Macular Chats

TRANSCRIPT

The Future of Age-Related Macular Degeneration and Geographic Atrophy: How Clinical Trials Are Paving the Way

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Featuring: Mathew W. MacCumber, MD, PhD

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Please note: This Chat has been edited for clarity and brevity.

DR. JIMMY LIU: Hello, and welcome. My name is Dr. Jimmy Liu, and I'm the Director of Vision Science Programs at BrightFocus Foundation. I am pleased to be your host for today's Macular Chat, "The Future of Age-Related Macular Degeneration and Geographic Atrophy: How Clinical Trials Are Paving the Way."

Macular Chats are a monthly program supported in part by sponsorship from Apellis, Genentech, and Regeneron, designed to provide people living with macular degeneration and the family and friends who support them with information straight from the experts. The information provided in this program is for educational purposes only and should not be considered medical advice. Always consult a qualified health care professional regarding any medical concerns or conditions. Please note that BrightFocus does not endorse or promote any specific brand or product.

BrightFocus Foundation's Macular Degeneration Research Program has supported over $56 million in scientific grants exploring the root causes and potential prevention, treatment, and cure of macular degeneration and is currently investing in 44 active projects across the globe.

Now, I would like to introduce today's guest speaker. Dr. Mathew MacCumber completed his undergraduate studies at Princeton University and earned his medical degree and PhD at The Johns Hopkins University School of Medicine. His retina training was at the Duke University Eye Center. Currently, Dr. MacCumber is a senior partner and Research Director at Illinois Retina Associates and professor and Research Director for the Department of Ophthalmology at Rush University Medical Center. He has been very active in organized ophthalmology, serving on the board and councils of many vision organizations. He has also received many awards for his work and has authored

or co-authored over 150 peer-reviewed articles. He serves as the principal investigator for over 25 multicenter clinical trials, and his research interests include pharmacologic, cellular, and surgical treatments for age-related macular degeneration, diabetic retinopathy, epiretinal membrane, retinal degeneration, and uveitis. Welcome to the Chat, Dr. MacCumber.

DR. MATHEW MACCUMBER: Thank you, Jimmy. It's a pleasure to be here.

DR. JIMMY LIU: So, let's get started with some background. How have clinical trials historically changed the way we treat AMD, and what could they unlock next, especially clinical trials for geographic atrophy?

DR. MATHEW MACCUMBER: Well, clinical trials have been performed for about 40 years in macular degeneration, believe it or not. The early trials were using laser treatment. That's all we had when I was in training 30 to 40 years ago. But over the last few decades, there has been an explosion in research in age-related macular degeneration and many advancements. We've had clinical trials with something called photodynamic therapy, which is a cold laser treatment for wet macular degeneration. And then, we had a real revolution with drugs aimed at a molecule, called vascular endothelial growth factor, and these are injections we give to the eye, and many clinical trials have shown benefit for age-related macular degeneration—the neovascular form—as well as diabetic retinopathy and other conditions. And then within the last 3 to 6 years, in fact, clinical trials that have shown benefit for another advanced type of macular degeneration called geographic atrophy. So, there's just been terrific progress, and it has all been driven by well-performed clinical trials by researchers around the world.

DR. JIMMY LIU: Perfect. Thanks so much, Dr. MacCumber, for that explanation. Many people ask: What are the different phases of clinical trials, and how long do most clinical trials last?

DR. MATHEW MACCUMBER: So clinical trials usually start with a Phase 1 study, and that's where a molecule is believed to have effect on a clinical condition developed in the laboratory, often with an animal model. And then, with the Phase 1 study, it's the first treatment in human where we see if it's safe and may have some signal for effect. Next, we move on to a Phase 2 trial, which is larger, usually in multiple sites, and that often has a control group—so, a placebo arm, which is compared to the active arm. We often investigate dose response, so we look at lower doses and move up to higher doses to see what would be most effective and safe. And then, following Phase 2—which studies often take anywhere from 6 to 9 months out to 2 to 3 years, depending

on the study—we move on to multicenter Phase 3 clinical trials. And usually, the Food and Drug Administration would like two Phase 3 studies where the optimal dose is compared against either standard therapy or placebo if there's no standard therapy. The studies go on for 1 to 2 years, typically; recruit typically several hundred patients; and then data is evaluated, submitted to the FDA; and hopefully approval of a new treatment for a condition such as age-related macular degeneration.

DR. JIMMY LIU: Perfect. Thanks so much, Dr. MacCumber, for that explanation about the different phases of clinical trials and how long they typically last. So, we talked about the different Phases of 1, 2, and 3. What typically happens after the trial ends?

DR. MATHEW MACCUMBER: Well, once the last patient has completed their last follow-up visit, then the results are analyzed by statisticians. Usually there's a primary endpoint, which from something like macular degeneration, it's typically whether vision is preserved or improved over standard therapy, or at least it's as good as other therapies, but it may have some other advantage. For instance, the treatment lasts longer. It's more durable. So patients won't need as many treatments and still have clinical effect. During the course of the trial, there's something called the Data Safety Monitoring Committee, which makes sure it's safe and so that if there is any concern, the trial can be stopped early. But if it looks like everything's good and the drug is safe, then it goes on, completed, all that analysis is done. Those results, if they meet their primary endpoint, are submitted to the Food and Drug Administration in the U.S., which then analyzes it. That could take several months, as well. And if they feel that it's effective and safe, it then would receive approval. And then, within a short order, a few months typically, it's available to the public.

DR. JIMMY LIU: Just to kind of summarize the last two questions, starting from Phase 1 all the way to FDA approval of a particular drug, how long or what is the time range would that typically take?

DR. MATHEW MACCUMBER: Oh, that could take sometimes 10 years from Phase 1 all the way to available to the public. In some cases, if it's a very important public health concern—for instance, like HIV, COVID—you can get approval much faster, sometimes within a couple of years, maybe even less if it really is a true emergency. But for something like a chronic condition like macular degeneration, it could easily take 8 to 10 years from beginning to approval, and even sometimes longer. It all depends on a variety of things—how easy the drug is to prepare, how much it has to be tested, the number of patients that need to be enrolled in the clinical trial. Usually drugs that are very, very effective over something previously used, you need a smaller number of patients, but if it's only a small benefit compared to the usual therapy, you would need

a much larger number of patients, which means the study would take longer.

DR. JIMMY LIU: Perfect. Thanks so much, Dr. MacCumber. So, what are the potential benefits of participating in a clinical trial for AMD, or specifically, geographic atrophy?

DR. MATHEW MACCUMBER: Yes, so we run about 18 clinical trials here at our office at Illinois Retina, and there are a lot of benefits for patients. For one thing, you can have access to some new treatment, which is typically not available to the general public. And as part of the clinical trial, you're given extra careful care. We measure vision in a very standardized way. We do special examinations. We often do special imaging techniques or other ways to measure visual function. And then, after the study is completed in 1 to 2 years, you may be able to continue the medication if it is shown to be effective, and you might even have early access of that medicine to the opposite eye. On top of that, for a clinical trial, typically the costs are all covered by the sponsor, be it the National Eye Institute or a pharmaceutical company. So, the patients do not have to pay for their eye care during the course of the study. They receive the drug at no charge. They can also receive transportation. Obviously, it's difficult for a patient receiving an eye treatment to come to a hospital or office and then go home, so transportation is covered, as well. And then there's a small stipend, as well, to help cover other small expenses for those visits. And then beyond all that, there is just the benefit of knowing that you may be helping thousands, potentially millions, of people with a medical problem. We only can make progress in medicine through carefully done clinical trials. And I know the patients that are in my trials feel very satisfied that they're not only helping themselves but helping the population at large—people just like them with the same condition.

DR. JIMMY LIU: Great. Thanks so much, Dr. MacCumber, for that information. And so the next question that we have is: What challenges or downsides should listeners realistically be aware of? And on another note, how about participating in a clinical trial in a particular phase, like the ones that you talked about, Phase 1, 2, or 3?

DR. MATHEW MACCUMBER: Right. Well, you have to understand that clinical trials have several characteristics that make them valid. One, the patients need to be randomized between the potential new therapy and standard therapy or even, in some cases, placebo, in an active treatment. That's really the only way to show that the treatment has benefit without being biased. On top of them being randomized, frequently, in ophthalmology, we say "masked." In other medical fields we say "blinded," but we don't like to use the term "blinded" in ophthalmology. So we say the trials are masked. So, in fact, neither the patient nor the physician doing the examinations knows which treatment the patient is receiving until the very end. Some trials have two

physicians and two sets of coordinators. One are considered masked, like the patient. We don't know what the patient's getting, so we're not inadvertently influencing the patient perhaps to take better care of themselves or in some way influence outcome. So there's that second set of unmasked physicians that deliver the treatment and an unmasked coordinator who coordinates that side. So, you have to be prepared that you may be getting standard therapy or even no treatment when there's nothing currently existing.

You have to understand that there's risks. The medicine is new. It hasn't been studied in many, many people. In Phase 1, it may never have been used in a human being before. So, you have to understand that there is additional risk from that unknown. You know, of course, the investigators should be fairly confident that it's safe and likely effective, but very rarely there can be reactions, and that you just can't predict. In Phase 2/ Phase 3, there's less chance of risk, but there, it's still possible. In fact, we don't really know all the risks of some of our treatments until after Phase 3. In a Phase 4, which is a real-world study, where we can look at thousands or sometimes hundreds of thousands of patients to find that really rare event—you know, that really unfortunate rare event that could happen from a drug. So there's constant monitoring, even after the Phase 3 studies are completed.

You have to be aware that we ask that you commit to the study that once you start, we want you to try to see it through to the end, because that's the only way we're going to get a good result. You know that you may not be available to participate in other trials or may not be able to have other treatments that might interfere with the clinical trial. There may be multiple visits you will be asked to make, and they may be longer than the typical visit. Instead of 1 hour, they may take several hours. So, patients have to understand that we ask them to commit to it, but of course, no one is going to make the patient do something they no longer want to do. Patients and the investigators have to understand if the patient wants to withdraw for whatever reason—for instance, a family member gets sick and needs extra help, so there's no longer time to complete the trial—then we all have to understand that in that situation or some other situation where the patient feels they want to discontinue, they can. So, many, many benefits, but also some downsides to being involved in a clinical trial.

DR. JIMMY LIU: Great. Thanks so much, Dr. MacCumber, for that very detailed explanation about the challenges and downsides about clinical trials. So another question that we have that also a lot of our listeners ask: How is eligibility determined for a clinical trial, and why don't all patients qualify for every trial?

DR. MATHEW MACCUMBER: Excellent question. So, the statisticians look at—with the

investigators—look at the drugs' effects, potential risks to it, and have to determine a safe population of people that may also have benefit. Not everyone with macular degeneration, for instance, could benefit from some therapies. We're talking today about geographic atrophy. So, geographic atrophy can grow at different rates in different people. It also can grow at different rates where it's located in the retina and how big it is. Very small lesions grow slowly, and very large lesions grow slowly, as well. It's those middle-sized geographic atrophy lesions that grow the fastest, typically, and so it's easier to show a benefit of a medication within the 1 to 2 years of the clinical trial. We also would like to see visual benefit. So, usually patients are enrolled where the geographic atrophy is not already involving the foveal center, so the patient has relatively good vision. And then we can see if the medication protects them from losing that vision, because, unfortunately, geographic atrophy over years typically does eventually affect the central vision.

We also have to make sure the patient's not taking any medications or has other conditions that may interfere with the therapy, and in the real world you may decide that that patient wouldn't be involved anyway. For instance, the patient has advanced glaucoma. You'd have to be extra careful in a patient like that. So, what we do is we go through a screening process. We measure the patient's vision. We take a careful clinical history, a medication history. We do some special imaging to assess the size of the geographic atrophy. We then send those to the coordinating center, the central chairman's office to evaluate that. The pictures go to a reading center where they say, "Yes, the geographic atrophy is the right size. It's the type of patient that would most benefit from this therapy, potentially." And then when all those results come back, we can inform the patient that, yes, it looks like they would qualify, and then we do the randomization.

DR. JIMMY LIU: Are there any age limits for these clinical trials, as well, to participate in them?

DR. MATHEW MACCUMBER: There can be, yes. For age-related macular degeneration usually involves individuals that are 55 or 60 and older, so that's typically the younger age limit. As for the older age limit, it varies. Some studies want patients that, for instance, they decide 80–85 is the upper limit. We know that older folks may have a harder time undergoing the clinical trial, making all the visits, things like that. But we do have some trials that have no upper age limit. Because macular degeneration increases over time, and I do have some patients in their 90s even that have screened and successfully randomized for the clinical trial. So, yes, age can come into it, and for macular degeneration, it's generally those older patients over 60.

DR. JIMMY LIU: Great. Thank you, Dr. MacCumber. So, you talked a little bit about in the previous question about the process of assessing patients in order for their eligibility for these clinical trials. I guess, afterwards, how do you help your patients weigh whether a clinical trial is right for them personally? For example, including understanding the possibility of receiving a placebo when deciding to participate.

DR. MATHEW MACCUMBER: Right. Well, we spend quite a bit of time discussing the trial with the patient before entry. There's something called the clinical consent form, which lists the benefits and risks of the trial, what's required in the trial, the number of visits, the length, so the patient understands everything that's involved. We often have a family member there, so they can assist the patient in deciding. Then, after that, the patient can answer questions, and we go through that at length to make sure that they want to commit the time to do the study, all the visits out for the 1 to 2 years that it may take, sometimes longer. We also make it clear to the patient that they may be receiving a placebo.

Now, with geographic atrophy, there are two medications that are approved by the FDA in the United States: Syfovre® and Izervay™. So, in some of the trials, we compare the new medicine to one of those standard therapies. However, in Europe, there is no approved treatment for geographic atrophy, and some of the drug companies want to make the results more generalizable so they can get approval for their medicine in the U.S. or in Europe or elsewhere around the world. So, even in the U.S., we do have some studies that have a placebo arm, so the patients have to understand that they may be getting an inactive treatment for the length of the study. Luckily, geographic atrophy is relatively slow-moving, so if it's not near the foveal center, it still may be reasonable because we're not risking their central vision, even though we're giving them a placebo. And then, they know they may have something that's very active sooner than they would otherwise. But some patients may choose to not be involved in the clinical trial that has a placebo arm, so they can go ahead and just have one of the active medicines that slows geographic atrophy growth, although it may not be as good as one of the new things we're investigating, which might even stop geographic atrophy, and that's the goal.

One other thing I can mention is that the two medicines that are available in the United States, Syfovre and Izervay, are given by intraocular injections. That carries a tiny risk of infection and inflammation, and patients may not want to have an intraocular injection. So, we are investigating some other avenues, such as subcutaneous medicine or an oral medicine, and then the patients may accept the fact that they're going to get a placebo because there is no systemic medicine for geographic atrophy that exists at this time for them. So, many things for the patient to consider.

DR. JIMMY LIU: Perfect. Thanks so much, Dr. MacCumber, for that thorough explanation. We're going to now move on to some of the trials that are currently going on for GA. Just as a note, we have received many listener questions about trials involving stem cells. We will not be specifically focusing on this topic today, but we encourage listeners to listen to our April Chat on our website or anywhere you can find our Macular Chats where we discuss this topic. Okay. So, Dr. MacCumber, one clinical trial that is currently recruiting is called GALLOP. Can you provide a high-level overview of the GALLOP clinical trial and its goals?

DR. MATHEW MACCUMBER: Yes, happy to. So, as I mentioned, there are two FDA-approved treatments. One is Syfovre, which is made by Apellis, and the other is Izervay, which is made by Astellas. Apellis would like their medicine, Syfovre, to work better, to be even more effective at slowing geographic atrophy or have the potential that we don't have to give it as often. And they've designed an excellent clinical trial called GALLOP where we're investigating the use of Syfovre, either with or without a systemic therapy—a subcutaneous medicine—that may help it work better.

Now, just to inform all our listeners, the medicines that are approved act on a system called the complement system. It's part of our immune system, and we know that complement is involved in causing geographic atrophy and macular degeneration. Both Syfovre and Izervay affect two different components of the complement system. Well, many of the complement factors aren't made in the eye. They're made, actually, in the liver or elsewhere in the body. So it does make sense that if we have some other systemic therapy that can be given in addition to the Syfovre, it can work better. And that's, in fact, what we're investigating.

So, in the GALLOP trial, patients are randomized to one of three treatments: either Syfovre alone with a subcutaneous placebo; or Syfovre given every other month, which is typical, along with something called APL3007 at a 400 mg dose every other month, and to see if that can work better than the Syfovre alone; and then in the third group, it's a higher dose of APL3007—it's a 700 mg dose—this time given at 3-month intervals. And the Syfovre is also given at 3month intervals, so less often than typically given. We're comparing those three groups to see which one may be better. Patients in the trial have to have geographic atrophy not involving the foveal center, so they still have to have relatively good vision. We're actively recruiting, and we've screened a number of patients for this already at our site.

DR. JIMMY LIU: Thanks so much, Dr. MacCumber, for that information on the GALLOP trial. So, the next question that we have is: Are there any other trials for geographic atrophy that might have results coming soon, so within the year or so? And what new

treatments or advances should listeners look out for?

DR. MATHEW MACCUMBER: Yes. We do have some results that are coming out this year. We've already had one from a company, Aviceda. That was a Phase 2 trial. It did meet their endpoint. But that was Phase 2, so they still need a Phase 3 trial. That may start later in the year. We also will have results from a company called Annexon on a different drug that affects a different part of the complement system, called factor C1q, and we're going to actually hear about results on that trial within a few months. So, that will be very exciting. That's the ARCHER II trial.

There are also some drugs that act on different pathways for which we'll get some results. There's a Phase 3 trial. Belite Bio has a molecule that acts on retinol. So, retinol is the light-sensing molecule in the photoreceptors, and with macular degeneration, it can form some toxic retinoids that can damage the retina with geographic atrophy. And this medicine is given orally, and in the PHOENIX trial, and it might slow the production of these retinoid toxic molecules, and we'll be getting those results also later in this year.

And then, another company, Stealth, has an eyedrop, bevemipretide, which is a Phase 2, which helps the energy capacity of the photoreceptors (the light-sensing cells). And that's a Phase 2, but we're going to get results on that also later this year. So, a number of exciting things to look at and to look out for. I should just add that although we're getting a lot of different results over this year and in the coming years, there probably won't be any new FDA-approved medicine for, I would say, probably 2 to 3 years yet for geographic atrophy. So, a lot of research, a lot of exciting things, but still a couple years off until we're going to have something new.

DR. JIMMY LIU: Awesome. Thanks so much, Dr. MacCumber. So the next question that we have is: What advice would you give someone who is interested but still hesitant about participating in a clinical trial?

DR. MATHEW MACCUMBER: Well, clinical trials aren't for everyone. You know, some people just want to receive the standard therapy that's available. I would say you should try to get as much information as you can. You can talk to your doctor. You can go to one of the research centers and talk to the research physicians. You might be able to get some additional information from BrightFocus Foundation, for instance. You can go to the American Society of Retina Specialists, the American Academy of Ophthalmology website, ClinicalTrials.gov, our own Illinois Retina site to get more information on what may be out there. Involve your family members. It often is helpful to have a friend or a member of your family come with you so you can think through whether a clinical trial

is right for you, whether you'll physically be able to do it, whether you want to devote the time, whether it may be the right thing for you. So, it's natural to be hesitant. I mean, clinical trials are something new. They do involve some risk, generally small, but they're there. And so you have to decide if you're the type of person who would want to participate.

DR. JIMMY LIU: Perfect. Thanks so much, Dr. MacCumber, for that advice. So, we have a little bit of time for some listener questions. So the first question that we have is: I know you discussed a little bit about some of the trials for GA. Are there any trials in the pipeline that aim to restore vision?

DR. MATHEW MACCUMBER: There are. Well, there are studies that some treatments that potentially can slow development of geographic atrophy to begin with, and so it prevent any vision loss. There's something called photobiomodulation. There's vitamin therapy, which may slow. There's still research on that. When you already have geographic atrophy, there are a number of small studies. I know some callers had called in about the use of stem cells. There have been some studies which have shown potential benefit with stem cells. It's a very hard thing to do, to study stem cells, however. It usually involves a research study where there's surgery and implantation of the stem cells under the retina, so there may be some additional risk from that. Stem cells can change over time. They can be difficult to prepare. So, I would keep your eyes and ears open for these trials. There are some small trials in the U.S. and around the world, but there are no large ones at this time about restoring vision. There are some low-vision aids that may help people function better, and there are some studies about that. And then, potentially there are treatments out there that also may improve vision, but right now, there's nothing in the near horizon, I'm afraid.

DR. JIMMY LIU: Awesome. Thank you so much for that information, Dr. MacCumber. And just for our listeners, if you would like to have more information about upcoming clinical trials, go into the Illinois Retina website or go into our website at BrightFocus. org is a great place to start. The last question that we have from our listeners that we have time for. I know you spoke briefly about Belite Bio's drug that's a pill form. One listener asks: Are there any new medications expected to be pills—or maybe you can elaborate, if there's not any other that are pills, more non-invasive that are not intravitreal injections?

DR. MATHEW MACCUMBER: Yes. So, we've already mentioned the GALLOP, which combines a subcutaneous therapy with one of the standard injections, Syfovre. But there are some clinical trials looking at just systemic therapy. One is called SIENNA. That's looking at a subcutaneous molecule that blocks a part of the complement

system, and that is currently in clinical trials. It's from a company, Regeneron—an excellent company. One of the medicines is already approved for another condition. And then there's a second medicine they're combining it with in the clinical trial, which may help it work better to slow geographic atrophy. There's also a trial from Boehringer Ingelheim of a pill called JADE. It's a Phase 2 study that's currently under analysis. It is fully recruited. So hopefully, we'll hear about that oral therapy in the near future and see if that may be of benefit. So several things in the works where you don't need an intraocular injection.

DR. JIMMY LIU: Great. That is super exciting, and thank you so much for that information, Dr. MacCumber. So, that is all the time we have for questions today. So, again, thank you, Dr. MacCumber, for answering so many of our questions and all the enlightening information you shared with us today. To our listeners, thank you so much for joining our Macular Chat. I sincerely hope you found it helpful.

I would like to mention that our website, BrightFocus.org, has a wealth of information about macular degeneration and clinical trials.

Dr. MacCumber, before we close, I have one final question. Regarding the future of AMD and geographic atrophy, what gives you the most hope based on today's research?

DR. MATHEW MACCUMBER: I think what gives me the most hope is all the talented people and dedicated patients who participate in our clinical trials. I think there's so much exciting research going on that the future is bright. I think we're going to have excellent ways to prevent and treat geographic atrophy and neovascular AMD in the future, and I don't think our patients should give up hope. I think that the future is bright as we all work together on helping people with these problems.

DR. JIMMY LIU: Perfect. Thanks so much for the message, Dr. MacCumber. So, we will be taking a short break for the month of June, so our next Macular Chat will be on Wednesday, July 29. Thanks again for joining us, and this concludes today's Macular Chat.

Useful Resources and Key Terms

BrightFocus Foundation: (800) 437-2423 or visit us at www.BrightFocus.org. Available resources include—

- Macular Chats Archive
- Research funded by Macular Degeneration Research
- Overview of Macular Degeneration
- Treatments for Macular Degeneration
- Resources for Macular Degeneration

Helpful low vision tools or resources mentioned during the Chat include—

Resources

- American Society of Retina Specialists
- American Academy of Ophthalmology
- Illinois Retina Associates

Treatments

- Photodynamic therapy
- Photobiomodulation
- Syfovre
- Izervay
- Bevemipretide

Trials

- GALLOP Trial
- JADE Trial