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Alpha-Synuclein-Specific RT-QuIC As a Tool for the Differential Diagnosis of Neurodegenerative Diseases Using Peripheral Tissues

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Guest: Melissa Ix is a medical physicist and doctoral researcher at the University Hospital Essen, Germany.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett.

In prion-like diseases, normally occurring proteins in the central nervous system become misfolded, taking on a non-functional shape that induces neighboring, correctly folded proteins to also become misfolded. Eventually, these misfolded proteins accumulate in certain areas of the brain, causing neurodegeneration and ultimately the classic symptoms we associate with Parkinson's disease and other related conditions.

By the time symptoms emerge, neurodegeneration has advanced beyond the point of early intervention, but a new technique aims to change that. A review article in the August 2026 issue of *Clinical Chemistry* describes the use of alpha-synuclein RT-QuIC in peripheral tissues. By adopting a less invasive technique, researchers hope to make a diagnosis much earlier in the disease process, facilitating the study of new therapeutics that slow or even prevent misfolded protein aggregation.

Today, we are joined by the article's lead author. Melissa Ix is a medical physicist and doctoral researcher at the University Hospital Essen, Germany. Her research focuses on the detection of pathological alpha-synuclein in peripheral tissues using RT-QuIC. So Melissa, Parkinson's disease is usually diagnosed clinically. Why are researchers now looking for biological markers for the disease?

Melissa Ix: Think of this: when -- are you, for example, going to a doctor's appointment? When everything is good or when you're fine? Most probably not. Many of us make doctor's appointments when we notice that yeah, something's off. Something's not like we, like it used to be before when we got symptoms, and that's totally fine when you have, for example, a flu or something like that. But it's something completely different when you develop a form of Parkinson's disease, because exactly at this point where the first symptoms even start to appear, a severe amount of the

nylons in the substantia nigra are already completely degenerated.

So, yeah, as you said, Parkinson's disease, or as I said, Parkinson's disease is still mainly diagnosed based on clinical symptoms. So, patients already experienced a severe loss of neurons when they have their first doctor's appointment. So early diagnosis, in my opinion, opens up a critical time frame for neuronal protection and also investigation in early disease stages. And I would say a second factor is that clinical diagnosis can be quite challenging, especially in the early stages when the symptoms may overlap with other neurological disorders, for example. So a biological marker that directly reflects the underlying pathology could therefore make diagnosis a little bit more objective and yeah, potentially allow us to detect the disease even a little bit earlier.

So I think this is one of the yeah, the main reasons why alpha-synuclein has become such an interesting target for biomarker research.

Bob Barrett: So, could you briefly explain what alpha-synuclein RT-QuIC is and how it works?

Melissa Ix: Yeah, if we are looking for biomarkers that directly reflect the underlying pathology, alpha-synuclein is obviously an obvious candidate, but yeah, how can we actually detect pathological aggregation-prone alpha-synuclein in a patient sample. So this is where RT-QuIC comes in. RT-QuIC stands for real-time quaking-induced conversion. So, in simple terms, it is a so-called seed amplification assay that detects the seeding activity of, in this case, misfolded alpha-synuclein. So, the ability of this alpha-synuclein for inducing aggregation, which is what we actually see in Parkinson's disease. So a patient sample may contain very, very small amounts of pathological aggregation per alpha-synuclein, which can act then as a seed and trigger the aggregation of the recombinant alpha-synuclein in the assay. And this amplification process can then be monitored in real time using a fluorescence dye, for example, thioflavin T, so THT, which binds directly to the aggregated forms of alpha-synuclein, for example, fibrils.

Bob Barrett: Why are peripheral tissues particularly interesting for alpha-synuclein RT-QuIC?

Melissa Ix: One of the major advantages of these peripheral tissues is their accessibility. We obviously cannot routinely sample brain tissue from living patients and CSF, so cerebrospinal fluid, could also be a little bit complicated for a routine screening basis. But tissues such as the skin or maybe also the olfactory mucosa can be obtained much more easily and also with much less invasiveness.

What became, yeah, particularly interesting to me when I was reviewing the literature was how many different peripheral tissues have been investigated as a potential window into the underlying disease processes. So, how many different parts of the body actually contain this aggregation-prone of synuclein that we see in RT-QuIC.

Bob Barrett: So, how convincing is the current evidence for detecting alpha-synuclein seeding activity in peripheral tissue?

Melissa Ix: Yeah, that's more of a trickier question. Overall, I would say the evidence is very promising, but it is also quite heterogeneous. The diagnostic performance can vary depending on tissue type, the sampling procedure, the sample preparation, and most importantly, I would say, the specific RT-QuIC protocol. One thing that, especially became very clear to us during the review, was that we cannot simply assume that a protocol that works extremely well on one tissue will perform equally well in another. So there's still a lot of work needed before we can directly compare results across studies. And I would say one of the biggest limitations is the lack of standardization.

Different laboratories, of course, use different substrates, reaction conditions, sample preparation methods, and most importantly, I would say, criteria for interpreting the results. So, although RT-QuIC is extremely promising, I think it is important not to see it as a perfect diagnostic test yet. And another important limitation is that RT-QuIC measures seeding activity, and gives us only a binary outcome. So, seeding positive or seeding negative according to the criteria rather than directly quantifying the amount of pathological alpha-synuclein in a sample, so the actual alpha-synuclein burden in a specific tissue.

Bob Barrett: Could peripheral RT-QuIC eventually be used for the early diagnosis of Parkinson's disease?

Melissa Ix: Potentially yes, and this is probably one of the most exciting possibilities. If we can reliably detect pathological alpha-synuclein in peripheral tissues before the full clinical syndrome develops, so before we actually got symptoms, RT-QuIC could potentially help identifying people in the prodromal stages of disease. But yeah, for that we still need longitudinal studies to understand how early these signals can be detected and how well they actually predict future disease. So, I think the potential is definitely there, but we still need to prove that this potential in prospective studies.

So, for me, the most important next steps are, as I said, standardization and large-scale validation. We need homogenized protocols and also well-characterized patient

cohorts and longitudinal studies. We also need to better understand how different peripheral tissues perform and maybe whether combining different biomarkers can improve diagnostic accuracy. And if we can address these challenges, I actually think RT-QuIC could become a very valuable component of biomarker-based diagnosis, maybe in the future. Yeah.

Bob Barrett: That was Melissa Ix from the University Hospital Essen, Germany. She wrote a review article in the August 2026 issue of *Clinical Chemistry* describing the use of RT-QuIC in peripheral tissues for rapid and non-invasive diagnosis of prion-like diseases, and she's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.