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Andrea L Benedet, Burak Arslan, Kubra Tan, Hanna Huber, Ilaria Pola, Guglielmo Di Molfetta, Hlin Kvartsberg, Anna Orduña Dolado, Shorena Janelidze, Kaj Blennow, Henrik Zetterberg, Oskar Hansson, Pedro Rosa-Neto, Nicholas J Ashton.

Diagnostic Value of Serum p-tau217 in Alzheimer Disease: Equal to Plasma in Levels and Clinical Utility?

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Guest: Dr. Burak Arslan from the Clinical Neurochemistry Laboratory at the Sahlgrenska University Hospital in Gothenburg, Sweden.

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 leading cause of dementia, and current estimates predict a dramatic surge in new cases, with an estimated 80 million affected individuals worldwide by 2030. The last few years have brought tremendous therapeutic advances, highlighted by the recent approval of monoclonal antibody treatments that can slow the rate of disease progression. However, accurate diagnosis remains a challenge, with misdiagnosis rates of 30% in specialized clinics and substantially higher rates in the primary care environment.

Clearly, there is a need for improved diagnostic tools and substantial work is focused on blood-based biomarkers to differentiate between affected and unaffected individuals. In a curious twist, most of the work to date is focused on plasma, but many hospital systems prefer serum. This raises the question, are there substantial differences in Alzheimer markers in serum versus plasma? And if so, can decision thresholds established using plasma be safely transferred to serum samples?

A new research article in the February 2026 issue of *Clinical Chemistry* tackles this question by measuring p-tau217 in paired serum and plasma samples from patients across the spectrum of Alzheimer's symptoms.

Today, we'll speak with one of the article's lead authors. Dr. Burak Arslan is working at the Clinical Neurochemistry Laboratory at the Sahlgrenska University Hospital in Gothenburg, Sweden. His work focuses on the validation and clinical implementation of fluid biomarkers for neurodegenerative disorders, with a particular emphasis on Alzheimer disease.

Dr. Arslan, let's get to the basics first. Could you tell us a bit more about fluid biomarkers in Alzheimer's disease? Why do

we need blood-based biomarkers and which ones are the most promising?

Burak Arslan:

Yes, of course. Alzheimer's disease is a chronic neurodegenerative disease and the most common cause of dementia. It is characterized by two key pathological features: first, extracellular amyloid plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau. For over a century, definitive diagnosis has relied on only neuropathological confirmation of these changes.

Today, however, we have some tools that can detect Alzheimer's pathology in living individuals. This is done using imaging techniques such as amyloid and tau PET, as well as well-established cerebrospinal fluid biomarkers, including amyloid beta 42/40 ratio, phosphorylated tau, and total tau. We know that since the biomarkers have become increasingly standardized and were introduced into clinical practice after 2020, with regulatory approvals and the development of certified reference materials for these biomarkers, these tools are now routinely used in specialized clinical laboratories to support clinical diagnosis of Alzheimer's disease.

More recently, advances in highly sensitive detection technologies, including mass spectrometry technique, single molecular array, Simoa, and highly sensitive immunoassays, have made it possible to measure these brain-derived proteins in blood. These advancements have now shifted much of the research focus toward blood-based biomarkers, which have the potential to provide a more accessible and scalable approach for detecting Alzheimer's pathology in vivo.

So, why do we need blood-based biomarkers for Alzheimer's disease diagnosis? In fact, there are several reasons why we need blood-based biomarkers for Alzheimer's disease diagnosis. First, compared to cerebrospinal fluid sampling and a PET imaging, blood tests are much more accessible, less invasive, and more cost effective, which makes them far more scalable especially in clinical practice. Second, blood biomarkers allow for repeated sampling over time.

So, this opens up the possibility of monitoring disease progression and potential treatment response, especially with the emergence of disease-modifying therapies which received FDA approval recently, although their use for treatment monitoring is not ready yet. And finally, I can say that these biomarkers can help identify patients who are eligible for such treatments, as well as for clinical trials, as many of them require objective evidence of Alzheimer's disease pathology.

In this context, blood-based biomarkers could play a key role as an initial screening triaging tool before moving to more advanced course of diagnostic methods.

What are the most promising biomarkers for Alzheimer's disease? The core CSF biomarkers are already well established and include amyloid beta 42/40 ratio, phosphorylated tau, and total tau. These markers reflect the key pathological features of Alzheimer's disease, and these are widely used in clinical and research settings.

In blood, the most promising biomarker at the moment is phosphorylated tau at the position of 217, or p-tau217. It is highly specific to amyloid-related tau pathology and has been shown to increase many years, up to two decades, before the onset of clinical symptoms. Importantly, it demonstrated that high diagnostic accuracy than compared to established standards such as CSF biomarkers and amyloid PET imaging.

More recently, additional promising fluid biomarkers such as MTBR tau-231 have emerged, which reflects tau pathology even more specifically and could provide complementary information, especially in the later stages of the disease. That said, p-tau217 is highly specific for Alzheimer's disease. Recent studies have shown that its levels can also be elevated in other conditions such as ALS, and this suggests that part of the signal in blood may originate from peripheral sources. To address this, newer approaches are being developed to target brain-derived forms of p-tau217, which may further improve disease specificity.

Bob Barrett: Doctor, I think I would be interested in hearing a bit more about why you undertook this study? Was plasma alone not sufficient for the measurement of p-tau217?

Burak Arslan: Well, at the time we initiated this study, most available p-tau217 assays had been developed and validated exclusively for plasma. However, they knew that at the time they initiated this study, many clinical laboratories and large biobanks have historically collected and stored serum samples rather than plasma. This creates a practical challenging question, because serum samples are often used in clinical chemistry laboratories, while the p-tau217 assays and the diagnostic cutoffs, they're only established for plasma.

At the same time, we are now at a critical stage in transitioning blood-based biomarkers into routine clinical practice. From a clinical chemistry perspective, it is important to consider real-world laboratory workflows across the globe. In many laboratories, especially in Europe, a substantial proportion of routine samples are collected as serum. In some regions, including Nordic countries: Sweden, Norway,

Denmark, and the Netherlands, this proportion is lower. Therefore, if the goal is broad clinical implementation of the p-tau217 assay, focusing only on plasma would not be sufficient.

Therefore, we performed a comprehensive comparison of serum and plasma using multiple p-tau217 assays across different analytical platforms, aiming to evaluate whether serum could serve as a reliable alternative matrix both analytically and clinically.

Bob Barrett: So, doctor, what are the main findings of your study and how are they clinically relevant?

Burak Arslan: I will approach this point from both an analytical and clinical perspective. First, from an analytical standpoint, our results show that serum can be used to reliably quantify p-tau217 across most assays. This was supported by our comprehensive validation experiments. While a few assays showed slightly higher variability in certain validation experiments compared to plasma, overall performance was acceptable. In addition, we observed strong correlations between serum and plasma measurements across most platforms.

Although plasma often yielded higher concentrations, this was not consistent across all assays, and this highlights the presence of matrix-dependent differences. From a clinical perspective, we evaluated the performance of serum p-tau217 in a well-characterized cohort using amyloid PET as the reference standard.

And we found that its diagnostic performance was comparable to plasma. However, the optimal cut-off values differed between the two matrices. Taken together, we believe that these results are clinically relevant, as these findings suggest that serum can serve as a viable alternative to plasma for p-tau217 quantification, provided that matrix-specific validation and cut-offs are carefully established.

Bob Barrett: Why are some assays showing higher p-tau217 values in serum, while others showed the opposite?

Burak Arslan: Well, this was actually one of the more challenging findings to interpret. First, it's important to note that all samples were paired and processed using standardized protocols. This makes it unlikely that the observed differences were driven by pre-analytical factors. We therefore focused more on analytical explanations. The assays we assessed used different proprietary reagents and antibodies to capture phospho-tau217, and these differences can influence how the analyte interacts with the sample matrix.

It is likely that matrix-specific effects, such as differences between serum and plasma, affect antibody bindings and assay performance. For example, in plasma, we know that the coagulation cascade is inhibited by anticoagulants, whereas in serum, clotting has occurred and fibrin-related components may still be present. These differences in sample composition could influence how p-tau217 is detected.

At the moment, we cannot pinpoint a single exact mechanism to explain such differences. Our findings suggest that these interactions between assay design and the sample matrix plays a key role in the observed differences in absolute concentrations between serum and plasma.

Bob Barrett: Finally, Dr. Arslan, what are the key take-home messages of this and are there any planned follow-up studies?

Burak Arslan: Yes, there are several key take-home messages and there is planned follow-up studies. First, we show that serum can be used as a viable matrix to reliably quantify p-tau217. Second, because absolute concentrations differ between serum and plasma, matrix-specific cut-offs are essential for clinical interpretation. If needed, transformation equations such as the ones that we published in our recent paper in *Clinical Chemistry* can be applied, although ideally each laboratory should establish its own approach based on their internal validation data.

Lastly, even though serum is a feasible alternative, each clinical laboratory should perform its own validation before implementing these assays in routine practice. Regarding follow-up work, we are particularly interested in newly brain-derived versions of the p-tau217 assays, which may offer improved specificity. We plan to apply a similar study design to evaluate these brain-derived assays across different matrices.

Bob Barrett: That was Dr. Burak Arslan from the Sahlgrenska University Hospital in Gothenburg, Sweden. He wrote a research article in the February 2026 issue of *Clinical Chemistry* evaluating the use of serum versus plasma in the evaluation of Alzheimer's disease, and he has been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.