THINKING THROUGH AMYLOID-RELATED IMAGING ABNORMALITIES

A Case-Based Exploration of Recognition, Evaluation, and Reporting of Novel Imaging Events of Alzheimer's Therapeutics

- Hey, welcome, everybody. We really appreciate your coming today. We think this is going to be a very educational session and really on a hot topic that's going on in Alzheimer's disease. And great to have my partners here with us. So this is between neurology and neuroradiology, which is always a fascinating partnership, especially now when we think about the cognitively impaired and this changing field that's happening as we talk about these new anti-amyloid therapies, monoclonal antibodies, and the side effects that come with it that are so critical to measure using MRI. So many implications here, the capacity issues of scanning so many individuals and how do we enter and optimally deploy these amyloid-targeting therapies. So we're going to be talking mostly about amyloid-related imaging abnormalities, both ARIA-E and ARIA-H, and then the frequent imaging that takes place when an individual's on amyloid-targeting therapy. So I'm James Brewer. I'm Chair of Department of Neurosciences at UC San Diego. I'm a neurologist and I head our Alzheimer's Disease Research Center there. And then I'm joined by Suzie Bash, who's the Medical Director of RadNet and a great close partner. We've collaborated for a long time. And Tammie Benzinger, also a great partner. She's a professor of radiology and neurological surgery at Washington University, and she directs the Knight Alzheimer's Research Imaging Program. So we really have a fantastic group to be able to kind of convey what we've seen of deploying these amyloid-targeting therapies. Dr. Bash will talk about monitoring for and diagnosing ARIA. Dr. Benzinger will talk about key considerations and red herrings, which are really interesting. I really enjoyed seeing her slides. And then I'll talk about partnership between the neurologist and the neuroradiologists, which are really going to be key partnerships in delivering these new drugs. Please make sure to do your cases on the iPads. This is very important. You're going to see what the correct answers are. So I think you're going to get a lot more learning out of it if you go ahead and do those cases beforehand rather than just having the answers spoon fed to you. And that's that. Okay, I'm going to turn over to Dr. Bash. Thanks so much.

- Thank you, Dr. Brewer. So I'll talk about monitoring for and diagnosing ARIA. 6.7 million Americans have Alzheimer's disease, and by 2050, we project that that number will more than double. So one in three of our seniors will die of dementia. And interestingly, death from heart disease is down 7%. But death from Alzheimer's disease is up 145% since the year 2000. And until recently, therapy had really been limited just to symptomatic management. So the first disease modifying therapies for Alzheimer's disease target amyloid beta plaque. And these are aducanumab, lecanemab, and donanemab. Aducanumab received accelerated approval in 2021, but is not reimbursable. Lecanemab received traditional FDA approval this past summer, and donanemab is under regulatory review, but we hope will be approved very soon. And so these therapies are really indicated for patients with mild cognitive impairment from Alzheimer's disease or mild Alzheimer's disease. And you see here the curve for beta amyloid involvement in a

brain, that's the green curve here, is much different than for tau involvement. So beta amyloid deposition happens early on, before the patient's symptomatic, which is why amyloid PET can pick up and can turn positive up to 20 years before the patient is symptomatic. Now, all of these drugs do an excellent job in clearing beta amyloid plaque from the brain. So in these charts here, you have the placebo with sort of the straight line across the top, and then the dramatic reduction in amyloid plaque for patients on therapy. Okay, so there are very exciting regulatory updates that happened this past year. July 6, 2023, lecanemab received traditional FDA approval. And immediately following that, on the same day, CMS said that they would cover the medication broadly. And this really allowed a pathway for drug access to the millions of Americans that are suffering from Alzheimer's disease. Then, October 13, just recently, CMS removed the national coverage determination for amyloid PET, ending coverage with evidence development and therefore permitting Medicare coverage determinations. And so that's really exciting because amyloid PET is less invasive than CSF analysis for confirmation of amyloid. Amyloid does need to be confirmed prior to starting treatment. This can either be done through CSF analysis or through amyloid PET imaging. And then a baseline MRI must be done, according to the lecanemab label, it must be recent. In my mind, one year prior is not recent. So ideally, within a month prior to starting therapy, use that to look for inclusion and exclusion criteria on MRI and also to gauge your ARIA risk. These are some of the clinical outcomes for the different drugs. Aducanumab had 22% slowing of cognitive decline, but that was really only seen in one of the trials, whereas lecanemab showed 27% slowing in cognitive decline throughout and met both the primary and secondary endpoints. And interestingly, just last month in October at CTAD, they presented the low tau substudy findings in which they found 76% had no cognitive decline at 18 months, and 60% actually had improved cognitive functioning at 18 months. So they were looking specifically at that low tau group. For donanemab, the study showed 36% slowing of cognitive decline at 18 months. And so it did a great job. And then 47%, almost half, had no progression at one year. ARIA again stands for amyloid-related imaging abnormalities. It's divided into ARIA-E and ARIA-H. ARIA-E is a parenchymal edema or sulcal effusion. So you see parenchymal edema on the image on the left there. And on the right, and the top row, sulcal effusions, which we use the FLAIR sequence to detect the ARIA-E. And then ARIA-H can be detected on your GRE or your SWI sequence. And we look for microhemorrhages or superficial siderosis, of which you see examples of both on that bottom row there. Now, ARIA-E, that edema is thought to represent leakage of proteinaceous fluid into the parenchymal interstitial compartment. And sulcal fusions are thought to represent leakage of proteinaceous fluid from the meningeal vessels. So here you see an example of edema and a sulcal effusion. Now, for ARIA-H, that's really defined as less than 1 cm size hemosiderin staining, deposition in the brain parenchyma for the microhemorrhages. And superficial siderosis is defined as leptomeningeal hemosiderin staining. So we see microhemorrhages on the left and superficial siderosis next to that. Now, all therapies do have an ARIA risk factor. It just goes with the territory. What I'd like you to focus on is symptomatic ARIA, which is the bottom row. So for aducanumab it's much higher at 26%. Lecanemab had less than 3% symptomatic ARIA. And donanemab, 6%. So lecanemab and donanemab both do have a very good ARIA profile. So most patients that get ARIA have no idea that they even have it. Now, risk factors for ARIA include being APOE ε4 homozygote. So you inherit one allele from your mom, one from your dad. If you have that, you have a much higher ARIA risk. It's

generally about double the risk. And by the way, that's why screening, genetic screening is recommended prior to treatment. It's not required, but it is recommended to gauge ARIA risk. Older people have a higher risk for ARIA, higher dose of therapy is a higher risk, and also a big one is proximity to initial treatment. That first three to five months, you're in your highest ARIA risk, and after that, much, much lower. If you have baseline cerebral amyloid angiopathy, you're also at higher risk. And if you have a lot of microvascular ischemic disease. Now, their symptoms of ARIA can present very differently. You have headache, confusion, dizziness, nausea, vomiting, visual disturbance. So it's a very sort of nonspecific neurologic findings. The key thing that you want to look for to report on the MRI is bleeding. So microhemorrhages and superficial siderosis. It's really critical to know that on your baseline MRI so that you're not calling something ARIA when it was just cerebral amyloid angiopathy prior to starting therapy. And then also any significant imaging findings like infarcts. So let's take a look at a baseline MRI. This is a patient of mine, 70 year old with memory loss. We see moderate cerebral atrophy. On the FLAIR sequence, we see multiple old infarcts in the left occipital lobe and really scattered throughout the brain. Left frontal lobe, left parietal lobe here. This was the patient's GRE, extensive superficial siderosis and some microhemorrhages as well. This is, again, something you would absolutely be critical to know before deciding whether or not to put this patient on therapy. This was an MRI in just a couple of months here, the patient developed another little acute infarct that I had read their follow up study. This was an FDG brain PET CT that showed statistically significant cortical hypometabolism in the bilateral temporal lobes, bilateral parietal lobes, and posterior cingulate gyri. And then here's a surface map with the FDG PET. Again, the blue areas and purple areas are hypometabolism. On the bottom row, you see an anterior and a posterior view. Again, in the temporal lobes, parietal lobes, posterior cingulate gyri, and hypometabolism is most profound in the areas of prior old infarcts. This is an FDG brain PET-MR Fusion. And again showing the same thing, these areas of cortical hypometabolism. So this patient actually had Alzheimer's disease, but they also had cerebral amyloid angiopathy. And they also had a vascular dementia component. This particular patient would not be a good candidate for therapy. So it's very important to know grading. As neuroradiologists, we actually have to list the grading when we interpret these exams. And we need to know if the patient is on therapy. So for ARIA-E, the most important thing to remember is it's all about size and whether it's monofocal or multifocal. So mild is monofocal but less than 5 cm. Moderate is monofocal between 5 and 10 cm. Multifocal, less than 10 cm in size. And then severe can be mono or multi, but it's got to be greater than 10 cm in size. And we have examples of each of these here. Now the great news is that ARIA-E almost always completely resolves within one year. So you see a patient here, they develop some ARIA-E. It starts getting worse, but by 300 days it's completely gone away. So that's very positive. ARIA-H, by the way, once you get a focus of microhemorrhage, will tend to persist over time on imaging. But the key thing for ARIA-H is count. So that's the big difference between ARIA-H and ARIA-E when you're trying to remember. So mild ARIA-H would be one focal area of superficial siderosis and/or less than four microhemorrhages. Moderate would be two focal areas of superficial siderosis and/or five to nine microhemorrhages. And then severe would be greater than two focal areas of superficial siderosis and or greater than ten microhemorrhages. So let's take a look at some cases here. Hopefully you have done the polls here. Here's a baseline MRI. And this is the post dosing MRI. You see some abnormal FLAIR hyperintensity there on

that FLAIR image. Let's see what people said. It looks like most people judged this to be mild in degree and that was in fact correct. It's mild because it's one area of involvement in the brain and the greatest diameter of that is less than 5 cm. So that is a mild case. Here's another case here. The baseline you see on one side, post dosing next to that and we see three areas of FLAIR hyperintensity that were not present on baseline. So let's see what people said here. It looks like the majority of people thought that this was moderate in degree. And that is correct. This was moderate because it's multifocal, but each area is between 5 and 10 cm. Here's another patient baseline on one side, post dosing next to that. You see two little linear areas of sulcal FLAIR hyperintensity. We'll see what people thought that was, looks like the majority of people thought that this was mild. This was actually moderate because it's multifocal. So we have two areas, one on the right side of the brain, one on the left side of the brain for this sulcal effusion. This next case here, this, we were looking at a GRE sequence and you see some sort of serpentine linear areas of hemosiderin staining on both sides. Here we'll see what people thought this was. So it looks like a lot didn't know what this was, and then some thought that was superficial siderosis, mild. Okay. This actually was moderate, and this is a tricky case. So it's pretty clear that the right side of the brain is superficial siderosis. That's one area. On the left side of the brain, the readers actually had the advantage of scrolling up and down. That's also a superficial siderosis. So two areas of superficial siderosis puts us in the moderate category here. But that was a tricky case. Here's another case here where we see some leptomeningeal hemosiderin staining and also some microhemorrhages. We'll see what people thought this was. So it looks like the majority of people thought this was mild superficial siderosis, and some were not quite sure. This actually was mild. And the reason why this is mild is the superficial siderosis. It was actually a contiguous leptomeningeal involvement. So it's one area. So if it's along the same sulcus, which again, you don't have the advantage of scrolling up and down, but it was one area, and then it's mild for superficial siderosis, but it's also mild for microhemorrhages because you see only a couple of microhemorrhages there. So mild overall. Now, that doesn't mean necessarily that Dr. Brewer would talk about what he would do in this case, but we as radiologists would rate this as mild. Now, a lot of MRIs are going to be needed. So we need to have again a recent baseline MRI. Then prior to the 5th, 7th, and 14th dose for lecanemab, and according to AUR recommendations, also prior to the 26th dose. Then if the patient develops neurologic symptoms, the neurologist may order MRIs that are non-scheduled. So we've got four to five scheduled. If you go by AUR, five, and then anytime they might have a significant symptom, another MRI. Then if they develop ARIA, you're going to need to repeat the MRIs, typically done about every two months after. So a lot of MRIs, that's going to be probably the biggest impact for imaging enterprises is the increased number. So of the 6.7 million that have Alzheimer's disease, I think about roughly 1.5 maybe candidates sort of on the earlier stage of Alzheimer's, candidates for treatment. If you take your five scheduled MRIs and maybe they have five headaches that year or something like that, or they develop ARIA, so maybe five more, ten scans total, that's 15 million new MRIs a year in the US alone. So obviously, big impact on imaging facilities. I also anticipate a significant increase in the number of amyloid PETs, especially now that we have some positive movement for coverage for amyloid PET. And so both beta amyloid confirmation and neurologists may want to use this for surveillance as well. The trials all use it for surveillance. And then I also anticipate an increase in the number of AI utilization for

both hippocampal volumetric tracking for patients and also for ARIA reports, which I'll talk about in a second. We need to educate our neuroradiologists that are going to be reading these, how to train how to read these ARIA cases. You see, they're not always so straightforward. It can be challenging. And need for consistent imaging protocols, which Dr. Benzinger will talk more about, and also, ideally, similar field strength and vendors, although that is often not possible in large imaging enterprises. If you do want help with the template, that is available on the ASNR website that you can use, and I'll show you some of these ARIA tools in development. This is an ARIA-E sample report. Again, these are not yet FDA approved, but they will be soon. And you can see here it's actually measuring the largest lesion for you. It's giving the volume change. It's telling how many sites of involvement and will actually rank the ARIA grading based on radiographic criteria. Manual ARIA screening and follow up can be very time consuming and difficult. In one study, 84% of local radiologists initially missed ARIA on MRI. That dropped to 14% once they were told to go back and take a look. But inter-reader variability is a significant challenge for ARIA screening, and accurate MRI interpretation of ARIA is really critical, as it will directly impact therapy decisions. Here's another sample report. This is an ARIA-H. It will track the count of both hemosiderin state and microhemorrhages and superficial siderosis for you. It will grade in each category. And so the ASNR ALZ/ARIA study group, which I'm a member of, which Tammie runs, we pulled the 2,700 member neuroradiologists. 63% of the responding neuroradiologists polled indicated that they did have an interest in automated AI for ARIA safety screening. And so again, that's why the companies are sort of developing this. This happens to be another company here. Similar thing where it's counting lesions for you for ARIA-H and also measuring for you for ARIA-E and telling you the grade and the change over time. A small study did demonstrate significant improvement in ARIA detection and severity assessment when you use these quantitative AI tools. Now, future considerations. Again, we're expecting, hopefully, FDA approval for donanemab very soon. And then also the other thing to think about is new formulations. So subcutaneous formulations are in active trials for lecanemab. Those results were just presented at CTAD last month and that will bypass the need for bimonthly infusions and also eliminate the infusion reaction risk that you might have. It actually had 14% greater beta amyloid plaque removal in sub-Q injection versus IV at six months and it had a better steady state exposure in the blood. So I'll turn it over now to Dr. Benzinger, who will take a deeper dive into ARIA.

- All right, thank you so much. So, really happy to see all of you here today. Hopefully we'll give you some challenging cases to go through as we move forward. So just to refresh this again, so this is just an example of a typical time course of ARIA. And that patient would have a normal baseline exam. The ARIA-E, we expect to develop over time and then resolve. But the ARIA-H, where you have the microhemorrhages develop, those will stay and persist on the findings to come. So what are the symptoms of ARIA? Well, headache, confusion, dizziness, nausea, vomiting, et cetera. Most of you are radiologists, like me, you work in the real world. We have patients coming in from the ER and from the clinic and these are really common indications already for a head CT or a brain MRI. There's a lot of overlap with other conditions, particularly acute ischemic stroke, infection, or even posterior reversible encephalopathy, or PRES. And so we really need to be, I know, we're already thinking about all of those other things. We need to add ARIA into that mindset as they're coming in. And in particular because of the way that the hemor-

rhages are a part of ARIA, we need to have a heightened awareness, particularly in the area of stroke, for potential for bleeding. So here's a case for you. So this is a 72-year-old patient who was on one of these therapies presented for asymptomatic monitoring. So remember, they get maybe four, five scans scheduled along the way before they get their next dose. And here's our MRI. And what you guys can see is there's, and I'm telling you what's new. So this FLAIR hyperintensity is new. This microhemorrhage is new. And this is our diffusion scan. So he is on therapy, and we didn't know about other causes. So this is just another example of a classic mild ARIA. You can see that, in the grid, you actually score these separately. So he has a mild ARIA-E and a mild ARIA-H for microhemorrhages. If he also had siderosis, as Dr. Bash was saying, that would also be a mild ARIA-H for the siderosis category. Okay, here's another case for you. 73-year-old, also on therapy, comes to the ER with increased confusion and they ordered a brain MRI. So the first question to think about is, what kind of protocol do you do? Some of us have multiple different types of brain MRIs that you might do in the ER. So what I just wanted to remind you of is we do have a nice consensus document that came out from the ASNR last year about the type of protocol. And if you look at what it requires, it's pretty straightforward. You don't have to have high resolution, you do need to have FLAIR, you need to have something to look for blood and you need diffusion. This is going to be your standard ER stroke protocol. If someone's coming in with symptoms, you don't necessarily have to wait and put them on an hour long 3D protocol. You can treat them as you would another acute stroke patient and look for these key findings. Okay, so here's a patient comes in and we get this brain MRI. We see that there is an area of edema more than 5 cm. There is some hemorrhage associated with it. But now we have a finding on our diffusion scan as well. So the question is, what is this? And thankfully, most of us recognize this as an infarct. So it would be actually very atypical for ARIA to present with a large territorial infarct like that. So the diffusion restriction. Okay, here are two cases, both of them presenting to the ER with headaches. You find out that they are on an antiamyloid therapy. So which one of the patients has ARIA? Some said one, some said both. And the truth is, these were both cases of ARIA. So just to kind of give us more examples, because these are cases that we see. We're going to see all the time. Okay, here's another patient presenting with confusion and weakness. And so here are the findings in this case. All right, so we still have FLAIR. We can see a lot of findings on susceptibility. Looks like siderosis. And then on diffusion, we've got some weird signal around that blood. Maybe this is an artifact from the blood products. But there's also another area that also has restricted diffusion. So this one was the infarct with hemorrhagic conversion. All right, here's another one. He has confusion, headache and hypertension. We've got the bilateral findings on FLAIR. No hemorrhage, no restricted diffusion. I'll give you a second. So question is, what is this one? Is it ARIA again? Is it infarcts? Is it mets, infection, PRES, not sure? And so, yeah, most of you accurately identified this. Now, obviously it could have been ARIA, so you have to go with some other findings, such as the fact that it was bilateral, he was hypertensive. And when they treated the hypertension, the findings resolved very quickly and in a time course, more faster than what you might expect for ARIA. But obviously going to be a lot of overlap in the presentations as well as the imaging findings for these patients as they come through. All right, here's another case, 83-year-old, confusion and a headache. So I'll give you a second to look at this one. So we definitely have a large area of edema more than 5 cm. We have multiple areas of hemorrhage and sider-

osis in both hemispheres. And then we have a very strange pattern of diffusion restriction that's almost more sulcal than cortical. And so what is this? Okay, so most of you thought it was ARIA. Absolutely, that would be something you would have in your differential. But I would argue taking off your hat and just thinking about this as a regular patient in your ER, not everything that comes in is going to be ARIA. And these patients are going to have other things that they present with as well. So in this case, your clues are normally you're going to get the siderosis acutely, co-occurs with the edema. So the fact that there's new siderosis in an area where we're not seeing something that we would call ARIA-E, that's a red flag. Second thing is, again, diffusion restriction is very atypical for ARIA. And in this case, I know you can't scroll through, but when you figure out that it's actually not even in the cortex, that it's diffusion restriction in the sulci, that helps you to know that that was actually a case of meningitis. And so just your everyday cases that we see, you have to think about in addition to ARIA. Okay, another case comes in with a seizure. What do you guys think about this one? So he has a small new area on FLAIR that has a hemorrhage, but it's also enhancing post contrast. So in this case, he happened to have a new presentation of lung cancer and metastatic disease. So all of these things that we see in real life, we're going to be seeing as the patients come through, we actually don't know a lot about what ARIA may look like with contrast enhancement. The clinical trials that were designed were non-contrast. So that's something that all of you will be contributing to and observing as these cases come through. Big question that we get asked a lot is, should you use contrast on these protocols? So the ASNR recommendation and what we're doing at Wash-U is actually we're doing a non-contrast examination if they're asymptomatic, but if they're coming in with symptoms, we treat them the same way we would any other patient with symptoms coming into our ER, which would be general brain protocol, stroke protocol with and without contrast. And that's to help us pick up those other things that might be on the differential diagnosis. Okay, another common question is, can we tell the difference between ARIA and just a pure subarachnoid hemorrhage that's maybe not related to these drugs? And the answer is from imaging, probably not. If you have ARIA-E and H together with siderosis, that's going to look like subarachnoid hemorrhage. But you can get some clues from it, obviously from the presentation, the location of the hemorrhage, if they're presenting with a sudden headache, the symptoms, the other things that you think about. And then finally, just to kind of summarize some of these clues to the differential diagnosis. So ARIA versus infarct diffusion is your key sequence. The ARIA, like pure edema versus subarachnoid hemorrhage on FLAIR, some of these other sequences for susceptibility can help you, as could a head CT. ARIA versus meningitis, other things like that. Again, it's going to be some mismatched locations where you're seeing perhaps hemorrhage or diffusion restriction in areas that don't have ARIA. And then finally, versus PRES. The main thing is the symmetry. ARIA is more likely asymmetric. They could both be posterior, but then the other thing is just that response to treatment, so different treatment response, treat the hypertension, treat the underlying cause, and the PRES will resolve very quickly. All right, just really quickly, some pitfalls to watch out for. And this is all from the ASNR white paper. You can go look at it in more detail. But again, just thinking about things like, did we switch scanners? So from one vendor to another vendor can be a real problem. We do need to develop standardized protocols to minimize that. Also, artifacts of things like hearing aid, supplemental oxygen, artifacts from motion, artifacts from phase encoding, all of the

things we think about all of the time in our everyday practice, we're going to have to think about a lot as we start seeing more of these patients on therapy. And then finally, something we've discovered quickly is as patients move through the system and they're going on different scanners or different protocols, it can be sort of hard when you're counting these microhemorrhages, wait, was that number eight or was that number nine? And was that the one they saw before or not? And so we're encouraging, if you're in a system where you can mark things up on your packs, to do that for your colleagues and the people who come after you, so you can mark them and number them and make it a little bit easier to follow up on that. And then finally, probably the most important message I can give you today, and Dr. Brewer will talk more about this, is communication. So finding ARIA changes the management for these patients. And so we really do need to let them know anytime we're seeing something that we think looks like new ARIA. Now, if it's mild, they may usually continue dosing according to the labels, but we still recommend at least a secretary makes a phone call to a nurse, some kind of communication that says that a lot of times they're getting their MRI the day before the infusion. And so if the doctor doesn't read the result until two days later, it's too late. But definitely if it's moderate or severe, the recommendation is that they need to hold the dosing. And so you absolutely want to make sure to get that result to them and communicate that with them. And we recommend a physician to physician conversation. And again, ARIA features. I think radiologists are going to be really good at recognizing these. These are things we see every day. But the reporting of it can be tricky. And so having some templates built to help you report it consistently will be really helpful. And remembering it on your differential diagnosis, particularly for those stroke patients in the ER. All right, and I'm going to hand it off to Dr. Brewer. Thank you.

- Thank you so much. So, great. That is amazing to see the skills that are being distributed now, because this is brand new for all of us, including for us on the neurology side. So now I'm going to talk a little bit about our communication across the specialties, which is going to be enhanced in this state where we are really trying to be as cautious as possible with these new medications that are, as you can see, causing some brain edema and bleeding. So have you experienced challenges with radiology, neurology, communication, regarding imaging patients with cognitive impairment? I threw you a softball. I'm sure there are challenges. We send you patients that are very difficult to scan, sometimes very severely impaired. They can't sit still. So there's going to be a lot of discussion here, because when we interact, we're going to have to know that this individual is going to have to be willing and eligible to receive multiple MRIs. And especially with the kind of safety concerns that are going on, we want to have a very highly accurate read because we're continuing to prescribe a drug that may have important adverse impacts. So it's helpful to have bi-directional communication. And I'll say that a lot of times that neurologists, at least in our practice, are going to really want to maybe even look at the images alongside you and say, understand, because we're all learning this as we go. Exclusion factors, as you've heard, you can't have an acute subarachnoid hemorrhage or infarction, extensive coexisting cerebral vascular disease or excessive ARIA-H risk, as has just been talked about, and an intraparenchymal mass or inflammatory lesion on that baseline scan would say, we're not going to be able to give this medication. And we're, again, even at this time, interpreting the label and trying to work alongside our other practicing physicians to understand how we're going to be

deploying this and who are we going? Almost like a tumor board, interacting together to kind of say, hey, do you think this person is okay to start on this journey of multiple doses, sometimes as frequently as every two weeks in the infusion center. So it's a heavy commitment that we're giving to this patient when we decide to put them on the drug. So there's a heightened need for cross specialty coordination and communication. We have to tell you, hey, this is going to be about instituting a new amyloid-targeting therapy. So you need to know that we're going to be pretty anxious about it. So I think over communication is going to be okay. I don't think we're ever going to say, why did you call me about this? Because right now we're very sensitive about what we're doing as we continue these patients on the drug. So each patient is a long term commitment. Patients also have impairment. So hopefully at early stage, that's part of the criteria. We don't put late stage individuals on this drug. It's not part of compliant with the appropriate use criteria or the label. But even at that stage, we may have compliance challenges and motion degraded images. Accuracy is going to be critical. So whatever one can do. Thank you for coming to such a CME to learn as much as you can, because that partnership is going to rely on these kind of expertise, interpretations. This attention to scanners and protocols is important. I know that just in the practicality of referring patients to your different scanners, 1.5 versus 3 Tesla, susceptibility weighted imaging versus the other sort of microhemorrhage detection tools, they're going to vary the sensitivity. And so we're going to have to kind of rely on you and your understanding of your own machines to say, "Where do you think this falls in terms of mild, moderate, severe?" And again, we're right at the beginning of this phase, so we're learning as we go. This is kind of at what we've just talked about. So just a refresh on the ARIA severity, and I'll talk about why this is relevant to us on the prescribing side, because it does impact whether we continue or suspend the dosing. So we look at both the symptoms, clinical symptoms. Most of these are going to be asymptomatic, some will be mild, a little headache or things that maybe even a person has already had even before starting the drug. But we still need to MRI them when they have that new headache while they're on this drug. And then severe would be something, say a seizure or something that puts them in the hospital. And that's going to really take us to probably pause the dosing regardless. In the moderate phase and the severe ARIA-E, we will typically suspend dosing and ARIA-E, hopefully allow that to resolve and then move forward. But on ARIA-H, again, even though there's some variability in the FDA labeling of this, that you do not have to suspend and permanently discontinue dosing. I think at this phase, where we are very attentive to our Hippocratic Oath and not causing harm, we're probably going to be pretty conservative and probably hold back on that and have a really serious discussion with our patients and their families about whether the risk benefit would warrant continuing dosing. So, this case, the 81 year old patient with mild asymptomatic ARIA-E follows up with the neurologist. Which of the following is recommended regarding continued use of the amyloid-targeting therapy? So you can see, would it be continued dosing, suspend dosing, permanently discontinued dosing, or I don't know? And our answer is, yeah, some say continue dosing, some say suspend, and that will be a clinical decision. But technically, you could continue in this case, because it's just a mild ARIA, a single area of ARIA, so you could continue dosing, but I think you would want to have a conversation with that family. Here's one, a 76-year-old with moderate asymptomatic ARIA-E follows up, which are the following in this case? Now you've got more areas of new ARIA. In this case, it's a moderate. And so one would take a pause. And in most

cases, this will resolve. And then you can re-continue, just like in the clinical trials that were conducted, and you would present all that information to the patient in the family, and they may still decide, "Hey, this is a little getting scary for me. I've got some edema in the brain." But you talk that through. Here's a case of an individual. This is the same case, moderate, and one would suspend at that time, wait for resolution. And here's one with ARIA-H, which is the one that really gives us a pause, because some of the cases that we've seen in the literature are severe bleeds that can happen with these drugs. In this case, we see a superficial siderosis. It's a single area. Let's see if we gave you some answers. In this case, you got one on the other side as well. So not only the right side of the brain, but also the left side of the brain. So this was two focal areas and moderate. And so the suggestion is to suspend dosing in this case. And this case is interesting. We talked about it before because this one would give us quite a bit of pause. But technically, this is still within the mild phase. It's got superficial siderosis in one area and fewer than four microhemorrhages in another area, both falling within the mild range, and one could continue dosing in this case, although I think in clinical practice, we'd be pretty cautious about it. So these are the key considerations. Standardize, when possible, across time points. Is going to be really helpful for us to get familiar with what you guys feel in terms of your comfort in reading these across scanners, across our partners, across your whole practice, who might be our best partner for interacting on this, on these tough cases. Standardization of reporting will be very helpful, and then automation tools, I think, are going to be very helpful, although you do see what Dr. Benzinger reported. A lot of these things are going to be in the gray area, so hopefully just be highly sensitive, and then use your expertise to over-read that and say, "Well, I think this is actually something else." So I think that imaging can help measure the disease progression. So we know that these patients continue to decline into severe dementia regardless of removing the amyloid, except in some cases we may be seeing some different things in pure Alzheimer's disease, but the standard is that these individuals have more than one proteinopathy in their brain. Actually, we're finding that as people age, that we're seeing not just amyloid and tau, but we're seeing TDP-43 and other features going on. So it's really going to be an interesting opportunity to track this longitudinal decline radiographically as the person gets their amyloid removed from their brain. So I think these quantitative tools are going to be really powerful, because we will not have amyloid anymore as our marker. We're going to have removed it. These drugs turn positive amyloid scans into negative amyloid scans. So we in the research field are really wringing our hands about, okay, now we've lost that very powerful marker. We now have a negative amyloid that we know started as an Alzheimer's patient. They're still considered an Alzheimer's patient. They still probably have the tau in their brain. Let's get some other markers of how we can continue to measure with biomarkers. And I think atrophy rate is going to become more relevant. Emotion and positioning, resilient. Cross study registration will be very powerful to kind of see where these changes are taking place. And then, very excitingly, are there some new tools or new diffusion based techniques that might be able to predict who's at most risk even before these kind of signals come up? Is there some sort of extra leakiness in the vessel? Is there some sort of water diffusion techniques that might be able to tell us that this person has a higher risk? Because right now, one of the things we're doing, and I just had a patient in the VA, very interested in the drug, very educated, knew all the risks and benefits, wanted to go forward, turned out to be homozygous ε4. In the VA, that's a complete hard stop.

And so she was really devastated. She basically has nothing to turn to right now. So we'd love to be able to say, "Okay, you're double ε4, but we've done some measures, and maybe this is a less risky than the other double ε4." That's a hope on the horizon. I know it's a tough one in the future, so let's talk about it. A really important thing that we're going to discuss here. A lot of our emergency room docs are terrified of the fact that they may need to have to scan with MRI on any headache patient that's coming in. This person's got, either they've known headaches, but now they have a headache on the ATT. So you're going to have to scan them, we think, and confusion in a patient with diagnosed cognitive impairment, dizziness, these are very common. You have to scan them with MRI because it's the only way we can detect it right now. And then the risk benefit of anticoagulants, I think is something we can bring up in the discussion session. I think this patient inflow increase is going to be something. I saw a lot of heads nodding about the volume here and the challenges for doing regular and timely MRIs, but it is an opportunity potentially to track trajectory, but that can be difficult across scanners and vendors. Improved understanding of ARIA risk across populations. And then really exciting are some of these new trials taking patients in the earliest phases of disease, including asymptomatic phases and maybe that stage of disease where there's not so much buildup in the vessels of these bad proteins. You may have a better safety profile and a better efficacy profile. So very exciting times. The dynamic landscape of AD is really changing our health system, I think, we're already starting to see it. Neuroradiologists are going to play an absolutely key role in decision making. It's going to take a great partnership, even more tight than what we've had in the past. Imaging centers will need the ability and the agility to adapt to increased scan volumes. And it's exciting, pivotal time in the history of neuroradiology. So thanks for your attention. Let's see what kind of questions we might have. So I just want to thank you for your attention and your time here. So I'm going to turn to. Yeah, maybe we can take. Go ahead with one.

- [Audience Member] When we started screening for ARIA, they did the initial criteria on GRE scans.

- Yes.

- [Audience Member] And you mentioned today both GRE and SWI, which is more sensitive. How have you tempered your grading now that most people are doing SWI? In fact, I've had to do both just to make sure I could use the standardized grading nomenclature, or standard, rather than the SWI, which is more sensitive. So I'd be very curious on that one.

- I could maybe start off and I'd like to hear Dr. Benzinger's input on that question as well. It's an excellent question. So different imaging enterprises are going to handle this differently. It's an extremely important thing to really talk about internally and come up with a standardized protocol. So I work for RadNet, which is the largest freestanding outpatient imaging enterprise in the US. We've got about 357 different imaging centers. Obviously we need to be standardized, otherwise we're going to see SWI here, GRE here, across our different scanners. So we have developed particular dementia imaging protocols. We've actually changed the name of our ordering so that the neuroradiologist knows whether the patient's on treatment or not. And our standard dementia protocol is going to be a routine brain study and the GRE is going to be a required sequence. We're going to use the GRE for the ARIA grading. Now, a lot of sites do do SWI, and they're welcome to continue doing that. So if they do SWI, you're just going to tack the GRE on so

that the ARIA screening can all be done on the GRE. And you'll see Dr. Benzinger might have a very different approach, but we're doing that and then we're doing internal training for our neuroradiologists. I'm putting together a webinar for ARIA training, sort of similar to what we did here. All of our neuroradiologists will be required to take that. They'll get sort of a certificate and none of our neuroradiologists will be reading the cases until they've had the ARIA training. But that's how we're sort of handling our protocols. It's a routine brain, but they will all be quant-capable, so 3D T1, so that if we want to use an ARIA screening, an automated ARIA screening tool, we can always do that if the refer would like that. But other than that, routine brain, GRE required, SWI optional. Dr. Benzinger?

- Yeah, so that was a major question that the ASNR study group was asked. And a challenge that was issued at our annual meeting last spring was, how are we going to handle it? And the study group has been working on it over the course of this year really closely with Siemens, GE, and Philips. And in fact, we just published the Siemens protocols. If you go to the, on the Siemens website, they have a thing where you can download protocols. You'll see the ASNR recommended protocols. What that has in it is those standardized FLAIR diffusion and GRE. If you run that with the SWI as well, on a 1.5 T scanner, it's about eight minutes, and that's on even the Espree and the Avanto, so older scanners. So we worked really hard with the vendors. Like I said, we've published that one. But to try to give something out there that if everybody employs the same thing, it's going to help you as they hop around. The second part of the question is, should you run SWI or GRE or both? My personal recommendation is that now that we've made something that's fast and easy like that, eight minutes, including both of those, just run them both, because that's going to help you to identify as a radiologist, you're never just looking at one sequence, right? Even if you see a hemorrhage on an SWI, you're looking at the MP RAGE, you're looking at the T2, you're looking at the whole exam to try to decide what the true finding is. And the recommendation we're making from the ASNR study group is report what you think is the truth. Don't say, "Well, I see five on SWI, but only four on GRE, so I'll call it four." No, we're saying, if you think there's five, call it five.

- Great. From a neurologist perspective, I'll just make a comment there. We want as sensitive as possible. We'll make that decision. We're probably going to be extra cautious in these first phases. So when you do a susceptibility weighted imaging and you see a bunch of microhemorrhages, even though on the standard GRE it may not be exclusionary, we're probably going to want that information. And it brings up the concept. I think we were going to bring up that all of us have heard of this case where what might have been an ARIA, or even it could have been an acute stroke, came in and went through the acute stroke protocol, received tPA and had a fatal hemorrhage. Dr. Benzinger, I think you've looked closely into that and it's one of the things that gives us great pause. And the ER physicians are really kind of freaking out about that, too, because their protocol is not ready to take in that MRI assessment before administering tPA. Your thoughts on that?

- Yeah, no, I did want to talk a little bit about that ER workflow. And I have several cases, I should put them in the talk next time we do it, of patients coming into the ER and getting the head CT. And what does the ARIA look like on the head CT versus the brain MRI? From my experience, a moderate ARIA-E shows up on that head CT as edema. So, as a radiologist, if you're reading that acute stroke protocol and you already see edema, even if you don't know they're on the medication, hopefully

you wouldn't put them on a thrombolytic because that would have precluded it from getting the treatment based on the CT alone. But we are also struggling a lot to try to figure out how do we triage getting them to an MRI, and not just at our main hospital, but these patients get infusions frequently. It's some of them every other week. And so they want to be treated close to home, and they're going to smaller hospitals out in the community where they may not have MRI coverage 24/7, or they may not have a 3T scanner. And these are things I don't have a good answer for. But I want radiologists to be aware of that and be thinking about it as you start to treat these patients in your networks.

- Dr. Bash, yeah.

- I was just going to say, just in summary, I really think that probably the most important point is consistency. Whether you choose SWI or whether you choose GRE, just be consistent, because you really cannot compare an SWI at one visit to a GRE at the next visit. And again, it could make a big difference in treatment where you might be calling something ARIA-H, but it may have actually been stable, but you just read the first one as a GRE and the second one as an SWI. So I think internal dialogue is very important. Come up with a consistent protocol for your imaging enterprise and just stick with it so that the ARIA-H is always read off of one or the other each time.

- And just to add a comment to that, so we have over 40 patients in treatment right now at Wash-U BJC. The first five cases, we called ARIA on all five, and I can tell you it was actually because they had a baseline scan that didn't match. So they all had out of network baseline scan at some place in the community where we hadn't set up a standardized protocol yet. They had maybe like a pituitary protocol or IAC protocol, or even just a community general coronal T2-star type thing, and we couldn't see the findings. And so the first time they came in for that monitoring scan. We had to say, well, it's new, so we have to call it ARIA. Then over time, we saw nothing else happened with them. They never had symptoms. And we decided, well, probably in retrospect, it was just that their baseline scan was either too long ago or didn't have the right protocol. And so thankfully now the neurologists in my practice are all very attuned to it and are ordering the baseline scan over again, even if they had one somewhere else six months ago.

- I think that's wise, because again, the label used to say within one year, one year really is not helpful. I mean, recent, they didn't put a specification on recent on the label, but I think that you've got to really be within one month, otherwise you just really can't compare. And again, you'll end up over calling ARIA if you don't have something very recent.

- And I think, again, from the neurologist perspective, we want to have that familiar person we trust having doing that baseline read because it's such an important discussion with our patients. We do the same thing on EMG nerve conduction studies. A lot of them come from outside. We say, "You know what, I want this done by my trusted partner here." And so I think we're going to do the same thing in our local sites with our radiologist. So I think that helped us cover one of the questions here, which was about inpatient versus outpatient radiological practices, the inpatient being those ER concerns. So it's not only just about the acute stroke. I have my ER docs really concerned about pulmonary embolism, other anticoagulation requirement, but patient is decompensating from some other thing that might need an anticoagulation. And we don't really know. We don't have the experience yet. So it's going to be a very difficult time. But we do talk to our patients before going on this drug,

that it essentially is going to be a contraindication to get antithrombotics. If you have a stroke, we may not be able to give you that standard of care. We might have to go toward an embolic retrieval or things like this as opposed to IV tPA. So a lot of places won't be able to do this. There's a lot of things that go into the first discussion.

- And the other thing, Dr. Brewer, is I do think there needs to be an educational initiative for neurologists as well, because that's not really a question that's typically part of the stroke protocol pathway. And so neurologists need to now start asking patients if they're on therapy before they push the tPA, because otherwise they could end up causing a massive bleed. So that is another component of the educational pathway.

- I spoke with Dr. Benzinger about that. Their practice is giving out a little card. We've been talking about medical alert bracelets or something, because sometimes these patients will come in aphasic, and you just won't be able to ask them that whether they're on this drug or not, going to be a tough time. So a couple of questions here. Are radiologists expected to make these recommendations about therapeutic management based on ARIA severity? I think my point is, it's helpful that we have that expert trained partner in making these calls, but it probably is on the prescribing doc to make that final decision. So it's on us. It's our medical license, not yours. But do help us by making the most accurate reads as you can.

- If I can add a comment on that,

- Sure, go ahead.

- And that is, for those of you who practice both in the academic center and at the satellites, what I'm seeing is a lot of variability, just as when I have a patient at the cancer center who's seen the oncologist, the oncologist already knows how they're going to treat them, but when it's at that satellite facility, the radiologist has to do a lot more. So I do have one patient from southwestern Illinois who's being seen by a private neurologist out there who has developed now severe ARIA-E and H. And I can tell you, every time he gets a scan, I have a 15 minutes phone call with that neurologist explaining the findings. And he's asking me, "Well, what would they do downtown?" Because a lot of times, radiology is serving a greater community. And so it's really important to be educated on this. It's hard to have that scoring system memorized. I don't recommend you try to memorize it, but just know how to call it up and how to make sure you include that in your report.

- Yeah, and somehow partnering and being able to help educate the neurologist on the other side, we're going to be very gun shy as soon as we have one of those cases. And you may just say, "I'm not doing this anymore." It's a difficult thing when you see it with that patient directly and their families and the impacts on it, although also withholding the drug, just like I talked about with that VA patient, that's a tough conversation to have. I don't really have anything for you because of your homozygous status. Question here. With the MRI radiographic ARIA changes and more concerning cerebral edema than was seen in the highly selected patients in trials, how open are you to treating patients who may be a bit more or less severe than the study participants? That is what we're all trying to get more comfortable with these medications to understand at where we feel most comfortable. But right now we're relying on appropriate use criteria and we really are very much trying to stay as close as possible to the trials because that's where the published data are. That's my thoughts. Any other thoughts?

- I guess the other thing would be most of the trials didn't include people with pacemakers, for example, because of the difficulty of getting an MRI with a pacemaker for research. But I can tell you 2 of our first 40 patients have pacemakers, because we have, if it's an FDA cleared device, we have a workflow for getting those scans. And so we're scanning them now. That adds a layer of complexity to, what are we thinking about with the imaging and what are the outcomes going to be?

- That's super. To have a partner like that that's willing to take that on. It's an extra burden, of course. To be able to have that piece. So if your radiologist and your neurologist are working together, you can kind of see that you might be able to take in some of these patients that would have otherwise been excluded in the trials.

- But it also adds a level of complexity, because most pacemakers are now MR compatible. But you still have to have medtronics come in and they change your heart rate and they monitor you through. And so when you're now doing numerous MRIs, that's a logistics for scheduling as well.

- Absolutely, yeah.

- One more, and then we'll finish it up. Thanks so much, go ahead.

- [Audience Member] Here's my ARIA-E question. You mentioned that it's most likely due to sulcal leakage of proteins from the vessels, or even in the case of the white matter edema. And yet we don't think it enhances, because we never did enhanced scans during the ARIA trials. But what's the mechanism for contrast enhancement? It's leakage from the vessels, the tight junction. So in acute ARIA, brand new ARIA, are we making that assumption just because we didn't see it, because we didn't give gad, or is it based on some physiology?

- So that's a great question. And there's really nothing that's published out there. I can tell you we had a series of patients at our hospital who had moderate and severe ARIA who we did put through this workflow of getting contrast with it for clinical care afterwards, and none of them had enhancement showing up in that short series. But we don't know what it's going to be out there. I think it's also, so we're talking about different questions that probably need to be addressed in research going forward, one of them being, what are the diffusion findings? Another being I think, what does it look like on perfusion? If you measure CBF and CBV, what are you going to get? If we put them through the hyperacute stroke protocol and they get perfusion, will we be able to detect some findings there that are different than a frank contrast enhancement? Probably, I guess.

- All right. Well, thank you all for your great attention, your great question questions, and looking forward to working with you as we work on this together in this new era in this new exciting phase of the treatment era of Alzheimer's disease. Thanks for your partnership.