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Released: 11/11/2026
Valid until: 11/11/2027
Time needed to complete: 52m

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# Unmet Needs in nAMD in 2026

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**Dr. Kiss:**
I'm Szilárd Kiss. Here with me today is Carl Regillo. Registry data show that long-term vision declines in patients with neovascular age-related macular degeneration despite intravitreal anti-VEGF therapy. Carl, why does this happen, and what can we do about it?

**Dr. Regillo:**
Well, it's an unfortunate reality of real-world practice. Taking a step back, for example, in the clinical trials where we do frequent regular dosing—monthly, every other month, fixed dosing for 1 to 2 years—we get excellent vision gains, and we maintain those gains. As soon as patients exit the trials, go into the real world, are managed by even the investigators, we see gradual loss of vision over time, pretty quickly within a few years. And then all the real-world data, from the very beginning of having anti-VEGF over 20 years ago up till now, show this consistent trend of some vision gains but loss of those gains within a few years. There's several reasons for that, of course. But a lot of it boils down to the limited durability of our anti-VEGF biologics.

They work real well. They just don't last very long. So there are other factors, of course: patient discontinuation, dropout, comorbidities, and illnesses. A lot of reasons why patients can't get to the office to get injections as frequently as they need to keep on top of the disease. So regular frequent injections, what does that mean?

Well, first-generation drugs, bevacizumab, ranibizumab, 2-mg aflibercept, median durations of only about 2 months with a range of 1 to 3 months. Our second-generation drugs, a little bit better. Faricimab and high-dose aflibercept probably averaging about 3 months according to real-world data, maybe a range of 4 to 16 weeks. But what ends up happening is it's pulsatile in nature, right? So the patients get recurrences when the drug wears off. And studies have shown that fluid fluctuation of >50 µm is clinically and significantly meaningful in terms of leading to vision decline over time, and especially if this happens time and time again.

So, basically, what that says is significant disease recurrence is detrimental to vision. You know, the risk factors for poor vision outcomes include patients then—well, I'm going to say on the top of the list are patients that need high-frequency treatment every 4, 6, 8 weeks, patients that are older, have comorbidities, have trouble getting to the office, have transportation issues, and so forth. And then there's limitations for what we can do to make us available to get the patients in on a frequent and regular basis. As I tell patients, to get the best outcomes, we have to stay on top of the disease. This is disease management, disease control. It's not a cure. So it behooves us all to try to stay on top of things.

But, frankly, we have a high unmet need for greater durability medicines.

**Dr. Kiss:**
Thank you so much, Carl. You know, what's clear is that we've got great medications, and patients do very well in our clinical trials. You


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know, many of them gain vision. Most of them maintain vision. What I think you've also highlighted is that we can do better in the real world. We can do better in the real world in terms of treating patients, making sure that they come back.

Question for you, Carl. Where does that 50 µm come in? You know, it's one of the first times I've heard it. Why is that detrimental to vision outcomes?

**Dr. Regillo:**
Yeah, what it does is—and several studies have shown this now—that it basically represents a significant amount of disease recurrence, especially if it's intraretinal fluid. But about 50 µm of central subfield thickness change or worsening, not just once, but time and time again, in particular, the cumulative recurrences is what nibbles away or erodes visual acuity. Smaller fluctuations tend to be relatively well tolerated. Small amounts of subretinal fluid can be relatively well tolerated. Intraretinal fluid in degrees of fluctuation >50 µm time and time again, studies do show that correlates with decreasing vision over time. You know, as you said, and I totally agree, we get great medicines. They'll dry up the macula in the vast majority of our patients, but keeping the macula dry and preventing those fluctuations, which in essence is saying preventing disease recurrence, allows us to maintain those gains that we get in the clinical trials, that we also get in practice, but we just can't maintain them in practice.

**Dr. Kiss:**
Very good points, Carl. Well, I think our time is up here, but stick around for the next episode where we take a look at some examples of patients at higher risks for that vision loss. Thanks again for joining us, and we'll see you next time.

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