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Utilizing the Stability of Individual Homeostatic Setpoints over Time - A Step Forward on the Path to Personalized Laboratory Medicine

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Guest: Dr. Aasne Aarsand is director of the Norwegian Quality Improvement of Laboratory Examinations (NOKLUS) and a consultant at the Norwegian Porphyria Centre, Haukeland University Hospital, Bergen, Norway.

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

"Is this test result normal?" Physicians, nurses, laboratorians, and patients ask this question multiple times a day, and they do so for good reason. Clinical laboratory test results help guide care decisions in every area of medicine. Typically, normal is determined by comparing an individual's test result against a population-based reference interval, or the spread of values from a group of generally healthy people. However, this approach has some notable limitations.

First, an individual without disease may have a value that falls slightly outside the population-based reference interval, prompting unnecessary further workup. Second, for many analytes, the variation within an individual is typically smaller than the full population-based reference interval, meaning that a notable departure from his or her personal set point could still be incorrectly dismissed as normal. A perspective article appearing in the September 2025 issue of *Clinical Chemistry* highlights efforts to address these limitations and takes an important first step on the path towards personalized laboratory medicine by evaluating a patient's result against his or her individual set point.

In this podcast, we are joined by the article's lead author. Dr. Aasne Aarsand is Director of the Norwegian Quality Improvement of Laboratory Examinations, or NOKLUS, and a consultant at the Norwegian Porphyria Centre Haukeland University Hospital Bergen, Norway. She also serves as chair of the EFLM Technical Committee on the Biological Variation Database. So, Dr. Aarsand, let's start with the basics. What are homeostatic set points and why is their long-term stability important for a more personalized approach to laboratory medicine?

Aasne Aarsand: Thank you for this question, Bob, and thank you for having me on this podcast. Homeostatic set points refer to the stable sort of individual specific values around which biological measurements, such as for example glucose, creatinine, or

hemoglobin, fluctuate under healthy, steady-state conditions. So these values reflect the body's tightly regulated physiological processes with the aim to keep homeostasis. For example, your hemoglobin level typically varies around a specific value that is unique to you and which is influenced by factors such as genetics and lifestyle. So how can homeostatic set points be utilized for paving the way for a more personalized approach for interpreting laboratory test results?

Traditional reference interval models are based on the concept of establishing the central range of population data, wherefore the conventional direct model, single measurement results from a group of reference individuals are ranked, and then the limits are established on this data. But the variation between individuals, which is what we call the between-subject biological variation, or the CVG, is for most measurands much larger than the variation within a single person over time, i.e. what we call the within-subject biological variation, or CVI. So this means that for most measurands, an individual's normal range will typically only cover a part of the population-based reference interval. When comparing an individual's test result to a population-based reference interval, we might miss clinically significant changes for that person or individual, as you also described in your introduction.

And this is where the concept of the stability of homeostatic set points becomes important. Because if, as recent data indicate, these individual homeostatic set points are stable over time, we can use this to construct a personalized reference interval around this homeostatic set point, and this would allow us then to compare a patient test result to their own specific reference intervals. And this would then, with a higher probability, allow us to detect clinically significant changes.

Bob Barrett: In your perspective article, you discussed the findings of a study by Foy and colleagues, published in *Nature* earlier this year. Can you walk us through the design and scope of this study?

Aasne Aarsand: Certainly. This study by Foy and colleagues, published in *Nature* this winter, analyzed complete blood count data from a cohort of over 12,000 adult outpatients who had at least 5 isolated complete blood counts--we can abbreviate for CBC--CBC measurements over a 20-year time period. These individuals were selected as they had no inpatient stays longer than 48 hours and they were alive at the end of the study period, and thus they represent a relatively stable and healthy outpatient population. The study assessed 10 key CBC markers that would be red and white blood cell counts,

platelet counts, hemoglobin, hematocrit, and various red cell indices.

For over 80% of this cohort, more than 10 CBC results were available, which allowed the authors to robustly estimate individual set points which they calculated using something called gaussian mixture modeling.

The authors also importantly replicated their findings in independent internal and external cohorts and used additional data sets to explore how the set points related to clinical risk, genetic factors, and other markers.

Bob Barrett: Well, that does sound like a very important study. Can you share the main outcomes?

Aasne Aarsand: Yes. This study confirmed that CBC set points were highly individual, i.e., specific to each of the included individuals, and also stable over the 20 years' observation period. This is in line with what our group also has shown for both CBC markers and others typical clinical chemistry markers previously, albeit for a much smaller study population. Furthermore, Foy and colleagues found that a typical subject CBC profile could be distinguished from 98% of the other healthy individuals when all the main CBC markers were considered together.

And this suggests, for example, the potential of using more sort of panel results rather than the results of individual markers when monitoring patients over time since they each have sort of a specific profile. The authors also investigated the effect of physiological changes such as menopause, chronic disease, and medical interventions in more selected data sets and found that such factors may influence set points of some sort of related markers to the scenario they were investigated. However, a significant fraction of the set point differences seem to be genetically determined.

And exploring this further, the authors used data from over 30,000 individuals who both had genotype information and multiple CBC measurements, and thereby identified nearly 400 genetic loci associated with the CBC setpoints. Another significant result from the study was the observation that 10-year mortality risk varied significantly based on set points, as well as the risk of diagnosis such as heart attack, stroke, diabetes, and kidney disease. The authors also suggested that changes in CBC set points could be used to enhance the diagnostic accuracy of other common diagnostic tests.

Bob Barrett: Now you have previously mentioned the concept of personalized reference intervals. How could individual homeostatic set points or personalized reference intervals improve patient management as compared to population-

based reference intervals? And where do you think this concept has the greatest potential?

Aasne Aarsand: Thank you for this question. Personalized reference intervals shift the focus from comparing a patient's laboratory test result to what is normal for the general population to what is normal for that specific individual. We published in 2023 another article in *Clinical Chemistry,* where we estimated both personalized reference intervals and population-based reference intervals from the same group of reference individuals.

And in this study, we saw that for most of the 40 included measurements, the individual personalized reference ranges were smaller than the population-based reference ranges as we expected. But at the same time, about half of the study participants had a personalized reference interval wider than the population-based reference interval for a few measurements. So, this highlights just some of the limitations in using population-based reference intervals when interpreting test results of individual patients.

Personally, I think the greatest potential is for areas such as chronic diseases and cancer. As here personalized reference intervals may be used to detect important significant changes for an individual earlier and thus be important to inform on the best follow-up and treatment.

Bob Barrett: Well finally Dr. Aarsand, from your perspective, how can personalized reference intervals make the jump to routine clinical practice?

Aasne Aarsand: Well, the concept of personal reference interval is not new, but there have been barriers for its implementation, including that previous historical models have been too complex and not gained traction or implement--people have not tried to implement them. And an important step forward for this is that we have recently developed a simple model for calculating personalized reference intervals. This model utilizes test result derived from a steady state setting to estimate the homeostatic set point. And thereafter the variation around the set point, i.e., representing the limits of the personalized reference interval, are calculated based on estimates of biological variation for that measurand. And these biological variation estimates can be derived either from population data such as those found in the EFLM Biological Variation Database, or derived from data of the individual in question.

So, there you have sort of the model, but in addition there are a number of other factors that must be considered prior to using personalized reference intervals in routine clinical practice. Firstly, the measurand must not be influenced by

trends biological rhythms, as then that will cloud your interpretation.

And there must also for the individual being assessed, be sufficient historical data from a steady state situation so that you're actually able to estimate the individual homeostatic set point. And for this scenario it's important to take into account that over time, laboratories may be using different measurement procedures.

Secondly, from a more practical point of view, routine use depends on the implementation of algorithms and flagging in laboratory systems or electronic health journals to facilitate their use. And very importantly, we also need further clinical studies on the utility and the usefulness of personalized reference intervals. The concept is very promising, but there is still today a lack of evidence that shows it leads to improved patient outcomes.

Bob Barrett: That was Dr. Aasne Aarsand from Haukeland University Hospital, Bergen, Norway. She wrote a perspective article in the September 2025 issue of *Clinical Chemistry* about using individual set points as an alternative to population-based reference intervals. And she's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.