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Alzheimer's Disease Blood-Based Biomarkers: Translation from Research into Clinical Use

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Guests: Dr. Lance Ladic from Siemens Healthineers in Princeton, New Jersey and Dr. Mari DeMarco from St Paul's Hospital and the University of British Columbia in Vancouver, Canada.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Alzheimer's disease is the most common cause of dementia with an estimated 6.9 million Americans age 65 and older living with some form of the disease. The causes of Alzheimer's disease are complex and incompletely understood, but we do know that brains of affected individuals are marked by atrophy, as well as plaques and tangles of abnormal protein. For many years, these abnormal proteins have been measurable with cerebrospinal fluid but this requires an invasive collection, which limits testing to a single time point or at best, a small number of time points in the patient's disease course. Recently, several blood-based biomarkers have been identified that offered similar diagnostic performance to those measured in CSF. While the applications of these novel biomarkers are still being explored, there is hope that they could address previously unanswered questions for affected individuals. What do laboratorians and clinicians need to know about these new blood-based biomarkers? How can these biomarkers transition from research to clinical use? And are they likely to change the way patients are managed?

A new Q&A article appearing in the November 2024 issue of *Clinical Chemistry* checks in with four experts in the field who share their thoughts on the current state of blood-based biomarkers for Alzheimer's disease and predict where the field is likely to go next. In this podcast, we're joined by the article's moderator and one of the panel experts. Dr. Lance Ladic is a director in the Innovation Community Management group within Siemens Healthineers and is based in Princeton, New Jersey. Dr. Mari DeMarco is a clinical chemist at St. Paul's Hospital and a clinical professor of pathology and laboratory medicine at the University of British Columbia in Vancouver, Canada. Her research lab focuses on the development and implementation of new protein biomarker tests. So Dr. DeMarco, let's start with you. Could you tell us about blood tests that are under development for Alzheimer's disease? How do these new blood tests compare with those already available for cerebrospinal fluid?

Mari DeMarco: To set the stage for discussing plasma biomarkers, I think it's important to understand current biomarkers more widely used and with regulatory approval in many countries. So as you mentioned, in CSF, the key biomarker that we measure is amyloid-beta [Aβ] that spans residues 1-42. It's the key biomarker for Alzheimer's pathology and CSF. And Aβ is, for optimal diagnostic performance, expressed as a ratio with either amyloid beta peptide spanning residues 1-40, or in a ratio with phosphorylated tau or total tau. These ratios--and you don't need to measure all of them, one will do--have the highest diagnostic accuracy for detecting amyloid beta pathology that occurs in Alzheimer's. While historically, these biofluid biomarkers would have been compared to neuropathology on autopsy, today that is rare and most commonly, fluid biomarkers are compared against amyloid PET, an imaging modality that detects the amyloid plaques in the brain. And this is what diagnostic performance is benchmarked against, so it's benchmarked against amyloid PET.

In plasma, now there are several methodologies that can detach both amyloid beta and tau proteoforms, which is a really exciting advancement and these as in CSF show high diagnostic accuracy for Alzheimer's pathology. Again, here we're talking about amyloid beta pathology specifically because of the comparison to amyloid PET, but different to CSF, is that specific phosphorylated tau proteoforms are posed to take over that key role that I talked about, that amyloid beta 1-42 occupies in respect to cerebrospinal fluid. While measurement of a single phosphorylated Tau proteoform like Tau phosphorylated at residue 217 has amongst the highest diagnostic accuracy for the detection of amyloid beta pathology. So that's also exciting that this has been distilled down to a single biomarker and plasma. It is worth mentioning that there are major analytical challenges for the measurement of both amyloid beta and Tau proteoforms in plasma, and those include their relatively lower concentration in plasma as compared to CSF and their increased matrix complexity of plasma as compared to CSF.

In blood, there is also peripheral production of these biomarkers that is they're not all coming from the central nervous system which reduces the mean differences in concentration between persons with and without Alzheimer's pathology compared to much bigger differences we see in CSF, so lower concentrations and smaller differences between groups.

For amyloid beta peptides, there is the additional challenge of degradation by endogenous proteases that are found in plasma if the sample is not very carefully collected, processed and stored prior to analysis. Particularly for the

measurement, amyloid beta peptides has been shown to be more robust in this respect. That's based on pre-analytical, analytical and diagnostic performance consideration. Current research favors the translation of Tau proteoforms into clinical care and those specific Tau proteoforms I mentioned. This is reflected in the revised research criteria for the diagnosis and staging of Alzheimer's disease recently published by the Alzheimer's Association Working Group which introduced a more prominent role for plasma-based biomarkers in their system.

Currently, these plasma biomarkers are only recommended for use in a diagnostic capacity and for individuals with symptoms suggestive of Alzheimer's disease. That means they're not a screening-type test used for asymptomatic individuals. However, other applications are under study and perhaps we'll discuss some of those today. There is this interest in integration of these biomarkers at multiple points in the care pathway for individuals with Alzheimer's disease including, as I mentioned for early, in differential diagnosis also determining eligibility for specific disease-modifying treatments as they become available and potential future areas such as monitoring response to therapy and tracking disease progression. It's, you know, our hope that these biomarkers provide practical and objective methods to help personalize therapy and ultimately slow the progression of this fatal disease.

Bob Barrett: Okay, thank you so much. Now, Dr. Ladic, how do blood-based biomarkers complement those used in CSF as well as imaging and other diagnostic tests for Alzheimer's disease?

Lance Ladic: Blood-based biomarkers for Alzheimer's disease are being positioned really as complementary tools to CSF testing and imaging modalities like PET. They fit within the diagnostic framework by offering a more accessible, less invasive, more scalable, and a cost-effective option. And in particular, I think that the increased access that blood tests could afford would be very important in countries where their health resources are not distributed equally across geographic regions. I think that this has the prospect of increasing care equity across healthcare systems, which is I think becoming more and more important. Blood-based biomarkers, particularly those tracking amyloid beta and phosphorylated tau, show strong promise for detecting the pathological hallmarks of Alzheimer's disease. These biomarkers can facilitate early disease detection, enhance diagnostic accuracy and streamline referral processes, especially in primary care where access to advanced diagnostics like CSF analysis and PET imaging may be limited.

Additionally, tests like *APOE* genotyping and polygenic risk scores are likely to have an expanding role in the future for

assessing disease susceptibility and the side effects of therapy. And I think with additional evidence, there could also be a role for blood-based biomarkers to help determine eligibility for emerging disease-modifying therapies. Currently, blood-based biomarkers are not recommended for broad population-level screening due to challenges such as pre-analytical standardization and the risk of overdiagnosis. Instead, they're primarily recommended for use in symptomatic individuals with cognitive impairment either as part of the initial diagnostic workup or to support clinical decision-making. I believe that they're particularly useful in helping to confirm Alzheimer's pathology and in stratifying patients for further testing.

In some cases where blood-based biomarkers provide borderline positivity or intermediate-level results, this would require confirmation by CSF or imaging. So in clinical practice, I think blood-based biomarkers are meant to be used in conjunction with other diagnostic tests such as cognitive and functional assessments, genetic markers, and imaging, rather than as standalone tools. They can complement existing tests by improving diagnostic confidence particularly when other resources are scarce.

Bob Barrett: So Dr. DeMarco, what are some of the major challenges that must be overcome before blood-based biomarkers are more widely-adopted?

Mari DeMarco: To assist in the translation of blood-based biomarkers into clinical care in a manner that improves the well-being and care of persons with cognitive impairment, I think it's important to take a step back and look at the bigger picture. That is looking beyond only laboratory considerations and diagnostic metrics. As part of the implementation of Alzheimer's disease cerebrospinal fluid biomarkers in Canada, via a study called IMPACT-AD, we sought input about the impact of biomarker testing from a variety of sources, not only physicians, but also individuals living with neurodegenerative disorders, that is patients and their family members helping them through the process. With that, I want to highlight a few key insights we learn from patients undergoing testing and their family members, as lessons learned from this group can possibly inform implementation of biomarker-based testing for Alzheimer's, not only for CSF, but potentially for plasma biomarkers as well.

For instance, in deciding whether to undergo biomarker testing, patients and their family members indicated that they place substantial trust in their physician's opinion of the value of testing and greatly relied on their expertise to determine whether they should have this testing done or not. As part of pre-test counseling, they valued having a confident understanding of both the advantages and disadvantages of

testing so that they could approach the process with a realistic picture of what the possible outcomes could be. It's also important to note that individuals undergoing testing were ones that were seeking answers as to the cause of their declining brain health, and related to this, valued outcomes of testing most for the clarity biomarker testing brought to their diagnostic journey. And this really reflects also current recommendations for appropriate utilization of these plasma biomarkers. That is in symptomatic populations with symptoms consistent with Alzheimer's pathology, again not for screening, and really this full understanding prior to testing before they make that final decision.

In the implementation of blood-based biomarkers for Alzheimer's, we need to consider not only the patient and family members' side, but also the physician side and this dyad combined--that patient-physician dyad--to ensure resources and supports are in place for everyone. For physicians, this could mean clear guidelines around appropriate and inappropriate clinical scenarios for testing and ample performance data clearly presented and cohorts relevant to the populations they serve. This in turn would better enable physicians to accurately advise their patients. And for patients and their family members, we need to consider support systems across the diagnostic journey. For instance, in a paradigm where an indeterminate or positive blood test outcome needs to be followed up by some type of confirmatory testing, whether that's cerebrospinal fluid testing or amyloid PET, it's important to ensure that realistic expectations have been set.

This includes relaying possible test outcomes and their uncertainty, and ensuring care pathways downstream of biomarker testing are in place and their access is defined. That is, does a patient know how long it will take to go to the next step or to get a referral and understand that wait time so they're not left in this potential state of anxiety? In conclusion, it's not just about readying the lab for the arrival of blood-based biomarkers but readying the entire healthcare pathway that the patient interacts with.

Bob Barrett: Well just to follow up quickly, I'd like to go back to the IMPACT-AD study, that observational study in Canada, where you explored how Alzheimer biomarker testing impacts medical and personal decision-making. How is this informing the implementation of blood tests in Canada?

Mari DeMarco: Well we learned so much, not only from physicians but patients and their care partners, so we want to make sure that their voices are heard again through this entire process. One, we understood that utilizing biomarkers improved confidence in the physician, for instance in their diagnosis, and then also supported the downstream effects we saw from

that. So for instance, we saw that utilization of biomarker testing resulted in less -- other types of diagnostic testing, both biofluid but also things like detailed neuropsych testing where they didn't have to rely on additional or repeat testing like a repeat brain MRI to arrive at a confident diagnosis. So we saw this overall decrease in resource utilization in the healthcare system related to diagnostics by adding one diagnostic test, so that's quite interesting. And then from the patient's perspective, we saw that the utilization of testing, when they had appropriate pre- and post-test counseling, reduced their anxiety about not understanding what was happening to their brain health.

And so we really want to incorporate this into implementation of plasma biomarkers where that interaction with biomarker testing might happen at an even earlier stage of care and really create those resources that patients are demanding. For cerebral spinal fluid for instance, we had biomarker resource guides, resource guides as well regarding what available resources there were in the community to help support them pre and post-diagnosis. And we really want to ensure all those pieces are in place for plasma-based biomarkers as well.

Bob Barrett: Well finally, Dr. Ladic we'll give you the last word. Let's look ahead; what are some future directions for blood-based biomarkers for Alzheimer's disease?

Lance Ladic: Yeah, I mean, I think some future directions in innovations for blood-based biomarkers and Alzheimer's, they're really focusing on things like improving early detection, diagnosis, and monitoring of disease progression.

And I think that these advancements aim to make Alzheimer's testing more accessible, cost-effective, and accurate. So for example, there's one innovation area, could be the development of more sensitive and specific assays. A key challenge, I think as Dr. DeMarco pointed out, is the concentration of these biomarkers in blood is much lower than that of CSF. So the challenge for example is being approached on several fronts such as the development of new detection technologies, techniques for pre-analytical optimization, and also things like improved antibody development.

Another area that I think is seeing significant growth over the past few years is the identification of genetic and even epigenetic markers for disease risk and stratification. I think one example here is the increasing focus on the *APOE* gene, particularly *APOE4*, where *APOE* for homozygous individuals are now being considered by some as having a genetic form of Alzheimer's disease. And maybe one additional example would be some significant interest that's developing in the

area of multi-marker panels for diagnostic algorithms. So these could include markers for targets such as amyloid beta, phosphorylated tau, NfL inflammation, metabolism, et cetera. And I think such panels could offer and provide a more comprehensive view of Alzheimer's pathology. They could help to reduce false positives and negatives, and also enable tracking of disease across different stages.

Bob Barrett: And doctor, earlier you were speaking to me about the PREDICTOM project. Tell us about that.

Lance Ladic: Yeah, one exciting future direction for blood-based biomarkers that I'd like to talk about is the integration of these markers with other diagnostic modalities and advanced technologies such as artificial intelligence, digital health tools, and imaging. And I think that this multi-modal approach holds great potential to significantly enhance the accuracy and timing of Alzheimer's diagnosis, enabling earlier interventions that could further slow disease progression. So a notable example of this is the PREDICTOM initiative as I mentioned before, supported by the Innovative Health Initiative and funded by the European Union, Horizon Europe Research and Innovation program. And PREDICTOM is a European consortium project that brings together industry, academia, patient groups, and hospitals, and Siemens Healthineers is a key partner in this initiative and is leading the biofluid-based activities.

The project has an ambitious goal of identifying scalable bio signatures for earlier and accurate diagnosis of Alzheimer's. It also aims to identify individuals at risk of dementia before symptoms appear. And although the project is in its early stages, its vision is I think really groundbreaking, seeks to allow participants to begin the screening process from the comfort of their own home by collecting finger prick blood samples and using digital tools like smartphone-based cognitive tests and eye tracking. These samples would then be sent to partner labs for analysis and AI algorithms on the PREDICTOM platform would analyze the blood test data together with digital -- other digital data to assess dementia risk. And I think that this integrated analysis of blood-based biomarkers with other forms of relevant data aims to create a more comprehensive and accessible diagnostic process with about 4,000 participants expected across Europe. The project hopes to set a new standard in early Alzheimer's disease detection, potentially enabling more personalized and timely interventions, and ultimately, more scalable and accessible care for Alzheimer's patients.

Bob Barrett: That was Dr. Lance Ladic from Siemens Healthineers in Princeton, New Jersey and Dr. Mari DeMarco from the University of British Columbia in Vancouver, Canada. They participated in a Q&A session describing Alzheimer's disease

blood-based biomarkers in the November 2024 issue of *Clinical Chemistry* and they've been our guests in this podcast on that topic. I'm Bob Barrett, thanks for listening.