Jill Harrison, PhD:

Hi, this is Jill Harrison, Executive Director of the National Institute on Aging IMPACT Collaboratory at Brown University. Welcome to the IMPACT Collaboratory Grand Rounds Podcast. We're here to give you some extra time with our speakers and ask them the interesting questions that you want to hear most. If you haven't already, we hope you'll watch the full Grand Rounds webinar recording to learn more. All of the companion Grand Rounds content can be found at impactcollaboratory.org. Thanks for joining.

Hello everyone. I'm Jill Harrison, one of the Executive Directors at the NIA IMPACT Collaboratory. I'm joined today by Dr. Kyra O'Brien, Assistant Professor of Neurology at Penn Memory Center at the University of Pennsylvania and Dr. Nicole Fowler, Associate Professor of Medicine at Indiana University School of Medicine. Thank you both so much for joining me today.

Kyra O'Brien, MD:

Thanks for having us.

Nicole Fowler, PhD, MHSA:

Thank you.

Jill Harrison, PhD:

The NIA IMPACT Collaboratory hosts a monthly Grand Rounds series each with a companion podcast. Earlier today you presented a well-attended Grand Rounds about the clinical implementation of Alzheimer's disease biomarkers. I'd like to ground ourselves a little bit before we dig into questions from our listeners. Can you please give us a high-level overview of your study?

Nicole Fowler, PhD, MHSA:

Sure, no problem. So today I presented on a pilot study where we tested the feasibility and acceptability of delivering blood biomarker results to primary care patients as part of their routine primary care. These were symptomatic patients who were identified through a digital cognitive assessment that was implemented in seven diverse primary care practices throughout Central Indiana. And of those patients who failed the cognitive screening assessment, they were approached to consent for this research pilot, to have their blood drawn, and then disclosure of those results done either by their own primary care provider or by the research team. Also, we included the primary care providers and asked them to consent to participate in the disclosure. And if they decided that they did not want to, then the research team would do the disclosure for their patient.

The education for providers was multiple steps actually. One was at the very beginning of the project where we just talked in general about what the overall protocol would be for both detection and then approaching patients for blood biomarkers. And then once we had the protocol live for patients who failed the screener to be approached, then we actually had both a recorded video presentation by one of our neurologists discussing the Precivity results, both what the report looks like and what the report means and in the context of the available data that we have. And then we were also available for consultation after that training was viewed. So that's the overview of the study.

We had about 236 patients who are potentially eligible and, of those, we consented 26 who were interested in having their blood drawn and disclosure for the results. Only about half of the primary care providers did consent to participate. And we interviewed a handful of those who did consent and do a disclosure, those who consented but ultimately never ended up doing a disclosure, and then those who

didn't consent. And I was able to present results from both the patients' perspective and from the primary care providers' perspective.

Jill Harrison, PhD:

You went into detail a bit on the education for providers and mentioned that roughly 46% of the primary care providers had declined to participate in the blood test disclosure discussion with their patients. What are some lessons learned from that? And you mentioned it was primarily the rationale or the qualitative results indicated that primary care providers just didn't feel like they knew what to do with the results or that someone else could better explain them. Where can we go from here? How can this fill a gap in our knowledge about the education and resources that primary care providers need in order to improve dementia care?

Nicole Fowler, PhD, MHSA:

Some of it actually may be demand, in the sense that, at the time of this study, it was in the spring of 2023, lecanemab had not been started as part of a treatment for our health system. And while I think the providers who had been part of this larger screening trial are very aware that the speed at which detection is happening both with clinical tools and with biomarkers, and then the treatments that are coming on the market, they realize it's happening very fast. So I do think that there is clearly that recognition.

And I think it was true by their active and willingness to participate in this overall large demonstration project. And I think when it comes down to the biomarker piece and their comfort, while we did have a lot of interest in the viewing of the materials that we sent, I think ultimately what their sense was that their ability to not even just have the disclosure discussion, but then also to be able to use it in the context of a larger care plan, they really felt like they would ultimately be referring to neurology. And I think just wanted that step to be up front.

And so I do think what we're going to see is primary care providers are going to recognize that the discussion of some of these biomarkers is really in their purview and that they're going to need to partner with specialist providers like neurologists and geriatricians to develop care plans for patients that include potentially treatment, care, and case management. And rather than handing off the disclosure and then the care to a specialist, really identifying that we're going to need to take a collaborative care approach and work between us in both primary care and specialty care to care for these patients. Whether it's those seeking then a pharmacological treatment or those who are ineligible or don't want to, and actually still need care and support throughout the journey.

Jill Harrison, PhD:

It would be interesting to understand from primary care providers if there were some sort of decision tree or algorithm, clinical workflow, for example, referral pathways, et cetera, if that was available within their healthcare system, would that change their comfort in participating in disclosing the results? Dr. O'Brien, anything that you wanted to add about the high-level overview of your study or the education that you had for providers?

Kyra O'Brien, MD:

So I'll give a brief overview of the qualitative study that we did. So essentially, we wanted to understand what clinicians thought about using these blood-based Alzheimer's biomarker tests in their clinics, and understand things that would make it more likely for them to use them, less likely. We interviewed clinicians across four sites, Penn, Wisconsin, Alzheimer's Institute Dementia Diagnostic Clinic Network.

And so we had people of varying degrees of comfort and knowledge in dementia diagnosis and care. And so we explored how these providers approached a cognitive evaluation, what their views were on the value of an Alzheimer's diagnosis and then talked more about plasma biomarkers, what they knew about them, what their perceptions of them were. And then explored different factors related to plasma biomarkers that might influence their adoption. So how complex they are, what the advantages are of the blood testing over spinal fluid or PET measures, how compatible it is with their needs and practice and their values.

And so, a lot of what we talked about already came up in these interviews. The fact that they really aren't comfortable performing even cognitive testing for Alzheimer's disease for that evaluation. If they do have someone with cognitive impairment, what are the appropriate tests they need to order? And so if you add in this biomarker, the same issues crop up. They don't know how to interpret them, they don't know what patients are appropriate referral. And so you mentioned a decision tree or pathway and that's exactly one of the things that the primary care providers in particular said would be helpful, is a clear next steps for getting this patient the additional testing they might need or the treatments they might need, and making the appropriate referrals to specialists or to community resources and social work. In addition to just basic education about how to interpret the test results itself, you have to have that entire care and referral pathway set up for providers to really feel comfortable.

Jill Harrison, PhD:

Thank you so much. Yes, it's a fascinating topic and it's ripe with ethical dilemmas and implications and really interesting questions. And I'm curious, you mentioned during the Grand Rounds today that you had consulted with the Ethics and Regulatory Core, that's part of the IMPACT Collaboratory. Can you describe that process and any decisions that you made in terms of how that consultation with this specialized group of subject matter experts in ethics and regulation of dementia care trials, how that impacted you or your project or your thinking on the subject?

Kyra O'Brien, MD:

The Ethics and Regs Core actually reached out to me given that they knew this was an area of interest and asked if I'd be willing to talk about it. So that's how I ended up doing the Grand Rounds. But I have interacted with their members for other projects and on collaboration in the realm of biomarker disclosure. So Emily Largent led an effort to create some initial best practice guidelines for how to disclose biomarker results. And so working with her through that process has really informed my own work in terms of making sure that the people who are delivering the results are trained in being able to deliver that and know what information to provide to the patient and the family member. There's a huge emphasis on pre-testing education. And so for one of my projects going on where we've implemented the biomarker at the Penn Memory Center, we've developed educational materials for the patients on the testing.

So some of it come from the AGREEDementia Decision Guide, and then we have more education specific to the actual test that we're using saying, "This is the cutoff, this is what it means if it's a above or below." And then we have, another important piece of the disclosure process is check-in after results disclosure. So we have a follow-up call with the participant within a couple of days of disclosure to see how they're doing and make sure there aren't any big issues. And so we assess mood and Impact of Event Scale and if they do have significant concerns, we notify their referring clinician, we notify social work to make sure that they have the resources they need. And then we do that again in two to three months after disclosure. So I've definitely implemented those best practices in my work.

Jill Harrison, PhD:

Could you speak a little bit about the nuances of disclosing ADRD biomarker results as it compares to disclosure of, for example, genetic testing for cancers and other diseases and conditions? What are the nuances for Alzheimer's disease and dementia biomarker disclosure?

Kyra O'Brien, MD:

That's a great question. So with genetic testing, to draw some parallels, some genetic risk factors affect your risk, but it doesn't mean necessarily if you have a risk factor, you're definitely going to get the condition. And so we're facing some of the same things with the Alzheimer's disease biomarkers. So, for example, in a cognitively unimpaired individual who has evidence of elevated amyloid, that means that they're at a higher risk of developing Alzheimer's disease, but it's not 100% certain that they're going to develop it. And so depending on which biomarker you're working with, it can tell you different information.

The tau measures seem to be much more correlated with risk of developing symptoms. So if you've got elevated tau, it's more certain that you'll develop Alzheimer's. And so the fact that each one means a slightly different thing adds a lot of complication and it's difficult to relay what that means to family members. There's also differences in how we describe these test results. We say "elevated" or "not elevated" or "positive" or "negative." And so, there's so many different terms being thrown around that that's another layer of complexity. And so I think, as best we can, we need to try to harmonize the language that we're using for each of these tests. I think that would be easier for patients to understand the results, easier for clinicians to understand and relay the results. But yeah, it's as complicated if not more complicated than the genetic testing world.

Nicole Fowler, PhD, MHSA:

I'd like to add, Jill, with regard to the nuance, and in particular in the population that we see in primary care who have multiple chronic comorbidities and have different profiles with regard to clinical symptomatology, that we really don't exactly know how these assays express in populations who, say, also have chronic kidney disease and are being treated, or have certain medications that they're taking, or different cardiac issues.

And so I think the other piece that's really, I think, still premature and there was a little bit of that I think in the results from our conversations with PCPs is they said, "Yeah, I know how to understand the sensitivity and specificity. But is that really on a population that I'm used to seeing? Is that what this will mean for them? I mean, can I have confidence that these results are going to reflect the patient population that I see?" And honestly, I think it's hard to say the answer is yes to that. I think we don't know yet. And I think that's where a huge area of research needs to happen is, now that we actually have these biomarkers and we've been able to use them in a research setting for quite some time now, how are we going to really think about testing them in real world populations?

Jill Harrison, PhD:

Yes, thank you. And you had mentioned the decision guide in terms of informing participants' standpoint on whether or not to participate. How does that work with people who may or may not be symptomatic but that aren't able to make the decision themselves for whatever reason? Either they have a substituted proxy or care partner that's designated to make decisions on their behalf about the biomarkers. What are the nuances of that?

Nicole Fowler, PhD, MHSA:

I mean, that's really interesting. I think, if I understand what you're asking, it's basically if the patient themselves aren't the ones who have the ability to consent for this blood test, for example, but it's a family member that's consenting for them, I think that brings up a whole host of other issues. And again, what's the purpose of the test? What's the value of the test? Why are they seeking out this information? Similar to maybe how the proxy would want information about how to help that person with their care, you could think through what that would mean from a treatment standpoint.

But there's also other risks involved, making sure that we're using the information appropriately. And I think there's still some uncertainty about what that information looks like when it's entered into people's clinical charts and how it may be interpreted for things like insurance status and other forms of services that they may be eligible for. So I think that's a tough question and I think that there's a lot of nuance in that, not just for the AD biomarkers, but a whole series of tests that maybe a proxy may be requesting.

Kyra O'Brien, MD:

This comes up all the time in my clinic, and so just as Dr. Fowler said, we probe very deeply into the reasons why they would want to have this testing. And I try to walk them through how it'll impact the patient, especially if it's someone who might not be able to tolerate the testing. Usually it's an MRI or something, or a lumbar puncture. But even a blood test, some patients, depending on the severity of their symptoms, it could cause a lot of hardship. So really trying to understand the value of it, potential harms to the patient, what they're going to do with the information, if it would change their management. So yeah, it's a lot of just education and information gathering.

Nicole Fowler, PhD, MHSA:

I want to add regarding the use of clinical decision making, not necessarily around the idea of a proxy requesting. But I think the other thing too is right now, if the reason for seeking this information is to find out if they have pathology, that they would then be potentially appropriate for a therapy such as lecanemab, do they actually understand what that means?

So we've actually run into scenarios where patients may start a potential clinical workup to see if they're eligible for lecanemab, which would mean start with obviously testing, but then biomarkers. And then they learn that it's something that they actually have to come in and get infused for every two weeks, somebody needs to be with them or be helping them monitor for side effects. And they almost then think, gosh, maybe I don't want that. And then you think about the treatment cascade. So what are we using this information for if ultimately you're not interested in getting the therapy? And maybe it is just to know what the source of the cognitive impairment is, but I think oftentimes we sometimes separate out what we'll do with that information versus the actual act of getting the information. And I think it's really important to consider that in this case.

Jill Harrison, PhD:

These podcasts are publicly available and we often have consumers, people living with dementia, care partners that tune in. For people who are interested in obtaining a biomarker test, where should they start? How readily available are they? Are these tests available through the average primary care provider?

Kyra O'Brien, MD:

They are orderable. Anyone can order them through LabCorp, through Quest, through Precivity. They have different costs, some are covered by insurance, some are not. And then I had mentioned there's the direct-to-consumer one, which I'm not advocating for that, but I would say that they're pretty accessible at this point. I would strongly recommend talking to a physician about the risks and benefits associated with getting these tests. I would look at the decision aid on the AGREEDementia website so that you truly understand what that testing result means before you go out and get one of these direct-to-consumer tests, if that's what you're thinking about.

But if you think you would be significantly impacted emotionally, if you would have anxiety over getting a positive test result, then you definitely shouldn't reach for one of these direct-to-consumer tests. You would want to be connected with a strong support network, a medical provider who can help take the next steps to follow up on a positive result before you do that. And I should also say that right now, biomarker testing clinically is only recommended for individuals who have cognitive impairment. So if you don't have cognitive impairment, it's not really clear what the benefit of testing would be because there wouldn't be any treatment options. And so right now, that's something that's only done in research. So I also probably wouldn't recommend going out and getting tested if you don't have cognitive impairment.

Nicole Fowler, PhD, MHSA:

The one thing I would add to that is for patients who are concerned because they do have symptoms and they're concerned about their memory or they've noticed changes in their memory and thinking, there's a lot of other reasons why that could be occurring and many of those things are things that they can take action on themselves. So talking first with their primary care provider about the medicines that they're taking. I think we often forget that the amount of medicine that older adults in particular take, whether it's prescribed or over-the-counter can sometimes be overwhelming and actually having real impacts on people's memory and thinking and their brain. And so starting with things that actually might be causing some of the symptoms, maybe it's depression that's untreated, maybe it's a lack of social interaction or physical activity. We know that there's lots of things in the lifestyle realm that can impact people's cognitive health.

So I guess my advice would be to really think about all of the different things that could be causing the concerns that you're having and having a thorough conversation with your provider. And then if you're still interested to find out if you actually have pathology, then as Dr. O'Brien mentioned, having that in the context of a specialist who understands how to have that result and those reports reviewed with you. So I think sometimes we jump immediately to wanting to find out a cause of something and oftentimes it can be things that we are as patients able to fix on our own, at least in some of the very early stages.

Jill Harrison, PhD:

Thank you both. Those are all great points. My last question is the IMPACT Collaboratory, our mission is really to build the field around these embedded clinical trials to improve dementia care, of non-drug interventions. And just want to ask your opinion, for researchers that are looking to build their competencies in terms of designing and overcoming any methodological challenges of conducting these pragmatic trials for people living with dementia and/or care partners, specifically around the use of biomarkers, what types of training resources would you recommend? Where should investigators that are interested in doing what you're doing start?

Nicole Fowler, PhD, MHSA:

I feel like I could talk all day about that as somebody who thinks a lot about research design and infrastructure. A couple of things. I think one is there is still really a tension between how we define pragmatic trials and what's truly able to be done in the context of a routine care setting. And so I think about all of the things that you may want to measure about the impact of biomarkers in the routine care. And many of those things I think are things that Dr. O'Brien and I showed today, and certain scales and measures that just aren't things that you can get from routine documentation from care. So I think the one thing would be is around the design. So it's thinking about where in the setting and delivery is this information going to be embedded. I think we thought a lot about the primary care setting and having it be as, "natural as possible," but recognizing that the system isn't quite ready. So I do think there are some questions that maybe just aren't quite ready for the pragmatic trial design.

But I think the advice for people would be to really understand what some of the information is that you can gather as part of routine care and the implementation process. But then I think also really identifying the right partners. I think that one of the things that made our pilot and our larger clinical demonstration project a success is that we had equal buy-in from clinicians who helped, for example, design the study. These were providers who aren't researchers, who see patients every day and giving us a lot of input about what they thought the right design was. And then multiple specialists who could participate and do the training, for example, or who could be able to identify what the right metrics are to pull from the medical record. So I think in this case, both the topic needs to be ready for a pragmatic trial and then also truly understanding who the other players are that you maybe need to involve that you wouldn't necessarily get involved in a study that wasn't pragmatic and try to be implemented in routine care.

Jill Harrison, PhD:

Dr. O'Brien, last word to you. Any parting thoughts?

Kyra O'Brien, MD:

I would just echo the importance of early stakeholder engagement. So even in the design of this study, as Dr. Fowler said. I'm working on this right now actually in terms of trying to get a plasma biomarker implemented in primary care. And so very early on, as soon as you have the idea, start talking with the people who are going to be crucial to the successful implementation of it and they will tell you what is and is not feasible and it will really make your life easier when you're actually starting the trial.

Jill Harrison, PhD:

Thank you both so much for sharing those important insights. And as we wrap up today, I just want to say thank you again Dr. Kyra O'Brien, Dr. Nicole Fowler, many thanks for sharing your important insights with our NIA IMPACT Collaboratory audience. And thank you so much for everything you do every day to improve dementia care.

Nicole Fowler, PhD, MHSA:

Absolutely. Thank you so much for having me.

Kyra O'Brien, MD:

Thank you.

Jill Harrison, PhD:

Thank you for listening to today's IMPACT Collaboratory Grand Rounds Podcast. Please be on the lookout for our next Grand Rounds and podcast next month.