Improving Early Alzheimers Detection in Women by Integrating Multimodal Data Into Clinical Decision Tools

Iris Broce-Diaz: Well, thank you so much for inviting me. Yeah, I'm Iris, and I'm in the Department of Neurosciences. Thank you for giving me the opportunity to talk, what, for six seconds for the work that I'm doing. I have this grant that I just recently got awarded from the Wellcome CARE Leap program. Really, their whole focus is on Alzheimer's disease prevention in women. Alzheimer's disease is a progressive neurodegenerative condition that really impairs your memory and cognition and affects millions of people worldwide. What I'm trying to do is develop these accessible, non-invasive, cost-effective tools that can help primary care and neurologists in an early detection of Alzheimer's disease. Really, to create a tool and deploy it in the clinics and make it accessible here and worldwide, we're starting with standard of care tools.

What's considered standard of care is very different in a high resource center versus a low resource center versus here versus Latin America versus Europe, and that's really interesting. But we are starting here at UCSD, and diagnosing dementia really does start in primary care. Usually, a patient will report a concern or the family member. Then the primary care, they don't have a lot of time, but they'll order some standard labs. They might do a screening assessment like an MMSE or a MoCA. Then depending on that, if it's abnormal, then they might go ahead and send the referral to neurology. Here in the US, standard of care or at least here at UCSD in our memory clinic depends on your insurance or whatnot, but Medicare at least will reimburse an MRI.

The primary care physicians know what to do with that. They rely on the radiologist, and so then what ends up happening is you go ahead and you send the referral to neurology. Usually, they send the referral once someone's abnormal on a cognitive assessment. The problem with that is that the disease process for Alzheimer's disease starts like years before the clinical symptoms. We're talking like 10 years. By the time you're sending them to the referral, it's a little late. Now with the anti-amyloid therapies, it's really important to identify those people who are imminent risk so that if they want to go ahead and start treatments they can, and this is when they actually qualify for these treatments.

It's really trying to work with primary care and neurology to create a tool where we can send better referrals, but also support patients in getting treatments. Here is the one slide where I have some of the assessments that I'm looking at. I chose these because these are the ones that are done either in primary care or in the memory clinic, and these are for the anti-amyloid treatments. We have the clinical assessment, MMSE, but there's also the MoCA. IHS, which is a brain imaging score, so essentially I got all the brain images and I created a score. We have genetics, APOE, and then PET. What I'm showing here on the x-axis is time to conversion. I modeled these in ADNI.

Essentially, that's a cool cohort because we had data from 20 years. People were healthy, then they had cognitive impairment, and then they went on to have dementia. I can leverage

all of that data. What you can see here is at the unimodal measures, so the individual measures, the model is pretty good. I validated it at five years. What you could see is that these different lines, these different percentiles, you have really good stratification. In the red and the blue, people are at low risk of converting to AD from MCI within five years, and in the green and in the purple, they're at higher risk. Then the other thing I wanted to show is at the bottom is that we have these multimodal measures.

As you combine these, we get better and better at being able to determine who is at high versus low risk of converting. If you're in this green and purple bin, then you're at imminent risk. We're talking within the next five years. What we're trying to do with family medicine is we're trying to actually deploy this in the clinic to support what is that imminent risk. One thing I wanted to show too is with the multimodal models is someone might be with the MMSE or just the IHS, the imaging score, that yellow in between. But as you add more information, they might change to a different risk bin.

We're doing this with different kinds of assessments because, like I said, we're trying to deploy this here at UCSD, but we're also working at UCSF and in Latin America, and everybody's doing different things. It's a fun project, for sure. Then here, what we're doing is we're starting off with the imaging score. We're actually deploying this. It'll be an Epic, so primary care physicians can actually use this, and we're working with the memory clinic with Liz Bevins and James Brewer to be able to work together and have a dementia care model. Now, what's important is and what most of you here are really interested in too is these women-specific variables. Alzheimer's disease affects women like two times more than men.

The whole idea, at least with the CARE Leap, is that women are going through all these biological changes around the same prodromal stage of Alzheimer's disease, and so we're trying to figure out what is going on at that time that might put women at higher risk for dementia. My goal is to work with some of those other investigators from the CARE Leap to integrate some variables into my models to improve the prediction in women. These models already are doing better in women than men, and I don't know why, but they are. But also, one of the things that I'm working on and internationally because it's difficult to get these large datasets, to do all these models, we're trying to integrate hormonal endocrine markers.

CARE is really interested in menopause history, whether or not people are using hormone therapies or their age of menopause, their reproductive history, and then just in general their symptom profile. What I'm trying to do is I'm trying to add these variables into the models in order to improve that. That's essentially our second phase. I'm excited to discuss further with you all who are experts in this to determine what might be the best variables. That's it. [Applause]

Speaker 2: Iris, that was so terrific. My question is, in the US, as you know in a couple around the world, there's some pretty well phenotyped menopausal transition cohorts that have matured that they should be in the Alzheimer's age range at this point. Do you have collaborations, for example, with SWAN or such folks because then it's not just age at menopause, but how we go through menopause as a predictor?

Iris Broce-Diaz: I do not. That would be excellent. It's interesting because we have all these cohorts too that we could validate like blood samples of women from their 40s, and we

actually have the samples when they're 40s and we know they go on to have dementia. It'd be great to be able to work with someone who has that data that we can model and then validate. Yeah, that'd be great. Thank you, yeah.

Speaker 1: Actually, Dr. Barbara Parry has a cohort of the mood disturbances with menopause, and she's here.

Iris Broce-Diaz: Cool.

Speaker 1: I can send you them. Dr. Rebecca Rakow-Penner, the radiology, she has a program on imaging for women's health.

Iris Broce-Diaz: Wow.

Speaker 1: It can be also potentially leveraged.

Iris Broce-Diaz: That's the really cool thing about these is you really can add any model to these because of the way that we just combine them. Yeah, I'm really excited about that. Thank you.

Speaker 1: Any other questions? Yes.

Speaker 3: Yeah, I have a question. I noticed you're talking about [inaudible] models of variables. [inaudible]

Iris Broce-Diaz: That would be excellent, yeah. I always think the same way that I did a brain imaging score, where it's like a feature reduction. I mean, get really fancy. I've done it so many different ways. It's not always best to go do something more fancy, but the combination of all of them. What does that look like in women? The combination of them as they get older, yeah.

Speaker 4: I think that the treatment guidelines for Alzheimer's recquire or recommend testing when symptoms or cognitive decline is already happening. Have you thought about how do you change the treatment guidelines to recommend this testing maybe in I'm thinking of a colonoscopy.

Iris Broce-Diaz: Yeah.

Speaker 4: How do we get it? Every five years some risk tiering maybe based on family history or something like that, but how do we get it that standard so that this actually makes a difference?

Iris Broce-Diaz: It is so interesting because you're right. Right now, the amyloid therapies, they're for people who have MCI already. How do you quantify that? Even if you have positive for biomarker testing, you're right. If you don't show overt clinical symptoms, it's hard to get it accepted by insurance. What we're doing is that it just depends. Yeah, it depends. I'm actually going to get on a flight to Norway right after this because we're talking about policy and changing policy because the difference is that in Norway, all dementia screening is happening

in primary care because the memory clinics are overwhelmed. Because they have healthcare and anti-amyloid therapies are expensive, that's not actually reimbursed. Just because they can technically prescribe it, you have to think about who's actually getting it.

We're actually working with them in Oslo to change policy using some of these models because we validated it in their clinical cohorts to see if we can essentially start thinking about who are those people at the highest risk. Then at least we're starting to make changes about who are these people who are likely the imminent risk of conversion. Because if you're going to convert in 10, 15 years, that's very different than if you're likely to convert in five years, and it's easier to track them in two to five years. Same in the clinical trials right now with the anti-amyloids. They're trying to bring them earlier and earlier. But that is the other issue, is how do you know who's going to convert.

It's very difficult to have power in a clinical trial when you have to monitor this for 10, 15 years. That's actually one thing we're trying to do. In Oslo, it just happens that the way that they're changing dementia care puts us in a privileged position to actually work with them to determine who would be those individuals, who would be getting the anti-amyloid treatment.

Speaker 5: One good model for that might be the breast cancer space because there's a Gail calculator for breast cancer risk, and now even people with a certain risk can get prophylactic treatment. Maybe something like that would work.

Iris Broce-Diaz: Yeah, that's awesome. Then the other thing is I've literally went to five different countries in Latin America, but I have collaborators in other places because I would just have to ensure that these models do generalize to everybody. It's a fun project and problem to be a part of.

Speaker 1: Thank you so much from UCSD Women's Health Symposium to Oslo. That's right. [Music]