# Bridging Community: Collaborative Efforts in Early Detection and Intervention for Alzheimer's Disease

**Ariel Cole, MD, CMD, FAAFP:** Hello and welcome to **Bridging Community: Collaborative Efforts in Early Detection and Intervention for Alzheimer's Disease.** I'm Ariel Cole. I'm a primary care physician, family-medicine trained with a specialty in geriatrics. I'm program director for a geriatric medicine fellowship with AdventHealth in Orlando, Florida. I have some excellent colleagues joining me today, and I'll turn it over to them to introduce themselves.

**Alireza Atri, MD, PhD:** I'm Ali Atri. I'm a cognitive neurologist. I'm the Chief Medical Officer for Banner Research. I take care of patients and families with early onset or atypical Alzheimer's and dementia.

**Elizabeth Poynor, MD, PhD:** I'm Elizabeth Poynor. I am a gynecologist, GYN oncologist, midlife women's health expert. I'm chair of women's health at Atria Health and Research Institute.

**Anton P Porsteinsson, MD:** I'm Dr. Anton Porsteinsson. I'm trained as a geriatric psychiatrist. I singularly focus on the care and study of older individuals with memory disorders like Alzheimer's disease. I'm the William B. and Sheila Konar professor at the University of Rochester School of Medicine.

**Dr. Cole:** Our learning objectives for this session are to integrate strategies into care plans that optimize brain health for patients with factors that increase the risk of cognitive decline and Alzheimer's dementia, describe the latest evidence supporting the need for the early detection of mild cognitive impairment in the Alzheimer's disease continuum, and develop patient-centered communication strategies to address brain health and cognitive concerns with patients and their caregivers.

Many patients and caregivers ask me what the difference between Alzheimer’s and dementia is. I explain, as you can see, that dementia is an umbrella term for a variety of disease processes that cause progressive memory loss, loss of memory and other thinking abilities severe enough to interfere with daily life. Alzheimer's is the most common of those, but there are other causes including Lewy body, frontotemporal, vascular, and mixed dementia (which is fairly common as well).

There are categories in the cognitive disorder spectrum. We're familiar with patients with early heart failure or chronic kidney disease. The same is true for Alzheimer's, and that there are patients who have disease process ongoing without symptoms yet. Those would be in the cognitively normal and then the disease progresses to mild cognitive impairment and dementia. Alzheimer's disease, as we said, the most common type of dementia, produces significant cognitive impairment affecting social or occupational functioning and representing a significant decline from previous level of functioning.

That decline is slow and progressive and has a long pre-symptomatic phase, probably in excess of 20 years. Dr. Alois Alzheimer when he published about this disease process, identified plaques and tangles. We now know that those plaques represent extracellular amyloid beta deposition, and the tangles are composed primarily of hyperphosphorylated tau proteins.

**Dr. Porsteinsson:** Alzheimer's disease has a complex neuropathology. There are multiple mechanisms that come together to contribute to the pathogenesis and progression. Brain amyloid accumulation is clearly involved, both soluble beta-amyloid as well as deposited beta-amyloid that forms the plaque, but it is also clearly not the entire cause of Alzheimer's disease.

How do we know that? There are multiple pathologies that we see when we look at the brains, but also even if we are able to fully clear beta-amyloid plaques with a new anti-amyloid antibody medication, if we start treatment at the stage of disease that is MCI or mild AD, we are yet to see this intervention truly improve cognitive function or reverse the cognitive disability. It may slow the disease, but it doesn't freeze it completely.

Now, we can also see elevated brain amyloid, especially plaque burden in the brains of clinically normal persons in post-mortem studies. There are other pathologies that travel alongside the amyloid. One of the best-known is the hyperphosphorylation of the tau protein. That has its own impact. It's probably connected to the elevation of beta-amyloid that triggers this cascade, but we know that tau protein is damaging to neuronal structure and functioning leads to cell death and actually is in some ways closer connected to clinical decline than what we see with amyloid.

Now, tau interventions are actually an active part of clinical trials, be that the antibodies that target, especially the MTBR forms of tau, but also kinases that stop the hyperphosphorylation of tau. As you heard earlier, Alzheimer's disease is a complex disease with a complex pathogenesis. Reflecting that, diagnostic criteria have changed over the years. With the advent of biomarkers, and those biomarkers are both fluid biomarkers, increasingly blood, but also cerebrospinal fluid, in addition to the imaging biomarkers that we see with PET scans and the MRI.

In 2018, Alzheimer's disease was actually given a biological definition, and that is that in order to have Alzheimer's disease, you needed to have elevated beta-amyloid, tau pathology, and neurodegeneration. This was further expanded in August of 2023 when the NIA-AA definition was updated to use the most well-validated biomarkers. I think it is important to understand that not all biomarkers are equal. The gold standard is probably an amyloid PET scan, but those are cumbersome and expensive to use. We're increasingly seeing fluid biomarkers, and particularly blood biomarkers.

These include measures of A-beta 42 but also p-tau 217, p-tau 181, and p-tau 231. I expect to see those blood biomarkers come more and more into doctor's practices over the next few years. The PET scans include both beta-amyloid PET, which we can access clinically, as well as tau PET, which mostly is done in research right now. There are other biomarkers, because Alzheimer's disease is more than just amyloid, tau, and neurodegeneration. We also have neuroinflammation as well as co-pathology through vascular injury as well as alpha-synuclein, which is actually the abnormal protein that we mostly see in dementia with Lewy bodies as well as Parkinson's disease but can be seen in Alzheimer's disease as well.

**Dr. Cole:** I was going to see if you had a recommendation on the p-tau blood tests as to which is most sensitive or specific.

**Dr. Porsteinsson:** In terms of blood tests, the test that is rising to the top is p-tau 217, which is a sensitive marker of the presence of amyloid pathology and is about 90% as sensitive as an amyloid PET scan.

**Dr. Atri:** I think one of the nuances is there's lots of differences in the different assays and vendors. Hopefully, we will have more FDA guidance about that very soon. There have been some long-established risk factors for just general dementia, not just Alzheimer's disease. We know that age really is one of the strongest risk factors. Women tend to also, particularly for Alzheimer's disease, be more at risk. They tend to live longer, but independent of that, there's something else.

Certain ethnicities in the US, for example, I think African Americans tend to have a higher risk of all-cause dementia. There are probably about 20 to 30 different genes, about 20 of them maybe

modifying some of your risk up and down. The largest one is E4 for Alzheimer's disease. That is a risk factor. Of course, anything that's bad for the blood vessels in the heart, so smoking, type 2 diabetes, metabolic syndrome, hypertension, all the things that I know Dr. Poynor, Dr. Cole, and Anton and I try to advise people about.

We're still trying to develop different dementia risk assessments to combine them. As far as risk, this is certainly an area, based on this program, you can see of great interest, combining everything from demographics and background history with results of certain genetic tests. We now have biomarkers, certainly, for Alzheimer's disease. We're developing others for things like alpha-synuclein.

Of course, one of the major things for case finding is really looking at someone's profile, either with kinds of testing or baseline neuropsychological evaluation in the appropriate setting. There's always an appropriate person for this, whether it's a risk or case finding. The information and how it's presented really has to be put in a nuanced way. I'm interested to hear if anyone here has any comments about how they usually do this.

**Dr. Cole:** As with everything in medicine, it needs to be individualized to the patient, right?

**Dr. Atri:** Absolutely. With that, I would say if you haven't read the Lancet Commission, it's worth a look at least to be on your desktop somewhere and to share with your patients and families. Basically, in 2017, they started doing a big review, identifying nine existing risk factors. Then in 2020, they added three more. The three more they added was alcohol consumption, head injury, and air pollution.

Basically, there's a lot of epidemiology and other evidence that suggests that, overall, from a population and also in an individual standpoint, you can modify your risk. It doesn't mean that you can absolutely prevent dementia, but could you delay it? Could you slow that impairment and get people to a different age where dementia doesn't really manifest itself? Ultimately, they suggest that up to 40% of the risk is modifiable.

Early education, for example, would give you more reserve. Anything that builds your resilience and reserve is good, and anything that really increases your vulnerability is bad. In midlife, hearing loss is really a big one. Head injury, hypertension, excessive alcohol use, and excess weight, so trying to lose that weight and have good weight in midlife is important. Even in late life. Really everything from even smoking, depression, social isolation, physical activity is a huge one.

**Dr. Cole:** A 52-year-old female with hypertension, obesity, a history of depression, traumatic brain injury, and a family history of Alzheimer's disease presents for a routine checkup. Despite being aware of her risk factors, the patient struggles with maintaining a healthy lifestyle due to socioeconomic constraints and a demanding job. Dr. Poynor, I imagine this is a familiar patient for you, as she is for me. I'm wondering how you would approach this patient.

**Dr. Poynor:** The average age of menopause in the United States is 51, so I would assume that she's probably perimenopausal or just soon after postmenopausal. I would love to see what her menstrual status is, actually, because we're going to talk about a little bit in the impact of estrogen on the brain. This is a time in a woman's life where everything gets worse. Blood pressure gets worse, insulin resistance increases, depression. Of course, if you have a history of depression, it gets worse. Lack of socialization. A lot of those behaviors of the time in menopause are antisocial. This is when women, I think, physiologically and lifestyle-wise are most at risk.

I try to, with the patients that I care for, point this out to them and say, "This is a time where you can really be proactive about your health, and this is a time really to harvest your health and really pay attention to it, and to really begin to look at everything and how you can impact it." I also think that a

lot of time when women are in perimenopause and menopause, that there is obviously a lot of depression and anxiety, but also a lot of worry about, "I'm feeling worse. I'm looking worse. I'm not as active." I try to highlight, again, that this is a time where if we pay attention, be proactive, we can really change the trajectory of our health and wellness, including cognitive abilities later in life.

**Dr. Cole:** Yes, absolutely. Knowing that she has some socioeconomic constraints, a demanding, probably stressful job, I would want to understand what her obligations are at home to a spouse or family. Even making small changes can build a snowball.

**Dr. Poynor:** Exercise is so important, that you don't really need to go to a gym. Or "I can't get to the gym, and I can't get to a class." You can do calisthenics at the end of your bed every morning, or you can do Zumba to a tape. There are all sorts of things that you can do that actually don't cost any money and don't cost a lot of time. Same thing with nutrition. I want to do, how do you go to Target and eat healthy? What can you buy? Frozen berries, that type of thing. I think especially when there's socioeconomic barriers to improve lifestyle, it's really important to help people get a plan that you don't have to go to a gym, you don't have to go to an organic food store, that you can actually eat super healthy and exercise with limited resources.

**Dr. Cole:** Absolutely. There are a number of apps and resources on the internet that can help people, even at no cost, to keep track of exercise and nutrition.

**Dr. Poynor:** I don't know that the Lancet study looked at menopausal status and that type of thing, and HRT use. That was just left hanging, I thought, in that study. More to come on that, I hope.

**Dr. Porsteinsson:** I couldn't agree with you more. Putting on my psychiatrist hat, I worry about the stage of life and the changes and the pre-existing depression, and how well is that treated? Because untreated depression can exacerbate so many of the conditions that she has. We know that is also a risk factor for developing Alzheimer's disease. She is at more risk because of her family history, and basically a comprehensive approach to treat some of the obvious problems but also encourage healthy lifestyle and healthy diet can really bend the curve. Maybe on multiple of the conditions that she either faces now or that she's at risk for later.

**Dr. Poynor:** Sleep also needs to be addressed in this patient. It's super important. About 80% of women have sleep disruptions at the time of perimenopause and soon after menopause, which is still perimenopause. Sleep can exacerbate all sorts of cognitive issues, of course, depression issues, nutrition. I would definitely address sleep in this patient also.

**Dr. Atri:** I completely agree. I think that along with sleep goes a bunch of other things, "Oh gosh, I can't sleep. I'm going to drink a couple of glasses of wine." How big are the glasses of wine? "Am I going to take some Tylenol PM with Benadryl in it, diphenhydramine?" All those other things add up. There's a challenge that requires teaming up with her and making some small changes, things that she's willing to do.

**Dr. Poynor:** I love that concept of teaming up with her. I think that's really important, because I think, again, at this time of life all of this can seem so overwhelming, and just to put pen to paper and help her get that plan is so important.

**Dr. Atri:** Encouraging her to take small steps. All of us fall off the wagon about what we want to do but just having someone who's advocating with her as a team member to say, "Hey, I'm interested in this with you. Let's have this part of the plan that we're going to check up on. No shame, just let's start to do small things."

**Dr. Poynor:** I have a 90%/10% rule:  90% of the time if you're good or 10% of the time if you fall off the wagon, it's okay.

**Dr. Atri:** I may be more lenient than 90/10.

**Dr. Poynor:** Maybe 80/20 is a good goal.

**Dr. Cole:** It's a good goal.

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**Dr. Porsteinsson:** Coming back to Alzheimer's disease, why is it important to identify early? Part of it is that there's power in knowledge and you can prepare. It's awful information to have. "Hey, you're on the road to likely developing Alzheimer's disease," but ignoring it or misattributing it isn't associated with better outcomes, for sure. Early diagnosis allows you, again, to make decisions to maybe change your lifestyle, do more exercise, manage your health, tell people how you would like to handle your life and end of life decisions during the course of the disease.

Basically, access medications such as the disease-modifying treatments, if that is something likely to help you. Ultimately though, early identification, particularly if we can identify people at the preclinical stage, will allow us to do prevention interventions. We've talked about some of the things that can bend the curve. Why is this important? Because current treatments are inadequate.

We know that through the use of biomarkers, we can identify people at risk, be that genetic risk factors or fluid biomarkers or imaging biomarkers, and prevention, be that lifestyle and exercise and diet, or possibly pharmacological interventions are most likely going to be more effective at this stage, because protecting intact neurons is a better proposition than trying to replace the ones that are already dead and gone.

**Dr. Atri:** When you think about the risk-benefit calculus of all the things we're suggesting for healthy brain strategies and behaviors, the downside is so little, but the potential gain may be huge. I always tell people, "I don't know what's going to interact, whether it's the medicines we're giving you or other things." If you get better blood pumping to your brain or other things, there may be a main effect of all this stuff and an interaction effect that could really help you. I don't have the crystal ball yet. I like how you present it.

**Dr. Poynor:** I'm going to shift over to female-specific largely related to estrogen risk and fluctuating hormone levels at the time of perimenopause and menopause on the female brain. There are definitely structural and functional changes that have been identified with the brain at perimenopause. Perimenopause are the years leading up to menopause. We typically define our reproductive hormones and how they decline over ovarian aging as late reproductive years, early perimenopause, late perimenopause, and menopause.

Late reproductive years will be between the ages of 35 and early 40s, and perimenopause for many women will start in the early 40s. Perimenopause is defined by maybe changes in menstrual patterns, maybe longer time between periods or heavy periods, but also you have to listen to the narrative of a woman. A woman will say, "My memory is changing. I may have some brain fog," far before she misses any periods. Super important to take that history and realize that women in their early 40s are actually beginning to have fluctuating hormone levels, especially estrogen levels.

The brain at perimenopause undergoes structural and functional changes, changes in energy metabolism, and cognitive and mood changes will also occur. Cognitive change is not related to dementia but related to just the declining hormone levels. The structural and functional changes that can occur are actually gray matter volume can decrease in certain brain regions during perimenopause, but interestingly, this will recover after menopause. There's some adaptation that the female brain goes through when she goes through perimenopause into menopause. How that impacts her risk of Alzheimer's disease is not known currently, and that research is being done.

Functional MRI studies also can show altered spontaneous brain activity at the time of perimenopause. Then multimodal MRI studies have revealed changes in brain structure, function, and also perfusion during the time of perimenopause. These functional MRI studies now are really ongoing on a large scale in the United States, the United Kingdom, and also in Australia. We really look forward to getting that information in the future.

Energy metabolism in the female brain also changes as estrogen levels decline. The female brain enters into a hypometabolic state where it can't rely on glucose the same way and actually depends more on fatty acids for metabolism. This actually leads to altered mitochondrial activity that you can actually see on imaging and also reduce cerebral glucose metabolism at the time of perimenopause.

Importantly, cognitive changes and mood changes can occur. We talked a little bit about mood issues which can occur. Depression can get worse. Anxiety can crop up for the first time in a woman's life at the time of perimenopause. This is actually really where the neuropsychology group comes in and can really key into this at this time in a woman's life in reproductive years.

Many women will notice what we call brain fog, which is some type of nebulous cognitive change at the time of perimenopause. Word-finding difficulty becomes apparent at this time. Verbal memory clearly is off with this word-finding difficulty. Women will also have executive functioning issues, ADHD actually that wasn't diagnosed before will be uncovered at this time of a woman's life, and she'll many times be totally terrified that she is having early dementia.

How this brain fog transmits into dementia risk in the future, we don't know. A lot of it may be related to vasomotor symptoms and other symptoms of menopause related to lack of sleep and other issues such as this. There are also elevated MAO levels during perimenopause, which also may be contributing to oxidative stress, apoptosis in the brain, and further influencing mood and cognitive function. Fluctuating estrogen, and I'll go over this in just a minute, actually really impacts the female brain at multiple levels.

We talked a little bit about this early for a health assessment for women at midlife because women go through metabolic shifts, cardiologic shifts, and also cognitive shifts at midlife. We always say that healthy heart health and healthy metabolic health is healthy brain health. Women have more than twofold increased risk of developing Alzheimer's disease when compared to men, and more than two-thirds of Alzheimer's disease patients are actually women. I don't think we really understand why, but a lot of the neurophysiologic impact of estrogen decline during menopause is emerging as the basis for this higher prevalence of Alzheimer's disease in females.

Only 0.5% of neuroscience studies look at women's health, despite there being many differences between men's and women's brains. From the research on looking at large epidemiologic studies, which include some randomized controlled trials along with observational studies, people are coming to the conclusion now that there is a critical window for neuroprotection when hormone therapy is used at the time of perimenopause, and menopause hormone therapy will actually help to correct some lipid abnormalities and help to also reduce risk of insulin resistance.

There's also now an emerging thought that it may have some impact on brain health and the risk of Alzheimer's disease in the development in the future. Some studies, this has been a very complex issue to look at, but the new emerging thought is if menopausal hormone therapy is initiated soon after perimenopause or menopause, that it is protective. However, if it's used later in life, it actually can be detrimental. Later in life, meaning over 10 years after the final menstrual period or over the age of 60.

Current guideline recommendations advise against the use of estrogen for dementia prevention, but data is really emerging on this topic, and people are beginning to look at this. This is really going to depend on timing of initiation and also type of estrogen used. In the past trials, especially the Women's Health Initiative Study, used estrogens and progestogen, which we don't use anymore.

The Women's Health Initiative Study, actually, used estrogen that is derived from a pregnant mare and used a synthetic progestin. There may be some differences in these types of estrogen on their impact in the brain because the types of estrogens used in the Women's Health Initiative Study, which showed little benefit of hormone therapy on dementia prevention, had a combination of estrogens with estradiol and estrone. Estrone may be inflammatory. We need to really clarify what types of estrogens are protected for the brain and which may actually be harmful for the brain.

These studies have been randomized controlled, like the Women's Health Initiative Study, which really demonstrated that hormone therapy, if initiated later in life was not protective against dementia, and if initiated early was maybe neutral with dementia. Some studies, larger, were observational studies have shown that hormone therapy may not be protective. We really need to drill down on this data and really get the appropriate studies in the future looking at estrogen and progestogen type, along with timing. It may be a great opportunity to use biomarkers to look at this in the future also.

**Dr. Atri:** No matter whether you're a patient, you are the spouse, symptoms, not symptoms, MCI -- it's really, really important to focus on brain-healthy strategies. The risk-benefit calculus is really in favor. People ask about what diet is the best, I say, "The best evidence is for the Mediterranean and antihypertensive diet. The mind diet. But really it's important to eat something that's well balanced." Not to spend too much money on nutraceuticals and things you see on TV that really don't have an evidence-based, not a bad idea to take a senior multivitamin.

Blood pressure, glucose, cholesterol, metabolic syndrome, weight, head trauma, stroke, smoking, but making sure you're not taking drugs like a long-term like anticholinergics, et cetera, that are on

the Beers list, that are bad for the brain. Sleep, really, really important. Sleep apnea, correcting that if possible. Then I really talk about managing stress and depression and stating that this is something that doesn't mean that you are weak if you have to take something or talk to somebody or do these kinds of things.

These are biological responses that if you are chronically in a stress state, then actually there are hormonal changes, cortisol changes, other changes that don't allow repair, so you want to get into that relaxation response. There are things we talk about there. We talk about how having a positive life perspective and attitudes and having meaning, a life purpose, is a commonality between people who have longevity and vital aging, and the people really shouldn't be defined by a disease. Yes, you have Alzheimer's disease, the Alzheimer's disease has been in the brain, the changes occurring over 20, 25 years. Now you have knowledge, and it's still important to have a realistic perspective but do things with purpose.

Connecting with yourself and others is really, really important. Social engagement. People ask about exercising your brain. I say, "Look, it's not about doing Sudokus day and night. It's not about getting frustrated to the point of making your loved one do these things where they're really frustrated. It's just about having the balance of the just right activities, multiple things that are novel, a little bit challenging, and fun. Learning a new language if it's possible, playing bridge, which is amazing as a social aspect, things like that.

I talk about participating in research when people want to know what they can do to help with breakthroughs and some of the aging studies and other studies, they can actually learn about their risk. Some are observational and some are treatments. Really, the number one, number two, number three thing that I talk about is physical activity and exercise. I say, "Look, if I put everything together and it could help your brain, I would give it to you, but I don't. It's called exercise."

I talk about the big muscles in the leg as they're activated, and the heart's pumping, how it affects DNF, the brain-derived neurotrophic factors, that really are the only things that are tipping the balance between building again. After age 30, we start breaking things down. Really talk about that. When they say, "What kind of exercise?" I say, "The kind that you're going to do." At least starting and partnering together to think about what that is and ultimately working up to something more on the lines of four or five times a week of being engaged. That barrier to starting is really, really important.

**Dr. Cole:** Great. Thank you. I suggest patients learn to dance that might be interested, because that's both physical and cognitively challenging. We've talked a bit about the genetics and the roles that different genes play. Many of our patients may even know their APOE4 status because that is reported in some of the over-the-counter genetic testing that can be done. About 25% of people carry one copy of APOE4. You got your alleles one from each parent, and you've got a copy of either two, three, or four from each parent. About 2% to 5% of the population in the United States carry two copies of APOE4. Carriers of one allele have three times the risk of developing Alzheimer, and two alleles have 10 to 30 times the risk of developing Alzheimer by the age of 75, compared to those not carrying APOE4 at all.

There are other mutations that have been identified that increase the risk of Alzheimer, some that cause overproduction of Aβ peptides like presenilin and amyloid precursor protein, some that reduce the clearance of that amyloid, and some that just generally produce inflammation in the brain. Then there are some rare patients that have a deterministic gene. These represent less than 1% of the total Alzheimer patients. Often there's a very strong family history, obviously an autosomal dominant pattern, and an onset of symptoms at a very unusually young age. There are several genes that have been identified that are involved in these families.

We do know that our patients with Down syndrome, with trisomy 21, the amyloid precursor protein, is on chromosome 21, and these people have a very high risk of developing Alzheimer at a younger age. There have been some developments in lab testing. Dr. Anton brought some of these up earlier. At this time, they're for use in patients with some cognitive decline.

**Dr. Porsteinsson:** Currently, the recommended biomarkers for a biomarker verification of patients that are going to undergo disease-modifying therapy with amyloid targeting antibodies, that would be lecanemab and donanemab, is either CSF fluid biomarkers or PET amyloid biomarkers. The reason for that is that certain ones of these are FDA-approved. With that, insurance is more likely to cover that or accept that as biomarker validation. In fact, though, the FDA does not specify that these are the only biomarkers that they can use. The way that I read the label is that you could use any biomarker that you feel confident is predictive of amyloid burden. We'll see if blood biomarkers become more common here as we establish better and better their validity.

**Dr. Cole:** All right. There is no shortage of rating scales for cognitive impairment. Like me, you may have learned the MMSE back in medical school. I personally use the Montreal Cognitive Assessment in my office. It takes 10 or 15 minutes, perhaps, and I find that that's manageable. In fact, on the next slide, I've got a picture of the Montreal Cognitive Assessment. This is accessible. It is not copyrighted. It is not completely intuitive to administer this test accurately. There is a training course produced by the authors that will walk you through for a fairly reasonable fee, a training in how to administer this test accurately.

I point out the Clinical Dementia Rating Scale because this is what was also utilized in a number of the studies on the newer monoclonal antibodies medications. For the most part, patients who improved with the use of these medications or showed a slowing of cognitive decline had a CDR scale in the 0 to 0.5 range. Once they got into the 1, 2, or 3, they did not show any improvement, or the improvement was much less. This is partly adding to the impetus to identify patients appropriately.

Next, we're going to move to talking about the newer monoclonal antibody therapies for Alzheimer. Aducanumab was the first of those that was approved back in 2021, with some controversy around that FDA approval at the time. It's a once-a-month IV infusion that showed some slowing of cognitive decline relative to placebo in those patients with mild cognitive impairment or mild dementia in one of the two studies that were ongoing. That's why it was granted this accelerated approval with a requirement to prove further evidence of effectiveness. It's not on the market anymore. The two that are currently available are lecanemab and donanemab. Lecanemab was approved in 2023 and donanemab in 2024.

Lecanemab is every two weeks IV infusion and donanemab is, again, once a month, IV infusion. Both of them are titrated doses, and both have shown some effectiveness in slowing functional and cognitive decline by reducing those amyloid beta plaques in the brain. In fact, these medications, I think we can say as a rule, are very effective at reducing and even eliminating with ongoing use the amyloid beta plaques in the brain. That seems to translate into about a 30% reduction in progression of cognitive impairment. Do you agree, Dr Ali?

**Dr. Atri:** Yes. I think the major thing is that we are -- I call this the end of the beginning. It's a foundational step for us with disease-modifying drugs. These are not cures. They don't have expectations of cures. They're our first generation of clinical drugs. There's a potential side effects and safety issues that we have to think about. Choosing the right people. Just like we did with MS 25 years ago, these drugs are doing something in addition to our symptomatic drugs that we already had for a long time, because they're affecting the biology.

On average, they're slowing down, very consistently, cognitive decline, functional decline, progression by about 20 to 40%. That's the average effect. That just gives us a toehold, which is very exciting that we can build on. This is not where we want to end up. What we're also understanding is that probably starting it earlier with people with less tangles, there's probably going to be a bit more efficacy for those folks.

**Dr. Porsteinsson:** Ali, you're absolutely right. This is the first step. Depending on the outcome measure for the disease-modifying treatments then, I'm referring to lecanemab and donanemab, we see about 20% to 40% slowing in the progression of the disease. We haven't seen that with anything else before. Obviously, we hope to find the people that are going to respond most favorably. It seems that those that have earlier disease and less disease pathology in the brain, for example, overall lower tau tangle burden and even possibly lower amyloid burden do better. In fact, some of the ones with the mildest disease had the stability for the full 18 months of the treatment. It brings home the message that we started out with, and that is early diagnosis, early recognition. Then the question becomes, how do we operationalize this?

**Dr. Atri:** One of the main things about ARIA is to define what it is. It's amyloid-related imaging abnormalities. This is not a symptom. These are things that for over the last 20 years, and I've been working on it in clinical trials for that long, that we've noticed is a system-wide, a class effect for these types of drugs. In clinical trials, basically, we've had surveillance MRIs that picked this up. There are two kinds. There's the edema effusion kind, swelling, or the hemorrhage kind, oftentimes microhemorrhages, rarely something bigger. That's what we have to worry about, the macrohemorrhages.

Generally, ARIA is something that in clinical trials, and as we've done this in clinical trials and now into clinical care paradigms, is something we pick up on imaging, on MRI surveillance. It's really, really important how we pick the right patients, as you mentioned, Anton, having a patient-centered discussion. They have to be in the right clinical stage. They have to be amyloid-confirmed. We have to know the E4 status. Why? Because the major risk of developing ARIA is actually E4 status. Individuals who have one E4 have a higher risk, two E4s have a much higher risk. They have basically more burden of amyloid plaques and they have leakier blood vessels.

Generally, again, this is picked up on imaging, not because there's a symptom. Somewhere between 5% and 15%, depending on the drug and the dose, et cetera, and the timing of individuals without any E4 can develop ARIA sometime during the first usually six months of treatment. Anywhere between 15% to 20%, 22% of E4 homozygous can have a developed ARIA at some point. As far as homozygous, the number's much higher. Somewhere between maybe a third to over 40% can develop this.

Again, 75% or so of these imaging abnormalities come without symptoms. Really, we want to pick it up so that we prevent it. We have an algorithm to know whether we continue, whether we pause because we don't want to continue to infuse somebody who may have mild ARIA that's not symptomatic or to become symptomatic or become really severe ARIA and become a problem. I'm part of a group called the ADRD Therapeutics Work Group that puts out these appropriate risk recommendations that really talk about how to translate this stuff from clinical trials to clinical care along with the prescription information.

One of the issues is that if ARIA is symptomatic, and that's, again, less common, it could show up with something that is very, very non-specific. They may say, "Oh, I have a small headache," and they may brush it off as something else. Certainly, things that are a change in mental status, a change in balance, gait difficulties, sometimes people say they become dizzy or nauseous, particularly visual changes if they have the ARIA in the back of the brain, which is not uncommon.

It's really important to have a symptoms checklist to talk about these with the patient or the family members, and prior to infusions, really talk about whether they've had any of these. As Anton mentioned, there are scheduled surveillance MRIs that are put in the clinical paradigms for these, but sometimes you may have to do it with unscheduled MRI, and you have to have the right kind of MRI. That's also important.

Rarely, very uncommonly, you could actually have severe reactions. Those are the things we're trying to prevent. People have had seizures, they've had status epilepticus, they've had blood pressure that is so malignant, they'd have to go to the ICU, intracerebral hemorrhages. Rarely have there been fatalities, both in clinical trials and now in clinical care. Again, all this can be mitigated by having a close relationship with prescribing physicians, with neuroradiologists, with EDs. This is not something that right now is a completely new paradigm of care, and that's where the gaps are. It's not that we don't know what to do in clinical trials. It requires that proficiency, communication of those resources, and those protocols and pathways to be placed.

In many communities, right now, that's lacking. We have to build that infrastructure, including proficiency of neuroradiologists, having access to the scans before having EDs, that's where actually a couple of fatalities have occurred. The burdensome part of it is also that right now, it's a pathway that is evolving.

**Dr. Porsteinsson:** Here, we have a 62-year-old male with concerns about memory loss and cognitive impairment that presents for evaluation. He has a strong family history of Alzheimer's disease and is anxious about his future. We are from four different specialties here, so maybe Dr. Poynor, this would be the least likely patient to show up at your door. Dr. Cole, this is what you probably see every day, someone in their 60s.

**Dr. Cole:** Absolutely.

**Dr. Porsteinsson:** How should someone who has a busy clinical practice and maybe is a non-memory disorder specialist navigate the practical challenges of early AD detection? What do you do?

**Dr. Cole:** I think this scenario is common. One of my favorite phrases is, tell me more. When you're saying you're having concerns about memory loss, I want to know more about that. Give me some examples. Who is involved in your life and has observed because we do know some patients forget that they forgot and might therefore somewhat minimize their symptoms, perhaps unintentionally. Family members, loved ones, people involved in their lives might really be able to corroborate that the cognitive impairment is having an impact on multiple domains, on executive function, et cetera.

It's also possible that having seen a family member struggle with this disease, this patient is worried about some changes that may not be clinically significant. There is some forgetfulness that is a normal part of aging. Teasing that out, and is this a change for him, and is this a change from what he should be expected based on his intelligence and functioning? Sixty-two in my world as a geriatrician is very young, but we do know that Alzheimer's can have an impact.

**Dr. Atri:** Dr. Cole, for me, 62 is right in my sweet spot. As an early onset cognitive impairment and dementia specialist, we arbitrarily have 65 or younger as the age of onset of changes. This would be right in the sweet spot. As you mentioned, I think folks like this have to tell me more in a structured way. I hear their concerns, think about their risk factors, think about cognition, function, behavior, motor changes potentially, go through that history, and then have some sort of standardized testing.

Unless one is really, really confident that one can say, this is really a cognitive change that is potentially age-appropriate, one can think about the diagnostic and evaluation pathway in someone

at this stage, if they're very, very mild and high functioning, potentially neuropsychological evaluation, and then, of course, all kinds of lab panels, MRI in the brain, and beyond. Very, very important in the same way that somebody shows up at 62 and they say, "Oh, I've got some pain right here." People don't laugh it off and say, "Oh, you're 62. Everybody has some chest pain." We do the evaluation. We take the history. We do the test. I think this would be appropriate also.

**Dr. Porsteinsson:** What I've been thinking about is, how do we facilitate the conversation between those in primary care, for example, and those in specialty care? Those of us that are in specialized memory disorder clinics, we don't have the bandwidth to take care of everyone. In fact, the majority of people with Alzheimer's disease are cared for in the primary care setting. How do we facilitate basically treatment and identification now that we have disease-modifying treatment options and that this early intervention becomes so critical? I'm not sure that we have fully worked that out.

**Dr. Atri:** Just the evaluation pathway for someone with suspected cognitive impairment that may be on the neurodegenerative spectrum, potentially. This is something that I have to say, after seven years, we've had an Institute of Medicine process with 7,000 plus reviews and a multidisciplinary work group, and these were just recently published. This is the Alzheimer's Association clinical practice guidelines for the Diagnostic Evaluation, Testing, Counseling, and Disclosure of Suspected ADRD. These executive summaries for primary care specialty and subspecialty care, the approach to the evaluation, the clinical instruments are in this Alzheimer's and Dementia special edition that was just published.

There are 14 articles, and a link will be given to them. The idea really was that for the first time, we want to update the approach to the evaluation in multiple settings, not just the cognitive behavioral neurologist, not a geriatric psychiatrist, but what is the best evidence for every setting. Again, it starts with seven cores. The first part really thinking about the who, the person that may have a concern, they themselves, the clinician may have a concern, there's a change, or a loved one may have. This is not just somebody without a complaint.

In that, the major core is to establish shared goals. This oftentimes involves the person and you may need a care partner, and what points of history to go through, what structured multi-domain systems reviews to go through, what instruments you may be able to use, what are the risk factors, all these are delineated in the executive summary, and backed up by, really, the gory details that are also online that are available.

Then it talks really about the care partners too, and how they're affected, and how it's important to partner with them. We certainly know that care partners at some points may become caregivers and that there's incredible stress and burden on them, both medically and psychologically, rates of depression are high. For every person with dementia or Alzheimer's, there's probably three people that are helping to provide the care. We know that we really have to focus on the diet. This is an interesting triadic relationship that usually doesn't happen in medicine, unless with pediatrics, where you have the clinician team, really partnering with the person with the illness, in this case, AD or ADRD, and another care partner.

Then we talk about really stigma and how that affects and how to encourage patients and families to be open to that and aware of that and to deal with it. I want to open it up to you, Dr. Cole and Dr. Poynor, and Dr. Porsteinsson, about your thoughts about some of these things, about care partners, stigma, how do you approach things.

**Dr. Cole:** Great points about supporting the care partner. There are a number of national organizations that are available to do that. The Alzheimer's Association is one of them. I appreciate

that they have a 24/7 free helpline a care partner could reach out to and call and ask for help about a specific concern or ask for help with navigating this complex healthcare system that is not easy for our patients. Other resources under the NIH and the CDC and the Alzheimer Foundation of America provided some websites there for you.

I think no one should leave an office with a diagnosis without some resources to access related to gathering more information. The American Academy of Family Physicians also has some resources on these websites, including a course on dementia care.

We've got a 75-year-old female with her daughter, and they are concerned about recent memory issues. The patient is resistant to discussing cognitive health with her healthcare provider due to fear and stigma. How can we approach brain health discussion with this patient and her daughter? One thing I like to say is that memory loss is common, but not normal. A lot of patients will say, "My friends say they're having the same problems." I say, "They may, but you're my concern right now. I am worried about what you're expressing, what your daughter's concerned about. Let's explore this further."

**Dr. Poynor:** I think also so many people with memory issues are just terrified. They don't think that there's any intervention. I think that we have to provide context that there's actually something that we can do to help you. That, I think, is super important.

**Dr. Atri:** The earlier the better to empower them to have the autonomy. I think it's not also uncommon to see this in my practice. They're brought in, they're concerned. Sometimes they're not concerned because they may not appreciate they actually have an issue also, which can be part of some of the illness. I always try to think about how I can partner with them to understand, what are your priorities? What are your goals for the next 5 years, 10 years? How does this fit in with that? How can this knowledge empower you to make the right decisions for you? I say, "Look, I'm your advisor. I will look you in the eye and I'll tell you the truth and guide you. What sort of knowledge is important? Because those are the kinds of things that I can empower you with."

**Dr. Porsteinsson:** That's a good point. I liked, Dr. Cole, when you pointed out that memory changes or memory loss are common but may not be normal. I point out that, yes, you're referring to the fact that the memory changes are common as we age, but sometimes that is a signal of an impending problem. Let's work together to make sure that that's not your situation. Sometimes that works, sometimes it doesn't, because you pointed out also, Dr. Poynor, that people are terrified. If they've had their personal experiences, this is one of the diseases that people fear the most.

We have to just acknowledge that it's life-altering, but the best we can do is to basically partner and say, "I'm here and I'm here to make sure that you are as functional as possible for as long as possible. If we determine today that this is not something to worry about, well, then we will part ways until maybe the situation changes 5 or 10 years from now. Today's the day and let's look at this in more details, so tell me more."

**Dr. Cole:** This is where primary care providers are really well positioned. They may often be the physician for the caregiver or care partner, as well as the Alzheimer patient. I think stigma contributes to why this is often not identified early because, unfortunately, there's some shame and avoidance of the symptoms.

**Dr. Poynor:** I think for the OB-GYN, I think to have a tool to begin to look at mild cognitive impairment, and not to normalize memory loss. I think for a lot of women, especially now as primary care providers become a little bit more scarce, at least where I am, and a lot of women will still see their

gynecologist, it's really important, I think, that we educate OB-GYNs in terms of how not to normalize, what tools can you use, and what are the resources available to you in your medical community to get the person the right care? Because time and time again, I've seen people drift away and don't go to the memory center but don't get any care, basically.

**Dr. Atri:** That relationship with primary care clinicians is really important. It's really foundational. I think we've done studies and we know the data. People trust their primary care clinicians. They want to be guided to where to go. That's really, really important.

**Dr. Poynor:** Especially for OB-GYN, when women have a higher burden of Alzheimer's disease. I think that the people who specialize in women's health should understand what tools are available to them.

**Dr. Atri:** Women are unduly also caregivers, oftentimes. I think there's a double hit there that happens.

**Dr. Cole:** Thank you all for your expertise and for participating in this course with me.