabetologists, general practitioners, obstetricians-gynecologists, and pediatricians. A variety of factors, especially the institution in which the clinician practices, will affect to whom these clinicians refer their patients. In addition, individuals may self-refer to an ophthalmologist or retinal specialist, sometimes after first seeking treatment at an emergency medical facility for a sudden loss of vision, or sometimes after a public-awareness campaign that alerted them to the symptoms of DME. In Belgium, people are able to self-refer directly to a retinal specialist; they do not need a referral from their general practitioner.

The summit experts acknowledged that there is a general awareness among health practitioners that people with diabetes need to have regular eye exams, but that the awareness needs to be raised to a higher, systematic level to ensure such exams take place.

The moderator then asked the experts this question: What patient-related factors influence the referral pattern? The experts noted that if a country has a law about who can treat people with DME, then, of course, the law determines the referral decision. In addition, some countries refer patients with multiple co-morbidities to universities or other facilities with a high level of coordinated medical expertise. Referral patterns are also influenced by different insurance systems in various countries.

Although DME is a slowly progressing eye disease, the experts stressed that there should be one simple message about screening for DME: It needs to occur every year. Indeed, that message is emphasized during World Sight Day (October), where the International Diabetes Foundation leverages their media campaigns, and during World Diabetes Day (November). Yet raising awareness about the need for annual screening is not enough, said the experts. It must be accompanied by easy patient-access to the screening. That access does not exist in all regions of the world.

Access, Intervention, and Long-Term Management

The discussion then shifted to the second part of the care pathway: access, intervention, and long-term management. The conversation began with an acknowledgement of the various forms of treatment currently in use: lifestyle changes, laser therapies, steroid treatments, surgery, anti-VEGF therapies, and general diabetes-related medical care aimed at glycemic control. It was also noted that many people with DME receive no treatment, or may begin treatment and then stop for a variety of personal, social, or financial reasons, thus becoming “lost” to care.

The experts stressed the importance of lifestyle interventions. One of the experts used the analogy of a boat with a hole in the keel: You can pump out the water, but the water will return if the hole isn’t fixed. Making lifestyle changes is like repairing that hole; without those changes, diabetes-related health problems will simply return. It was also pointed out, however, that although glycemic control may help prevent the onset of DME in people with diabetes, there is no evidence that it helps treat established DME.

The experts then discussed the lack of international treatment guidelines for DME. It was pointed out that in countries that have their own guidelines, retinal specialists are more likely than general ophthalmologists to follow them. Individual clinician preferences are also deciding factors in treatment choices. Clinicians usually prefer treatments that they have been trained to use or for which they may already have the equipment (as with lasers). In some instances, treatment choices are also limited by concerns of being sued for malpractice. Such preferences and concerns can hold back clinicians from adopting newer treatments, even when those treatments are evidence-based.

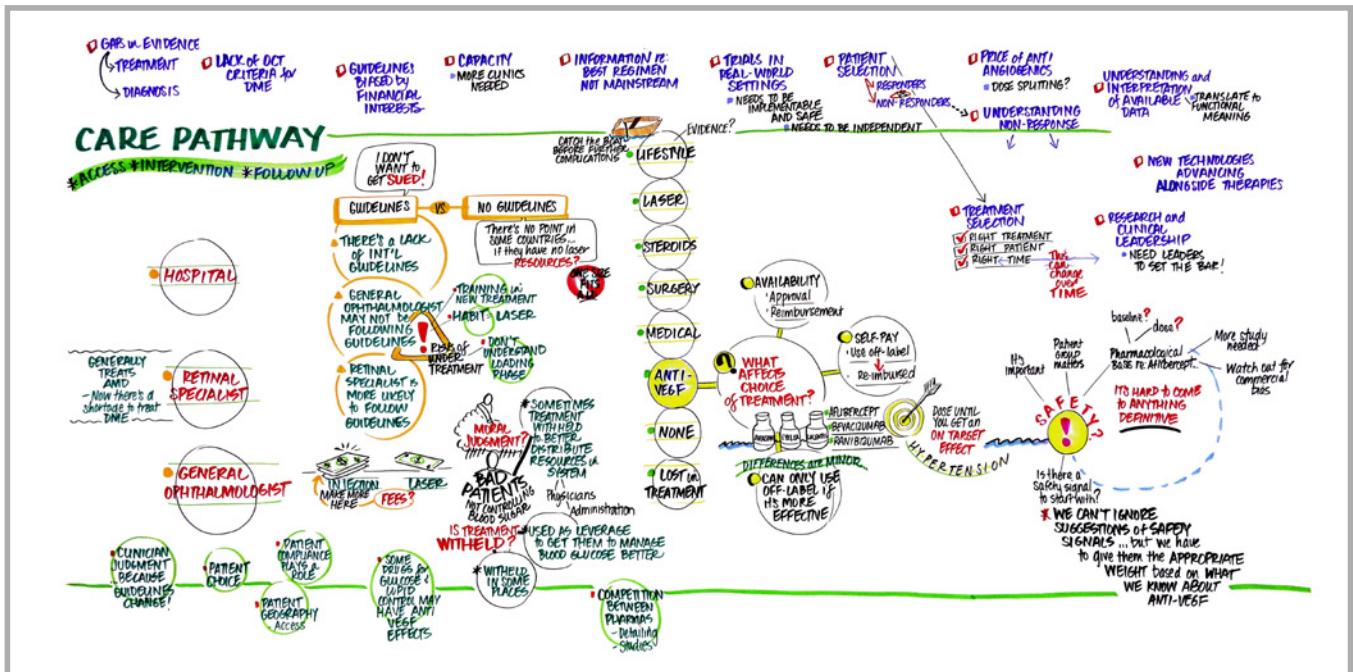


Figure 9. Graphical representation of the second part of the DME care pathway: access, intervention and follow-up

Although not widespread, the practice of denying anti-VEGF treatments to people with DME who do not have their blood sugar under control occurs in some regions. In one country, for example, anti-VEGF drugs are frequently denied to people with DME who have a hemoglobin A1c (HbA1c) level above 7.9%. Some doctors believe such denial of treatment is a way of pressuring individuals to get their blood sugar under control. Yet, as the experts at the summit pointed out, there is no evidence that glycemic control helps with the treatment of established DME. Some evidence does suggest, however, that drugs used for the intensive control of blood sugar may actually harm the macula and lead to a worsening of DME symptoms, at least initially.²⁸ (Other drugs used to treat diabetes, including certain statins, appear to have anti-VEGF effects, which may be protective against DME.²⁹) In addition, noted the summit's experts, glycemic control is not always possible for all individuals with diabetes, even when they make extraordinary attempts to achieve it. For these and other reasons, the European Medicines Agency's guidelines for the treatment of DME do not make controlling blood sugar a prerequisite.³⁰

Patients, of course, also influence treatment choices for DME. Despite the effectiveness of anti-VEGF therapy, patients often reject it. Leading reasons for this rejection are a fear of injections, insufficient or non-existent insurance coverage, and an inability to easily access the medical facility where the treatment is provided. Sometimes, the summit experts noted, patients will start anti-VEGF treatment, and then, when their vision starts to improve, fail to return to finish the full treatment course, mistakenly believing that they are "cured."

Several factors affect which specific anti-VEGF therapies clinicians use. These include, of course, whether or not the drug is approved for DME treatment in the clinician's country, as well as access to the drug if approved. Safety is not usually a factor because research has found no significant differences in safety profiles among the approved anti-VEGF drugs used to treat DME. Anti-VEGF drugs appear to pose a small risk of increased intraocular pressure. In some countries, clinicians may treat DME with an off-label drug that has been approved for non-ocular or a different ophthalmic disease, such as wet AMD or RVO. In other countries, however, such off-label use is not permitted.

Analyzing Gaps in the DME Care Pathway

After mapping the various current DME care pathways, both pre- and post-diagnosis, 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 making DME a health priority**
Although diabetes has been made a health priority in many countries, the same has not been true for DME. Diabetes-related resources have tended to focus on treating other complications of the disease, such as those involving the heart and kidney. A major reason for that oversight has been the lack of effective treatments for DME. Anti-VEGF therapies have, however, changed that paradigm, for they offer improved outcomes for people with DME vision loss. Now is the time to educate policymakers about the effectiveness of the new treatments and about the benefits of making the diagnosis and treatment of DME a health priority. Yet, currently, there is no large-scale advocacy “ownership” of diabetes-related vision loss as there is for other serious eye diseases, such as wet AMD and glaucoma.
- **Gaps in the transfer of information**
This gap occurs at several levels. On the individual patient level, for example, gaps frequently occur in the transfer of the patient's clinical information among clinicians. The result: inefficient and sometimes even harmful “silos” of care. At the broader societal level, large gaps exist in the transformation of information about DME to the general public, policymakers, and others.
- **Gaps in financial resources**
Necessary DME-related services, including screening, diagnosis, treatment, and ongoing care, are often not covered by insurance providers, whether public or private. This gap is sustained by a lack of precise data on DME's true financial cost to individuals, society, and governments.
- **Gaps in communication**
Patient advocates, clinicians, and policymakers hold the key to unlocking more financial resources for DME-related services, but these groups of stakeholders seldom come together to talk about how best to accomplish this goal.
- **Gaps in standards of care**
Breast cancer patient-advocates have made mammograms a standard of care. A similar advocacy movement is needed to standardize annual eye-screening programs for people with diabetes.
- **Gaps in the capacity to deliver treatment**
More clinics and hospitals that offer state-of-the-art DME screening and treatments need to be established. Furthermore, these facilities need to be geographically distributed to reach all people at risk for DME.
- **Gaps in evidence about the effectiveness of diagnostic tools**
Currently, good evidence in support of OCT diagnostic criteria for the diagnosis of DME is lacking. Such criteria exist for wet AMD, and it is used to guide therapy for that disease. Similar evidence-based diagnostic criteria are needed for DME.
- **Gaps in the availability of diagnostic equipment**
Such equipment is particularly needed in low- and middle-income countries and communities. Gaps also exist in the number of personnel who are trained to use the equipment.
- **Gaps in treatment guidelines**
Universally accepted treatment guidelines for DME are needed. These guidelines must be unbiased by financial interests. The International Council of Ophthalmology (ICO) released its updated Guidelines for Diabetic Eye Care late in 2013.³¹ These guidelines are helpful, but they are likely to change frequently in the coming years as researchers and practitioners gain a greater understanding of anti-VEGF treatment regimens.

- **Gaps in knowledge about treatment non-responders**

Although patients with DME respond to anti-VEGF treatments significantly better than they do to other methods of treatment, the response is not universal. One three-year trial found, for example, that about 10% of patients with DME did not respond to anti-VEGF treatments. Understanding the biological mechanisms for that non-response is crucial, for it would help with the development of alternative treatment approaches for those patients. Also needed are biomarkers or other tools that would help clinicians distinguish responders from non-responders early in the treatment process. Such tools would help make sure that the right treatments are being delivered to the right patients.

- **Gaps in “real-world” clinical trials**

Studies involving anti-VEGF therapies need to better reflect “real-world” clinical practice settings. For example, current practice guidelines for anti-VEGF therapies require nine injections during the first year of treatment. That number of injections is impractical in many clinical settings. In addition, the data from the clinical trials needs to be translated so that it has “real-world” meaning. Saying a treatment enables people with DME to read one additional line on an eye chart may or may not have any functional value for many of those individuals.

- **Gaps in independently run clinical trials**

The findings from industry-sponsored clinical trials need to be confirmed by independent researchers. Long-term results regarding anti-VEGF effectiveness and safety for the treatment of DME are also needed. Research and clinical leaders also need to get ahead of industry and set the pace and tone of the research being conducted on anti-VEGF therapies for the treatment of DME.



Figure 10. Experts discuss the gaps in the DME care pathway.

Action Agenda

In the final session of the international summit, regional co-chairs Francesco Rodriguez, Ramin Tadayoni, and Tien Yin Wong presented an initial set of recommended actions. The summit's experts then discussed those recommendations and identified the following specific "next steps" for improving outcomes for people with DME.

1. **Create an ophthalmologist-led, multi-disciplinary task force that will take the lead in advocating for improvements in the diagnosis and treatment of DME worldwide**

- Meet regularly to develop specific initiatives to close the gaps between DME-related stakeholder values and care pathways that were identified during the summit.
- Invite patients to form a sub-committee of the task force.
- 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.
- Bring disparate organizations together. Collaborate rather than compete.

2. **Determine the cost of DME-related vision loss**

- Develop an evidence-based socioeconomic cost-savings model for DME.
- Make sure the model includes the most cost-effective treatment protocol.
- Use the model to educate policymakers and others about how much it costs not to screen/treat people with DME.
- Use it also to make the case for national screening programs and for government/insurer reimbursement for effective treatments.

3. **Develop a simple, internationally understood message for DME screening**

- Frame the message as a patient-rights issue.
- Emphasize within the medical community that annual eye screening for people with diabetes is an ethical standard of care.
- Explore all media channels, including social media, to spread the message to various stakeholder groups.
- Reach out to the International Diabetes Federation, the Angiogenesis Foundation, and other advocacy groups to help with the development of the message and with the funding of any related media campaign(s).

4. **Remove the "silos" in patient care**

- Encourage the development of multi-disciplinary care teams for people diagnosed with DME.
- Model them after other successful multi-disciplinary teams, such as those that have been formed in some communities to contend with diabetic wound healing.
- Support the development of healthcare systems that allow for the smooth, timely transfer of need-to-know patient information among all of the patient's clinicians.

5. Educate DME stakeholders

- Make sure that information presented to patients, families, clinicians, and others about DME and its treatment is evidence-based and unbiased.
- Extend educational efforts beyond ophthalmologists to all clinicians who treat people with DME, including diabetologists and general practitioners.
- When appropriate, use existing educational materials. The Angiogenesis Foundation has launched, for example, a patient-oriented website called "The Science of DME," (www.scienceofdme.org), which is in the process of being translated into many different languages. The Foundation is also developing an interactive training session on DME for clinicians.
- Advocate within professional medical organizations to make diabetes-related eye diseases part of medical conferences.

6. Create a strong DME-related research agenda

- Encourage research aimed at bridging the evidence gaps regarding the underlying biological, epigenetic, and genetic mechanisms of DME, as well as its natural history.
- Advocate for more "real-world" clinical trials (ones with meaningful endpoints).
- Advocate for more clinical trials that investigate systemic treatments and the long-term safety of anti-VEGF therapies.
- Encourage the development of DME animal models.
- Bring experts together to update diagnostic and classification definitions of DME.
- Serve as forecasters of where the DME research field is going.

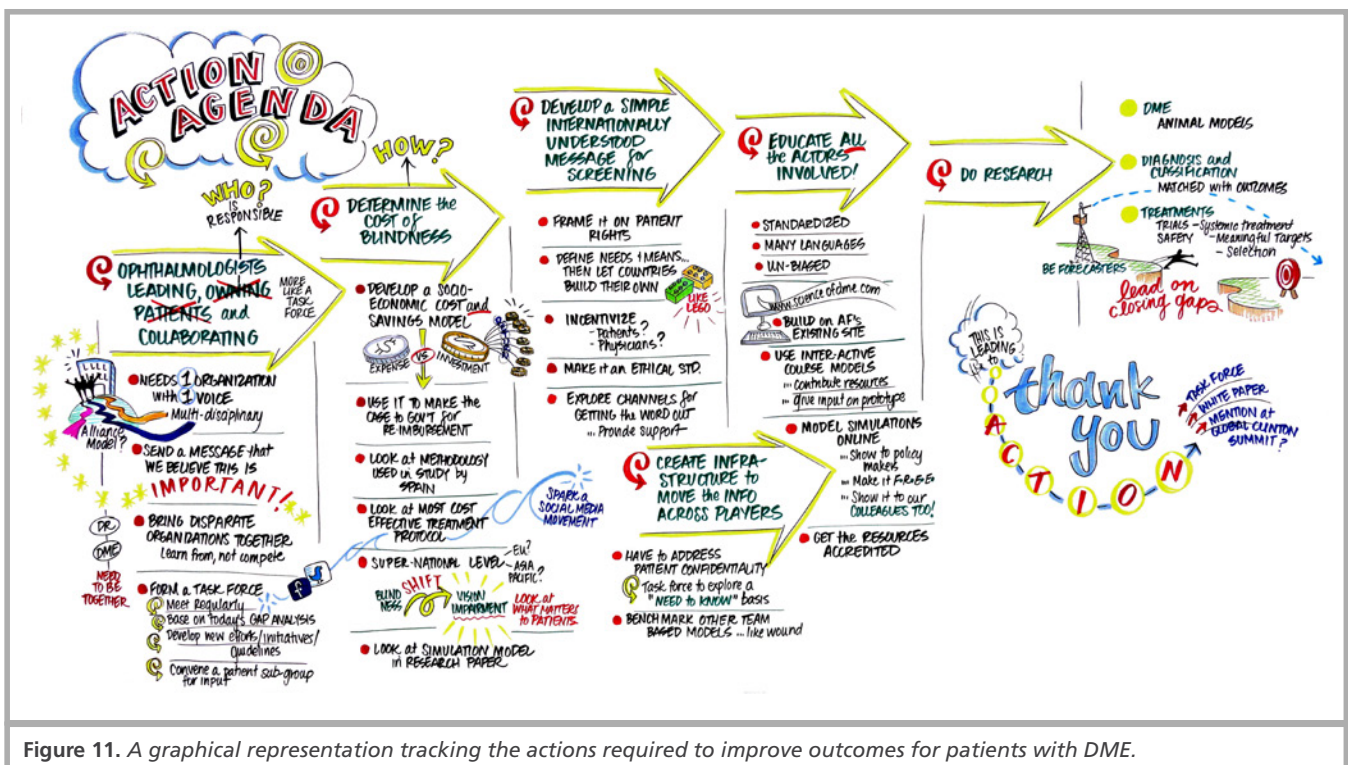


Figure 11. A graphical representation tracking the actions required to improve outcomes for patients with DME.

References

1. Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. *JAMA*. 2007;298:902-916.
2. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy ETDRS report number 9. *Ophthalmology*. 1991;98(12):1464-1474.
3. International Diabetes Federation (Europe). Diabetes & blindness due to DME. Brussels, Belgium: International Diabetes Federation. Available at: www.idf.org/sites/default/files/IDF%2520Toolkit_Backgrounder_FINAL.pdf. Accessed August 2014.
4. Klein R, Klein BEK, Moss SE. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. *Ophthalmology*. 1984;91(12):1464-1474.
5. International Diabetes Federation. IDF Diabetes Atlas, 6th ed. Brussels, Belgium: International Diabetes Federation, 2013. Available at: www.idf.org/diabetesatlas. Accessed: August 2014.
6. U.S. Food & Drug Administration. FDA approves Lucentis to treat diabetic macular edema. Silver Spring, MD: FDA; Aug. 10, 2012.
7. Novartis. Novartis shows continued commitment in Japan with Lucentis approval in fourth Japanese indication, diabetic macular edema. Basel, Switzerland: Novartis; Feb. 21, 2014.
8. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012;119:789-801.
9. Elman MJ, Bressler NM, Qin H, et al.; the Diabetic Retinopathy Clinical Research Network. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2011;118(4):609-614.
10. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology*. 2014;S0161-6420(14)00426-6. [Epub ahead of print].
11. Yau JW, Rogers SL, Kawasaki R, et al.; the Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35(3):556-564.
12. Access Economics. The Global Economic Cost of Visual Impairment (prepared for AMD Alliance International). Canberra Barton, Sydney, and Melbourne, Australia: Access Economics. March 2010.
13. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy: IV. Diabetic macular edema. *Ophthalmology*. 1984;91:1464-1474.
14. Browning DJ, Altaweel MM, Scott IU. Diabetic macular edema: what is focal and what is diffuse? *Am J Ophthalmol*. 2008;146(5):649-655.
15. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report no 1. *Arch Ophthalmol*. 1985;103:1796-1806.
16. Wilkinson CP, Ferris FL, Klein RE, et al., Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology*. 2003;110:1677-1682.
17. Bandello F, Battaglia PM, Lanzetta P, et al. Diabetic Macular Edema. In: Macular Edema — A Practical Approach. Dev Ophthalmol. Coscas G, Cunha-Vaz J, Loewenstein A, Soubrane G. (eds). Basel, Switzerland: Karger. 2010. Vol. 47:73-110.
18. Brown JC, Solomon SD, Bressler SB, et al. Detection of diabetic foveal edema: contact lens biomicroscopy compared with optical coherence tomography. *Arch Ophthalmol*. 2004;122(3):330-335.
19. Kang SW, Park CY, Ham DI. The correlation between fluorescein angiographic and optical coherence tomographic features in clinically significant diabetic macular edema. *Am J Ophthalmol*. 2004;137(2):313-322.
20. Diabetes Control and Complications Trial Research Group. Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. *Ophthalmology*. 1995;102(4):647-661.
21. Aiello LP, for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Diabetic retinopathy and other ocular findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. *Diabetes Care*. 2014;37:5-7.
22. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lower in type 2 diabetes. *N Engl J Med*. 2008;358:2545-2559.
23. Diabetic Retinopathy Clinical Research Network. Three-year follow up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. *Arch Ophthalmol*. 2009;127(3):245-251.
24. U.S. Food & Drug Administration. FDA approves Ozurdex (dexamethasone intravitreal) implant for the treatment of diabetic macular edema in patients who are pseudophakic or are phakic and scheduled for cataract surgery. Silver Spring, MD: FDA; June 28, 2014.
25. Haller JA, Qin H, Apte RS, et al.; Diabetic Retinopathy Clinical Research Network Writing Committee. Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. *Ophthalmology*. 2010;117(6):1087-1093.
26. Elman MJ, Qin H, Aiello LP, et al.; Diabetic Retinopathy Clinical Research Network Writing Committee. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. *Ophthalmology*. 2012;119(11):2312-2318.
27. Ohji M, Ishibashi T, for the REVEAL Study Group. Efficacy and safety of ranibizumab 0.5 mg as monotherapy or adjunctive to laser versus laser monotherapy in Asian patients with visual impairment due to diabetic macular edema: 12-months results of the REVEA study. Paper presented at: Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO); May 9, 2012; Fort Lauderdale, FL.
28. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. *N Engl J Med*. 2000;342:381-389.
29. Dulak J, Jozkowicz A. Anti-angiogenic and anti-inflammatory effects of statins: relevance to anti-cancer therapy. *Curr Cancer Drug Targets*. 2005;5(8):579-594.
30. Bandello F, Cunha-Vaz J, Chong NV, et al. New approaches for the treatment of diabetic macular oedema: recommendations by an expert panel. *Eye (Lond)*. 2012;26(4):485-493.
31. International Council of Ophthalmology. ICO Guidelines for Diabetic Eye Care. San Francisco: ICO. 2014. Available at: <http://www.iapb.org/news/ico-issues-updated-diabetic-retinopathy-guidelines>.

Participants

Chair:

William W. Li, M.D.

The Angiogenesis Foundation
Cambridge, MA USA

Regional Co-Chair:

Francisco J Rodriguez, M.D.

Fundación Oftalmológica Nacional
Bogotá, Colombia

Regional Co-Chair:

Ramin Tadayoni, M.D., Ph.D.

Université Paris 7 - Sorbonne Paris Cité

Regional Co-Chair:

**Tien Yin Wong, M.B.B.S., M.M.E.D., M.P.H.,
Ph.D., F.R.C.S.E., F.R.A.N.Z.C.O., F.A.M.S.**

Singapore National Eye Centre Singapore

Norbert Bornfeld, M.D.

Zentrum für Augenheilkunde
Essen, Germany

Francesco Boscia, M.D.

University of Sassari
Sardinia, Italy

Bora Eldem, M.D., F.E.B.O.

Hacettepe University
Ankara, Turkey

Takao Hirano, M.D.

Shinshu University
Matsumoto, Japan

Michelle Hutnik, D.Sc.

The Angiogenesis Foundation
Cambridge, MA USA

Maria Isabel Lopez Galvez, M.D., Ph.D.

Hospital Clinico/ Ioba Valladolid
Valladolid, Spain

Lydia Makaroff, M.P.H., Ph.D.

International Diabetes Federation
Brussels, Belgium

Toshinori Murata, M.D., Ph.D.

Shinshu University
Matsumoto, Japan

Zeynep Osar Siva, M.D.

University of Istanbul
Istanbul, Turkey

Alicia Pareja Rios, M.D., Ph.D.

Hospital Universitario De Canarias
Tenerife, Spain

Diana Saville

The Angiogenesis Foundation
Cambridge, MA USA

Patricio Schlottmann, M.D.

Organización Médica de Investigación
Buenos Aires, Argentina

Sobha Sivaprasad, F.R.C.S., D.M.

Moorfields Eye Hospital
Essex, United Kingdom

Andrea Sodi, M.D.

University of Florence
Firenze, Italy

Francesco Viola, M.D.

University of Milan
Milan, Italy

Marita Wernsing

Diabetes-Zentrum Quakenbrück
Alfhausen, Germany

Other Contributors

Vincent Li, M.D., M.B.A.

Robert Mittman

Susan Perry

Lisa Arora

Maria Aufiero

Katherine Pierce

Thomas Raffoux

Jennifer Maggio

The Angiogenesis Foundation