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Diagnosis Delays in Stargardt Disease

**Alexis Warren:**
Hi, everyone. Welcome to the New Retina Radio Journal Club with VBS. My name's Alexis Warren from the University of Chicago. And today, I'm joined by Jesse Sengillo from the University of Miami.

**Jesse Sengillo:**
Hi, thank you for having me.

**Alexis Warren:**
And Sruthi Arepalli from Emory University.

**Sruthi Arepalli:**
Hey, everyone. Glad to be here.

**Alexis Warren:**
Today, we'll be discussing a paper called Factors: Influencing the Delayed Diagnosis of Stargardt Disease and Impact on Therapeutic Opportunities by Lee, et al., published in Retina in September of 2025.

So I'll start with Dr. Sengillo to summarize this paper.

**Jesse Sengillo:**
Absolutely. So this was a chart review done out of Duke of patients with confirmed molecular diagnoses of Stargardt disease who were evaluated by an IRD, or inherited retinal disease, uh, specialist at their academic institution. So this wa- the purpose of this was to characterize the delay between symptom onset and diagnosis, and early, intermediate, and late Stargardt disease, and identify possible factors that may have contributed to this delay. 87 patients with a molecular-confirmed diagnosis were included. Average time from symptom onset to first IRD specialist visit was 10.9 years. Average time between seeing a subspecialist, which in the paper was defined as either a retina specialist or a pediatric ophthalmologist, and an IRD specialist was 8.1 years. Interestingly, the intermediate onset group had a significantly longer delay, a mean of 13 years, compared with the early onset and late onset groups, which had 5.0 year and 3.1 year respectively delay. Visual acuity significantly decreased between the subspecialist visit and the IRD specialist visit, which was statistically significant. Uh, late onset Stargardt patients were more likely to have an intact subfoveal ellipsoid zone, compared with early and intermediate-onset patients.

Some other findings, Stargardt patients experienced long delays between symptom onset and diagnosis. Intermediate onset cases showed the greatest diagnostic delay. Visual acuity declines during the- during the delay period between subspecialists and IRD specialist visits were present, and late-onset patients retained more intact subfoveal opioid zones than early and intermediate onset patients.

So the authors concluded that Stargardt patients essentially face extended delays from symptom onset to achieving a molecular diagnosis with genetic testing. Um, and this, uh, can result in progressive vision loss between those, um, timeframes, from initial symptom onset to evaluation with an IRD specialist, and possible missed opportunities for clinical trial enrollment. Some contributing factors they, um, hypothesize may be, um, age of onset, types of initial symptoms, and transitions in care from the subspecialist to the IRD specialist that may play a role. And finally, doctors suggest that multimodal screening, um, streamlined referral pathways and expedited genetic testing, um, in addition to greater awareness of the different Stargardt phenotypes may help reduce these delays ultimately.

**Alexis Warren:**
Great. Thank you for that nice summary. Um, Dr. Arepalli, let's get some quick reactions to you about this paper. Um, what stands out to you most about these delayed, uh, length of times that we see in this cohort?

**Sruthi Arepalli:**
Yeah, you know, I think reading this paper, it almost seems shocking, the amount of time it takes to get to an IRD specialist. There's things like an average wait time of about eight years. Um, and I think what struck me is I tried to put my- myself in the shoes of someone referring. So I have the luxury right now of having IRD specialists at my institution, so I think the wait time is generally not that long.

Uh, but I think if I were practicing in the community, and I was seeing a patient that I thought was classical Stargardt, so in this paper, to me, the intermediate phenotypes seem like the classic presentation that I would recognize, and say I was practicing 10 years ago, I think I'd probably hold onto those patients, and I'd probably tell them, "I can send you to an IRD specialist that may be far away, um, and it may be expensive, but what are they really gonna do for you?" Because we didn't really have therapies at that time."

And so I think part of the delay, in addition to misdiagnosis probably for the other phenotypes, may have just been, "We know what it is, but what can we really do for you even if we get you to that specialist?" And I thought for that pa- this paper also did a really nice job of breaking down the other two types of phenotypes as well, uh, that can be a little bit harder to recognize, like in the younger patients who have that sudden vision loss. To me, that's not what I classically associate with Stargardt's disease. And so I can see myself working them up for other things outside of that disease for a long time, and maybe even never really landing on the diagnosis of an IRD. Um, so while I think the time to IRD specialist was long, um, I do think it's justifiable, if you think about the factors that go into referring and not referring.

**Alexis Warren:**
Yeah, I think those are really great points. You know, um, as you said, when you look at the number and you think of yourself or your family member, you know, 8 to 10 year, you know, these numbers to getting, um, this referral, these diagnosis is- is pretty scary. But, you know, being on our side, understanding the diagnosis the way we do, understanding the disease process the way we do, what we understand is that, unfortunately, you know, we're not in the place necessarily where we have some of these things to- to really change the trajectory, right? Yet, so we're holding these patients on, telling them, you know, as soon as we know something, as soon as we- we find something that can help them, we can send them to these specialists. So something important to think about.

Dr. Sengillo, any thoughts?

**Jesse Sengillo:**
Yeah, definitely. I- I would agree. I think it is surprising the amount of time that passes. But I- I would tend to agree that with Stargardt, although there's, um, some phenotypes that can lead to misdiagnosis and can kind of, you know, represent a diagnostic dilemma, the phenotype is- is pretty readily identifiable in- in the majority of cases.

So, um, I would be a little bit more optimistic in thinking that a lot of the referring providers were, um, diagnosing it clinically, um, accurately, and managing it, you know, well. And ultimately, the patient years later would be seeking clinical trials at a tertiary care center or, you know, looking to, to see, you know, what some of the changes in the field are, which may have led to some of the delays. So I- I would, I would agree with Dr. Arepalli on that front.

Um, but what I thought the, the paper did a great job doing was, um, identifying how, you- potentially big of, uh, an access problem there may be for, for IRD patients. The average distance they traveled was 85 miles, um, which is, you know, quite- quite far for these patients. And although, you know, we may not think of missing out on opportunities of enrolling in- in clinical trials as potentially being devastating, uh, you know, for a patient, what, um, worries me is that when we do have something that's approved and that, you know, FDA- FDA-approved, that if patients are having access issues to get to providers for a disease where earlier intervention is more beneficial, um, this may be, you know, something that we really would wanna, um, bridge in terms of ... you know, bridge a gap, so to speak, before we have some of these therapies available for patients so that they can- they can get in touch with IRD specialists and tertiary centers that treat these conditions faster.

**Alexis Warren:**
Yeah, I totally agree. I think access and some of these nonmedical, these more socioeconomic factors that play into these diagnosis and- and treatment and clinical trial enrollment for these patients is- is really something that we have to think about, and maybe we can talk more about after the break.

Um, so for now, we'll head into the break, and I'll remind the audience that we'll have a more in- depth discussion on the other side.

**Voiceover**:

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**Alexis Warren:**
Welcome back to the New Retina Radio Journal Club with VBS. Let's get into a little bit of a longer discussion here, um, with the paper that Dr. Sengillo summarized in the first part of this episode.

Uh, so we were talking a little bit about access and socioeconomic factors that may play a role into this. Maybe we wanna dive a little bit more into that, and your guys' thoughts on how that plays into the delayed diagnosis, or even the presentation to begin with, um, of patients with their symptoms and, and seeing any subspecialists?

**Jesse Sengillo:**
Yeah, absolutely. Definitely a- an important piece for this condition in all IRDs in particular. I think there- there's likely a lot of, um, socioeconomic and- and social factors that we aren't aware of that play a part in- in access to care that are just tough to measure, but definitely play a role. I think one of the biggest advantages of seeing an IRD specialist, uh, may- may actually be the genetic counseling, um, you get, because I think that's something that isn't always a major part of our- our training as retina specialists. And a lot of these patients are looking to start families, and wanna know about risk to kids, and may be interested in certain, um- um, uh, prenatal- or, uh, pre- yeah, prenatal care that can help mitigate the risk of passing it on.

So a lot of those types of, um, opportunities for patients to- to learn and be educated about their condition, and how it affects their future generations, I think can come at tertiary centers and from IRD specialists. So that'd be my- one of my major concerns about the delay in access, some patients are being a little bit deprived of that.

**Sruthi Arepalli:**
Yeah, I think that's a great point. Um, the genetic counseling portion in particular and family planning. Um, and you had mentioned earlier about socioeconomic restrictions and things like that that prevent patients from coming in. You know, I think IRD patients, in a way, are not super different from our bad, like, posterior uveitis patients or diabetics. You know, when you have poor vision, you rely on a system outside of yourself to get to an academic center or a referral center, um, no matter what your underlying disease process is. And we've had literature that's shown that diabetics tend to fall off, and I think part of that is their systemic conditions. But probably part of that as well is their, um, lower visual acuity and ability to navigate by themselves. And I- I see that being the same case for people with IRDs, who have had them for a decade or more.

**Alexis Warren:**
Yeah. Yeah, I totally agree. I s- I see a lot of these, uh, kinds of patients on the south side of Chicago, um, and, you know, thinking about what it took for them to get to these appointments to begin with, right? And to follow up, and to, you know, be able to take a symptom and say, "I'm gonna go to the doctor the next day, the next week." A lot of these people don't have access to that or even the mindset that that's a possibility for them. So it's important- important to think about a patient in their whole context, you know?

Um, another question I had when looking at this study was, um, they talked about a confirmed molecular diagnosis of, of Stargardt's. And, you know, how important is that, you know, in our criteria of- of this diagnosis? I think if we talk again about, uh, these more marginalized patients or minority patients, that- that can be hard for them to even get something like that because we don't have them in our da- databases. We sometimes don't even know, um, some of these specific molecular changes that we're looking for in these patients. So, you know, was that something that concerned you about this paper?

**Jesse Sengillo:**
Yeah, I think that's a really interesting point. Wh- when, when they say molecular diagnosis and kind of knowing exactly what that entails is important. Uh, you know, in many cases of clinical- clinically-diagnosed Stargardt, we can only find one mutation in a large fraction of- of patients. So, um, you know, there may be some delay in finding the second mutation, which certainly happens in many cases, and that may add to the time of, um, delay for getting a- a formally genetic diagnosis of- of Stargardt.

I think also over the last decade, we've had an increase in access to genetic testing, and a lot of sponsored testing, um, where, um, a different, uh, payer will, um, sponsor the test for the patient. Um, so I think over the past, uh, decade, we've had an increased amount or increased ability to- to kind of nail down a genetic diagnosis for patients, which may contribute to some of the delay that was seen in the paper. Some of these eight to 10-year averages might just be that patients didn't really have great access to genetic testing at the beginning of their care, even if they had a clinical diagnosis of Stargardt for a long time, and were managed like that as such.

**Sruthi Arepalli:**
I- I totally agree. I mean, I think it's- it's so wonderful that we had these sponsored genetic testing now, um, to help solidify the diagnosis.

Um, and it makes me wonder what IRD was like 20 or 30 years ago when we didn't have it. And I totally agree, there have been, um, a delay that was contributing there as well because we just couldn't make the diagnosis.

**Alexis Warren:**
Yeah, for sure. Um, what about, you know, the authors here, they talk about this delayed diagnosis and the missed opportunity for clinical trial enrollment, and therefore limiting therapeutic effectiveness. But how convinced were you that this link is really here? You know, is this diagnostic delay? Does it really mean therapeutic opportunity lost? You know, for these diseases, what we know is as we're learning more and having more clinical trials, uh, part of that process is just getting the information from the patients, right? To be able to make these therapeutic changes. But are we there yet? Do we have the therapeutic changes to really affect the masses of these IRD patients?

**Jesse Sengillo:**
It's tough to say. I think, you know, obviously clinical trials are super important for pushing the boundary of our field, and, you know, trying to find some kind of cure for these untreatable diseases. I think as it pertains to this paper, that's a little bit hard to measure in terms of missed opportunity of a clinical trial. We have to remember a lot of these trials have really strict criteria. They often, um, have age requirements as well, which might be what the paper's referring to. But, um, I'm not sure that this delayed diagnosis or decreased access has a measurable or statistically-significant or even clinically-significant effect on enrollment in clinical trials, but it- it- it perhaps does. It would be really hard to measure, though.

Um, but I think kind of the other things we talked about, the kind of adjacent side effects of the delayed access, such as not getting the counseling, um, not being plugged in so that when there is an approved treatment, you can be contacted. Um, I think a lot of patients also get a lot of, uh, reassurance and comfort from knowing a diagnosis. So if they truly don't have a confirmed diagnosis yet, um, being able to get that at a tertiary center with an IRD specialist is very useful. So I think some of those other aspects might be a little bit more important, but I definitely see where the authors are coming from.

**Sruthi Arepalli:**
Yeah, and you raised a good point about the clinical trials and- and the metrics. So I agree, I'm not convinced that there's a one-to-one relationship. Uh, I think what I worry about as well as this paper, I think one of us brought up that patients travel, like, an average of 85 miles or something like that. Even if we're enrolling them in clinical trials, having them come back for metrics, uh, after that first visit, I think is gonna be really tough too, uh, and something to consider when you're treating patients from a really wide radius.

**Alexis Warren:**
Yeah. I think one thing that this paper did for me, um, because there were some links that I- I weren't sh- I wasn't sure I was convinced of, but what it did tell me is that ... I- I'm not an IRD specialist, and I think one service I could do to my patients is even though I may not think of or know of a clinical trial that fits in exactly, doesn't harm you to the minute you meet the patient, to send them automatically to that IRD specialist, to get under their care, to really get that counseling that we talked about, um, and all the services that- that, um, are important for their disease, um, prognosis, you know, in the future.

Awesome. Well, great discussion, guys. Uh, I wanna thank the audience for listening to New Retina Radio Journal Club with VBS, and stay tuned for further episodes.