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Reimagining Alzheimer's Disease: New Thinking, New Choices

Announcer Intro:
Welcome to CME on ReachMD. This activity, entitled "Reimagining Alzheimer's Disease: New Thinking, New Choices", was developed through the joint providership of the University of Cincinnati and CORE Medical Education, LLC. and is supported by educational grants from Biogen and Lilly USA, LLC.

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Dr. Russell:
Alzheimer's disease, or AD, is the most common cause of dementia. Today's program examines recent advances in the development and utilization of tools that help with the early diagnosis of AD leading to a newly improved and emerging disease-modifying therapies, as well as non-pharmacologic strategies for the management of patients with AD.

Coming to you from the ReachMD studios in Fort Washington, Pennsylvania, this is CME on ReachMD. I'm Dr. John Russell. Joining me to discuss the latest in the management of Alzheimer's disease is Dr. Scott Turner. Dr. Turner is the Director of the Memory Disorders Program and Professor of the Department of Neurology at Georgetown University Medical Center in Washington, D.C. Dr. Turner, welcome to the program.

Dr. Turner:
Thank you for having me.

Dr. Russell:
So, Dr. Turner, why don't we start today by looking at the big picture. Can you give us an overview of the prevalence and impact of Alzheimer's disease?

Dr. Turner:
Yeah, Alzheimer's disease is the most common cause of the dementia in the United States, 1 in 3 seniors dies with Alzheimer's or other dementia. Currently an estimate is at more than 6,000,000 Americans are living with Alzheimer's and that approximately 11,000,000 are providing unpaid care for people with Alzheimer's and other dementias. Between 2000 and 2019, deaths from Alzheimer's increased 145%, whereas some of the other major killers have actually decreased.

Dr. Russell:
Well, certainly that's taking up a lot of space in, medicine. Are there any new progress in the diagnosis and management of dementia for, myself as a primary and you as a specialist?

Dr. Turner:
Yeah, people think Alzheimer's disease has been a relative backwater, uh, research because there hasn't been really a new drug approved until this year for almost 20 years. But there has been a lot of progress in biomarkers and now we're starting to get some progress in treatment. The first commercial blood test for Alzheimer's became available in 2020, which is Precivity. The first tau PET ligand was FDA approved in 2020, which is flortaucipir. And the first, first disease modifying-treatment for Alzheimer's was FDA

approved in June 7th of this year, which is aducanumab. We also started in 2020 another prevention trial with another anti-amyloid antibody called lecanemab and this is, uh, looking for volunteers who are cognitively normal but have the earliest stage of pre-clinical Alzheimer's, which means they have just starting to get elevated amyloid on their PET scan.

Dr. Russell:
So, I have patients that come into my office and have, worries or family members has worries. So, for screening for Alzheimer's, what validated instruments are available to quickly screen for mild cognitive impairment in dementia in the people I'm seeing in the office?

Dr. Turner:
Yes, there are some quick cognitive tests, which are available at the website Alz.org, which is the Alzheimer's Association. And there are two types of screening tools; some of them are addressed to the patient and others to the partner or family or someone who knows the patient well. Some of the tests available for the patient are tests such as the Mini-Cog, which is a 3 minute patient screening tool of a three-word delayed recall and a clock drawing test. There's the GPCOG, which is a general practitioner assessment of cognition and the MIS, Memory Impairment Screen. I would recommend just picking one of these and becoming familiar with it. It does not have to be the physician who administers these tests, but some other medical professional in the office. And the website has the tests available to everyone with instructions for scoring and interpretation. I there's an abnormal score, then you would want to pursue either longer tests or refer onto a specialist.

The other, tests are addressed at the partner because we often get a very different story from the patient and the partner. Often the patient will say everything is fine but the partner reports, , clearly cognitive and functional decline. And test are available f- to, , the partner are things such as the AD8, which is an 8 item informant interview that differentiates aging and dementia. The Short IQCODE, which is the short informant questionnaire on cognitive decline in the elderly and the GPCOG, which is general practitioner assessment of cognition. Does not have to be the physician administering these, but other medical professional can become very expert in doing these g-, quick screening tests. And all of these, are available at Alz.or to download with instructions for scoring and interpretation.

Dr. Russell:
So I will see a lot of adults who come in and they'll be very worried, my parent had Alzheimer's, what should I be telling this patient about their genetic risk? And in 2021/2022, what are some of the genetic tests I can offer to my patients who had a first-degree relative with Alzheimer's disease?

Dr. Turner:
Yeah there is some familiar genetic component to Alzheimer's disease. There are a few pedigrees or families in the world that have an autosomal dominant mutation in one of three genes, either APP presenilin 1 or presenilin 2. These are very rare, but they, we've learned a lot about Alzheimer's disease from these rare pedigrees. But the more, common gene of interest or specific to the sporadic form of Alzheimer's disease is the APOE gene and we have two copies of the APOE gene and APOE4 is the high risk gene. So, if you have one copy of APOE4, you're at three times the risk of people who don't have an APOE4, and if you have two copies or homozygous for the APOE4 gene, you have eight times the risk of individuals who don't have an APOE4. And approximately 25% of the U.S. population has at least one copy of the APOE4 gene. More recently, we've discovered the TRAM2 gene, which is associated with inflammation, which also has a variant which increases risk.

The APOE gene is important because not only does it increase the risk of Alzheimer's disease, but also c- increases the risk of amyloid deposition. It shifts the curve to the right of amyloid deposits increasing with age. So, the APOE22 is the lowest risk and rarely gets any amyloid deposition or in- or very low risk of Alzheimer's, but this c-, combination is very infrequent in the population. The highest risk is APOE44, which, increases risk of Alzheimer's and you start to see amyloid deposits in the 40s, 50s, and 60s and then the other combinations are in between those two curves.

Genetic testing is available to the public at, companies such as 23 and Me, which is direct-to-consumer testing, for APOE and other risk genes. In the clinic, we sometimes order genetic testing through commercial entities such as AthenaDiagnostics.com to look for the APP, PS1, or PS2 mutations, as well as the APOE genotype. And then last year, we can also do a blood test for Alzheimer's, which looks at the plasma-a beta ratios and also tells you your APOE proteotype.

Dr. Russell:
So, can we switch gears for a minute and talk about the use of imaging in the diagnosis and management of Alzheimer's disease? Are glucose PET, amyloid PET, and tau PET scans useful in the diagnosis and management of patients with mild cognitive impairment and dementia?

Dr. Turner:
We certainly recommend either a CT scan or MRI. MRI is preferable, and quantitative analysis is also a bonus to add to the, MRI scan.,

the FDG-PET scan is covered by insurance; it's, difficult to, order because of coverage but it's useful in distinguishing, frontotemporal dementia from Alzheimer's disease Amyloid PET and tau PET are still mostly in the research, , stage. There are three, amyloid PET ligands that are FDA approved. These are florbetapir, flutemetamol, and florbetaben. These are all usefully in detecting amyloid in the brain. This technology's been available to us for 10 to 15 years, but is not covered by insurance; it's certainly incorporated, , in our clinical trials, and more recent technology is the tau tangle PET scan. There's only one FDA approved ligand, which is flortaucipir, but there are others that are in the pipeline. So, these PET scans are allowing us to see the plaques and tangle pathologies int he brain of living individuals, whereas in the past, we had to wait until someone died and lo- look at these pathologies at autopsy. These imaging biomarkers have also been useful in telling us that these pathologies are starting 10 to 20 years before the onset of cognitive decline. So, amyloid PET scan it begins to become positive, 10, 15, maybe 20 years before cognitive decline occurs. This is followed by abnormal glucose metabolism on glucose PET scan. And then this is followed by abnormal tau pathology on tau PET scan. You can also measure these proteins in spinal fluid as are corollary of what is found on the, PET imaging.

Cognitive decline is, when you convert from normal aging to mild cognitive impairment and then when the cognitive decline begins to impact ability to function in your daily life, that's when you cross the line between mild cognitive impairment and dementia. But we know now that these, cognitive decline and the functional decline is actually occurring very late, 10, 20 years after these biomarkers are changing.

Dr. Russell:
So, what are the role of biomarkers? And how are biomarkers being incorporated into the diagnostic criteria for Alzheimer's.

Dr. Turner:
Traditionally, we've diagnosed Alzheimer's and other dementias based purely on the history and physical examination. And if you don't have any biomarkers available, then you would still base it on the history and exam. But we're trying to incorporate biomarkers more and more, not only into diagnosis but useful for prognosis, for prediction, for finding high, , risk individuals who will convert to mild cognitive impairment and dementia. And of course, we use these biomarkers as outcome measures to see if our new drugs are, hitting the target. So, we've divided these biomarkers into what's called the ATN classification. 'A' stands for amyloid and these are things like, , a-beta levels in spinal fluid as- or amyloid PET scan. The 'T' stands for tau or neurofibrillary tangles and these are measures such as CSF or plasma, phospho-tau or tangle PET scan. And then finally, there's 'N' or, markers of neurodegeneration and this is volumetric MRI looking at atrophy of the brain, glucose PET scan looking at hypometabolism, or CSF total tau or other proteins, such as neurofilament light. We, now, incorporate these biomarkers into diagnosis. So, if someone has a dementia and their amyloid positive, tau positive, neurodegeneration positive, this is clearly Alzheimer's., and if someone is cognitively unimpaired and all of these biomarkers are negative, then this is clearly normal But we now have different shades of gray, depending on someone's cognitive status and biomarker status. So, what's, , between normal and Alzheimer's disease. And some of these individuals are mild cognitive impairment, of course. But there's all possible combinations of these biomarker abnormalities.

An individual with, Alzheimer's disease we'd expect to see hypometabolism on a glucose PET scan. We would see more atrophy on an MRI scan, although there's a lot of overlap with normal aging on MRI. And we would see a positive amyloid PET scan, meaning an amyloid accumulation., compared to a normal individual who would have robust glucose uptake on a glucose PET scan, less atrophy on the MRI, and no amyloid uptake on the PET scan.

We've also now, come to a controversy about when Alzheimer's actually begins. So, traditionally we waiting until someone has dementia to diagnosis Alzheimer's disease, but now that we've discovered that these biomarkers are changing, 10, 15, 20 years before any cognitive decline, when someone is still, clinically intact, is that when Alzheimer's begins when we begin to see these tau and tangle and amyloid pathologies in the brain? Or do we have to wait until someone is demented? So, currently the consensus is we wait until someone is demented to diagnose them with Alzheimer's. But the tendency in the research world has been to shift to the left of the mild cognitive impairment and the prodromal Alzheimer's disease when we begin to see these biomarkers changing.

We also have discovered new categories because, , these there are all different combinations of these biomarkers. If someone is Alzheimer's, looks like, Alzheimer's dementia but their amyloid negative, is that Alzheimer's disease? We've called that SNAP or Suspected Non-Alzheimer's Pathophysiology. If someone is amyloid negative but tau positive, they may have primary age-related tauopathy, so their dementia is primarily treated by tau tangles and not amyloid. And then there's a group of individuals who are amyloid negative and tau negative, but demented and may have something called LATE or limbic, predominant, age-related TDP-43 encephalopathy. And so, no plaques and tangles, but aggregates of a different protein called TDP-43, which is driving their dementia.

So, recent technologies have been in imaging biomarkers, glucose PET, MRI, amyloid PET, tau PET. We've then had a wave of, , spinal fluid biomarkers and these are a-beta levels, phospho-tau, total tau neurofilament light chain and other proteins in spinal fluid. And then more recently it's, sort of, the holy grail in our field has been a blood test for Alzheimer's disease and there's been tremendous progress

in the last few years about these blood tests such as a-beta 42/40 ratio, neurofilament light, phospho-tau 181, phospho tau 217, other phospho tau epitopes in plasma. So, our, our blood tests are getting, , very close to prime time and perhaps maybe useful as a screening instrument to decide who would go on to get a spinal tap or a PET scan.

These, CSF and plasma biomarkers are commercially available. So far, not very well covered or is a battle for, third party coverage. But, we can get spinal fluid phospho-tau, total tau and a-beta 42, , levels from AthenaDiagnostics.com. We can also get a-beta 42/42 ratio and APOE proteotype from Precivity.com. These are commercially available and I think in the future, they would likely be covered once we do develop, , disease-modifying and more effective therapies.

Dr. Russell:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. John Russell and I'm speaking with Dr. Scott Turner about newly available strategies in Alzheimer's disease.

So, Dr. Turner, what treatment for Alzheimer's are newly available or on the horizon?

Dr. Turner:
Once a diagnosis of Alzheimer's is made, we recommend, one of the three cholinesterase inhibitors, which are donepezil, rivastigmine, or galantamine. These support cholinergic neurotransmission, at the synapse in the hippocampus. These drugs were approved 1996, 2000, 2001, all very similar in their efficacy and side effect profile. Once someone advances to the moderate stage, we add memantine to the one of the three cholinesterase inhibitors. This drug was approved in 2003, has different mechanism of action, is used in conjunction with one of the three cholinesterase inhibitors, has very little in the way of side effects. And as you note, our last drug approval until this year was memantine, which was 2003, which means all of our phase 3 clinical trials have not been effective until this year, June 7th of 2021, when the FDA approved aducanumab, which is anti-amyloid antibody. And it was approved not on clinical benefit, but based on amyloid-clearance from the brain, as measured by amyloid PET scan. This is the first disease-modifying therapy which is available for prescription use. it's not covered by insurance yet; we're waiting for a Medicare, CMS decision in January, effective April or early next year.

In the meantime, there are three other antibodies, anti-amyloid monoclonals called lecanemab, donanemab, and gantenerumab, which are similar and targeting the amyloid and all have demonstrated removal of amyloid plaque from the brain as measured by amyloid PET scan. And they are also seeking approval for MCI and mild Alzheimer's based not on clinical benefit, but based on CNS, , amyloid removal. There has been some encouraging results in showing clinical benefit with many of these antibodies. Some of the preliminary work with aducanumab clearly demonstrated a dose-dependent reduction in amyloid burden in the brain of those who got the drug, compared to those who got the placebo. The bigger question or the bigger controversy is whether this actually has a clinical benefit. And some of the earlier data with, aducanumab showed a dose-dependent, improvement in clinical outcome, meaning that the placebo group declined at the anticipated rate in measures such as the Clinical Dementia Rating Scale or the Mini-Mental State examination score. Whereas those who got the highest dose had less decline or no decline during the course of these, studies. The controversy comes with the phase 3 clinical trials of aducanumab, these were stopped early because of futility analysis suggested that there were not going to be effective. But one of these studies called the MERGE showed that the highest dose did have a significant benefit in reducing clinical decline in primary and secondary endpoints. However, the other parallel phase 3 clinical trial did not show any clinical benefit and hence the controversy is, continuing and ongoing.

There was, in a post-hoc analysis of the engaged subjects, those who got the highest dose for the longest time had some positive findings similar to those that were found in the successful phase 3 clinical trial. Both studies clearly showed reduction in CNS amyloid burden as measured by amyloid PET and both showed some encouraging results in other biomarkers, such as plasma phospho-tau. They both, had significant risk of side effect and this was called ARIA-E or amyloid-related imaging abnormality, mostly presenting as headache or confusion, although most of it was asymptomatic and detectable only on MRI scan. And this drug was surprisingly FDA approved 7th of June, because a review panel gave it a negative review and did not recommend approval but the FDA approved it, , and it's now available. The initial approval was broader and was approved for Alzheimer's disease but about a month later, the FDA revised the indication to a narrower group of individuals, similar to those who were in the phase 3 clinical trials and this was a group of individuals with mild cognitive impairment or mild dementia due to Alzheimer's disease. So, this was scoring, for example 17 to 30 points on the MoCA or 21 to 30 points on the Mini-Mental State examination or basically mild dementia. There had to be, proof of amyloid positivity, either on amyloid PET or by CSF testing of amyloid levels, medically stable, not on anti-coagulants because of the risk of ARIA-H or hemorrhagic, , stroke from the antibody. We recommend, , APOE genotype before initiating of treatment because the risk of ARIA is much higher in APOE4 carriers. And individuals have to have an MRI scan and those with, mini-microhemorrhages at baseline, we would not recommend, because of the risk of hemorrhage or ARIA-H and the patient has to be willing and able to undergo repeated MRI scans to look for this, potential side effect.

Some of the encouraging results with donanemab also show a very, potent effect in removing amyloid from the brain and some indications in clinical and functional cognitive testing that there is a slowing of the decline in the treated group compared to those who got the placebo. So, the phase 3 trials are ongoing, but some of the preliminary data look very encouraging in showing a clinical benefit of amyloid removal from the brain by these anti-amyloid monoclonal antibodies. But the major side effect and most, probably a dose-limiting side effect is this ARIA-E and ARIA-H or the, amyloid-related imaging abmr- abnormality edema or looks like vasog- vasogenic edema on an MRI scan, which was found in 36% in donanemab, trial compared to 1% in placebo. Most of it is asymptomatic, detectable by MRI scan only, reversible after 1, 2, or 3 months. And the, if it's asymptomatic, the treatment can be continued, but if it's symptomatic and severe, the drug may have to be discontinued either temporarily or permanently. The other major side effect is ARIA-H or microhemorrhages or larger hemorrhages or hemorrhagic stroke, possibly as a result of removal of amyloid from the blood vessels. In donanemab, this was found in 11% of individuals compared to 4% of individuals in the placebo group.

There are some advantages of these, antibodies compared to aducanumab. Aducanumab was the first out and the first approved, on the 7th of June, but donanemab looks like it may be more potent in removing amyloid from the brain. Lecanemab looks like it may be safer in having a lower risk of the ARIA-E and gantenerumab has the advantage of being administered by subcutaneous injection instead of intravenously, therefore not requiring, infusion center to give the drug. A phase 3 trials for donanemab, lecanemab, and gantenerumab are all in progress and aducanumab is still being studied, even though it's post-approval.

Dr. Russell:
So, I guess that brings us to the $56,000 question-

Dr. Turner:
(laughter)

Dr. Russell:
-do you think mild cognitive impairment in Alzheimer's can be prevented?

Dr. Turner:
Yeah, there's increasing evidence that certain lifestyle or environmental factors may prevent or delay Alzheimer's disease onset, perhaps by even 5 to 10 years. And some of these are things like, exercise, physical activity, maintaining an ideal body weight, Mediterranean diet, no smoking, limited alcohol, avoiding traumatic brain injuries, etc., things like that., we are still gathering more evidence to, sort of, test this hypothesis but, definitely I think lifestyle factors are playing a role in, Alzheimer's disease onset.

We've also started prevention trials. So, we look for individuals who are cognitively normal but what we consider high risk and high risk may mean having a positive amyloid PET scan, for example. And one of these is called the A-4 study and the antibody is solanezumab with results of the A-4 anticipated in 2023 or 2024. Unfortunately, these prevention trials take many years to, complete. We launched a new prevention trial in 2020 called the A 3-45 study, or AHEAD and these are also enrolling older individuals who are cognitively normal but we consider high risk and high risk again means positive amyloid PET scan or positive, amyloid spinal fluid profile. And, this study is enrolling individuals at the very earliest stage of amyloid accumulation; just above what we consider a negative amyloid PET scan. So, again, this is going to take many years to, test the hypothesis that the antibody call lecanemab will prevent the onset of mild cognitive impairment and, Alzheimer's disease by removal of amyloid. So, this particular study is recruiting healthy, normal individuals at sites across the United States, who may be interested in finding out their amyloid PET status and if it turns out to be positive, then perhaps joining a prevention trial.

Dr. Russell:
So, I'm asked by my patients all the time what are some things that they can do? What are some non-pharmacologic interventions that they can do that you would recommend to your patients as part of this treatment plan to enhance outcomes for preventing, cognitive impairment leading to Alzheimer's?

Dr. Turner:
Yeah, for our patients and families or caregivers, we certainly recommend getting as much education and support as possible, not only from us but from other sources including the Alzheimer's association and other websites and perhaps local senior centers, would also provide, , resources for education and support to learn about what to expect, you know, as the disease progresses. You know, we also have a discussion about, in-home care, hired help, or more family help versus moving to a assisted living or nursing home depending on the level of, of dementia. We recommend advanced directives for everyone, even healthy people should have advanced directives for, a surrogate to make decisions should they be, not be able to make their own decisions for legal, medical, and financial affairs. Obviously, you'd want to screen and discontinue any drugs that may be impairing memory and cognition. We recommend getting glasses and hearing aids, if these are needed and, and this includes cataract surgery, as well. So anything that impedes sensory information

coming into your brain, should be removed as much as possible. And then we also get questions from family members about what they can do to avoid having to make an appointment in a memory clinic and these are things that I mentioned before such as exercise and physical activity, Mediterranean diet, mental activities, social connections and activities, high quality sleep, limiting alcohol, no smoking of course, and r- avoiding traumatic brain injuries. In, in older people avoiding traumatic brain injuries usually means, things like fall prevention and sometimes recommending physical therapy, consult if, this would help with fall prevention and, traumatic brain injuries. So, these are just some of our general recommendations for our patients and families and, and everyone.

Dr. Russell:
So, Dr. Turner, that was terrific and we certainly covered a lot of ground today. Could you go over what you think are the most important points, for our audience to take away from our conversation today?

Dr. Turner:
One important point is not to, ignore, memory complaints in your patients or in family members but actually do s- one of these five-minute screening cognitive tests to see if there's any indication of cognitive decline. Many of the patients are not aware or not fully aware of their cognitive decline, which is much more apparent to individuals around them, family members or clinicians. Some people call this denial, we call it more anosognosia or lack of awareness or lack of insight. So, certainly take it seriously. If you don't have time during a regular clinic visit to do, to address this issue or to do a cognitive test, then set up another appointment to specifically, address any cognitive issues and do a quick, cognitive screening test.

If anyone is interested in referral to, a specialist or to an academic medical center, then they can get, more evaluation, more diagnostic testing, perhaps some of these new biomarkers and if they're interested and eligible for clinical research, we would certainly welcome participation in, in clinical trials, probably less than 1% of eligible individuals participate in any research whatsoever and I think part of the bar- part of this is the barriers are getting a diagnosis, getting an evaluation, and learning that there are research opportunities available, are available now.

The major breakthroughs in Alzheimer's technology has been in biomarkers, not in treatment but we think these biomarkers are leading us to better diagnosis, prognosis, and measures of drug efficacy. So, I think in coming years, we actually will have more effective disease-modifying therapies. And although a lot of this is not covered by insurance now, we hope that eventually this will change in coming years as, as these effective drugs shift the cu- the, inflection points so they become cost-effective and risk/benefit positive ratios. So, it's, interesting times, but also, kind of, difficult times because we have this technology available but it's not really reimbursed and only in research. So, certainly evaluate your patients, refer them on if they're interested for further evaluation, diagnosis, and clearly if there's any interest in research, we are in desperate need of clinical trial participants to make progress in this field.

Dr. Russell:
So, Dr. Turner, that was really terrific and a lot of great points to keep in mind as we come to the end of today's program. I'd like to thank my guest, Dr. Scott Turner for helping us to better understand the latest in the management of Alzheimer's disease. Dr. Turner, it was great speaking with you today.

Dr. Turner:
Thank you for having me. I enjoyed this discussion.

Announcer Close:
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