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What is the Role of APOE4 Testing in Alzheimer's Disease?

Announcer:
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Dr. Isaacson:
Welcome to another episode of the Frontline of Alzheimer's Care, where we provide you with answers to pressing questions from real clinicians about amyloid-targeting therapies in Alzheimer's disease. I'm Dr. Richard Isaacson, and helping me answer these questions today, are doctors Gayatri Devi and Pierre Tariot. Dr. Chong has a very interesting question for us.

Dr. Chong:
As you probably know, Chris Hemsworth, who plays Thor, amongst other characters tested homozygous for APOE4 in one of these commercially available genetic tests. And it actually changed how he's living his life right now, actually. And so, now that genetic tests are more widely known because of this, I'm guessing more patients are actually doing these tests. And I'm wondering how often it changed your thoughts about things diagnostically? And whether change things clinically? And more specifically the role that they play in choosing amyloid-targeted therapy? And in terms of the discussions about potential benefit and potential risk?

Dr. Isaacson:
Yeah, so I get this question all the time. And I think the first thing a person should do when they find out their APOE4 status is take a deep breath. Having an APOE4 variant does not mean the person is going to get Alzheimer's. Having two copies of the variant does not mean a person is going to get Alzheimer's

I do think in terms of the value of APOE4, especially two copies of the APOE4 variant, is to really understand the differential risks versus benefits of anti-amyloid therapies. People with two copies of the APOE4 variant almost across every trialhave an increased chance of side effects and adverse events related to anti-amyloid drugs. You know, does a person with two copies of the APOE4 variant need a different titration schedule? Should they have additional MRIs more frequent to make sure that we are tracking patients more closely? People without APOE4 are half of my practiceum and they may get Alzheimer's too, and they're going to have different genes, and polygenic risk is really the key.

So what I would say here is I think education really needs to be enhanced when it comes to what can be thought about with the APOE4 versus not. And in terms of ARIA by APOE4 status, donanemab in terms of homozygotes, two copies of the APOE4 variant had a 44% chance of ARIA-E at the highest dose. Lecanemab had a 33%, and aducanumab was 64%. In APOE4 noncarriers, there's only 11% chance of ARIA-E with donanemab, 7% with lecanemab, and 20% with aducanumab. So I really do think this opens the door for precision-based dosing and monitoring in terms of care.

Dr. Devi, you and I have shared more than one patient with either one, two, or no copies of the APOE4 variant. What are some of your thoughts from a practical clinical perspective?

Dr. Devi:
I personally did not generally check patients for their APOE genotype until the anti-amyloid therapies became available. And then I started checking. The reason being, before that, I did know that when patients had a copy of the E4 allele, yes, they were at higher risk, but it was not an absolute risk. You could have two copies and conceivably still never develop Alzheimer's disease with two copies of the APOE4 allele. Very unlikely but possible.

But subsequent to the approval of aducanumab, I started to check APOE status in every patient who I was going to think of as a candidate for going on the amyloid therapy. And the reason for that is because there's a substantially increased risk for developing brain bleeding and brain swelling. And I know we tend to think more about brain bleeding as being the more alarming of the two. But the truth is, the edema can also be quite dramatic in these patients, whereas the hemorrhage sometimes is a non-event, it's just small microhemorrhages in the brain. So I tend to clump both the brain bleeding and amyloid-related hemorrhage, as well as amyloid-related edema together to give patients a sense of what their risk is for some kind of potentially significant adverse side effects. And the risk from donanemab and aducanumab in patients who have at least a copy of the E4 allele – one copy of the E4 allele is fairly high, it's about 40-45%. Whereas with lecanemab, the risk is much lower. It's about 23% in my practice.

Dr. Isaacson:
Great. Well, very valuable perspective for someone with their boots on the ground, you know, giving these treatments, and interesting to hear the evolution in your perspective here.

Dr. Tariot, what are your thoughts?

Dr. Tariot:
I'll keep it brief. The only actionable step in terms of knowing your APOE4 carrier status is in relation to risk of adverse events on these anti-amyloid antibodies.

Dr. Isaacson:
Very brief, concise, but impactful.

So thank you to Dr. Chong for that highly topical question. I invite all of our viewers to check out our other episodes to hear more of what clinicians want to know about amyloid-targeting therapies. Thanks so much for listening.

Announcer:
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