Clinical Chemistry

# Influence of the Confounding Factors Age and Sex on MicroRNA Profiles from Peripheral Blood

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**Guest:** Dr. Andreas Keller is Chair for Clinical Bioinformatics at Saarland University in Saarbrücken Germany.

Bob Barrett: This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

MicroRNAs measured in blood samples are promising, minimally invasive biomarker candidates that have recently been the target of many case control studies. However, the influence of age and gender is confounding variables and MicroRNAs remain largely unknown.

In a paper appearing in the September 2014 issue of *Clinical Chemistry,* researchers from Germany systematically explore the impact of age and gender on MicroRNAs in over 100 normal individuals.

Dr. Andreas Keller was Senior Author of that paper. He is Chair for Clinical Bioinformatics at Saarland University in Saarbrücken Germany, and he joins us in this podcast to discuss this paper.

Doctor, what is it about MicroRNAs that make them special biomarker candidates?

Dr. Andreas Keller: You know MicorRNAs are specifically expressed in different tissue types and bodily fluids filled with serum and they have shown to have a huge diagnostic potential. Besides this, they have also large regulatory influence. Having said all of that was also for Messenger RNA (mRNA), but just few of these Messenger RNA markers that have been claimed also as good candidates one decade ago and made it to clinical routine.

I think what makes the difference for MicroRNAs is that they're very stable. So if you measure the profiles in the morning, at noon, and evening, and even at night, you get more or less the same results. So they are really stable, across let's say one day, two days or even a week. There is big difference as compared to this Messenger RNA (mRNA).

Bob Barrett: Why is the important to consider the age of patients?

Dr. Andreas Keller: Many biomarkers that are included in clinical routine, I think we are used to that we have one fixed threshold and if the value of the patient is above this threshold value, then it's diseased, and below it's considered to be healthy.

I think this is a little bit different, we have found first of all that MicroRNAs, although they are stable over a short period of time as I have told you just a minute ago, they show a huge variance depending on the age. So we started to explore it by investigating young and adults and also long lived individuals, so people that lived longer than 100 years, and we have seen tremendous difference. That is why we measured more and more samples. We have a continuous range, and this is also the reason for our study that we have published in *Clinical Chemistry.'* We have seen that's already a difference of 20 years has a huge influence on the MicroRNA pattern.

So now let's assume for a minute we carry out a case control study and for what reason ever -- you do not have a matched control cohort; that means that maybe the patients are 10-15 years older than the controls that you have. And then you indeed detect more the difference, I mean the age ,and not whether you have a healthy or a diseased patients. And that was the reason why we carried out our study here, such that now people can upload their signatures to web service and they get back these candidates that are potentially influenced by the age.

Bob Barrett: What really take to translates circulating MicroRNA biomarkers to routine?

Dr. Andreas Keller: You know, finally I think this depends on the clinical value and on the unmet clinical needs; the bigger this need is, the easier it will be to translate them. So I see one big problem, most of these studies are currently carried out just on small cohorts. So the first thing that has to done by us and other researchers is to carry out larger replication studies, and we see that these studies are now more and more carried out. But moreover I think, from these classical case control studies, we have to go really to controlled clinical trials and that we fully finally get clinical studies that leads to FDA approval.

And I think one big prerequisite that we have to solve still is a measurement system, which is compatible to this clinic routine workflow. So this will most likely not be a next generation sequencing or something like this, but really a technology which can apply on the whole day routine in many central labs and this is something which is still missing to a certain extent, but it is a prerequisite that we do seek these markers in clinical routine.

Bob Barrett: How long will the translational process take?

Dr. Andreas Keller: It is really hard to answer, as researchers I think we tend to underestimate the time spent that it needs to translate our basic research to patient side, bedside, tremendously. I would say we have now or we are now down the road five years, but it will take for sure at least three more years, so this is something like that. And at least I am clear on that. But to be honest with the FDA approved MicroRNA test to be standard routine this can easily to take 5, 6, 7 more years.

Bob Barrett: Okay. Well finally doctor, which clinical indications are of highest importance?

Dr. Andreas Keller: This is substantial research in the area of cancer, so there are breast cancer, prostrate cancer, lung and colon carcinoma as the big four cancer entities investigated to really substantial amounts. From my perspective and our main focused area is Neurological Inflammatory Disorders, for example, multiple sclerosis, also Alzheimer research where we are now seeing increasing interest.

Finally it's also the cardiac entities that will be considered more and more, for example, acute myocardial infarction, may be as an companion test with ethical markers like MP or TNT that let's say are really, really sensitive, but show a lack of specificity, there I think we see a good potential for MicroRNAs to add on the specificity for such tests.

Bob Barrett: Dr. Andreas Keller is Chair for Clinical Bioinformatics at Saarland University in Saarbrücken Germany. He has been our guest in this podcast on the effects of age and gender on MicroRNA profiles and peripheral blood.

I am Bob Barrett, thanks for listening!