

**Article:**

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Personalized Reference Intervals in Laboratory Medicine: A New Model Based on Within-Subject Biological Variation
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Guest: Dr. Abdurrahman Coşkun is a professor of medical biochemistry at Acibadem University in Istanbul, Turkey.

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.

Physicians make many of their clinical decisions based on laboratory test results, and usually they compare patients' test results to reference data or cut off limits and make decisions accordingly. Such reference data, what the older literature sometimes called "normal values," are typically based on data from a certain population. When a specific patient's test result is within that reference interval, the test result is usually accepted as normal. If it is above or below then it is considered potentially pathological. However, reference intervals are not universal. Different ones can be obtained from different populations, and it is common practice for each laboratory to determine or at least confirm their own reference intervals: a time-consuming process. In many cases, the variation of the concentration of a specific measure and within the individual is small compared to the variation of the concentration of the same measure and among individuals. This means that a personal reference interval will be narrower than a population-based one, and could be highly beneficial to both clinicians and patients.

A paper appearing in the February 2021 issue of *Clinical Chemistry* may help address the question of personalized reference intervals. The lead author for that study is Dr. Abdurrahman Coşkun. He is a professor of medical biochemistry at Acibadem University in Istanbul, Turkey. His main research area is standardization of laboratory medicine, biological variation, and biomarkers, and he's our guest for this podcast.

So, first of all, Dr. Coşkun, why do clinicians need reference intervals in the first place?

Abdurrahman Coşkun: Yeah, for the diagnosis of diseases, clinical laboratories use patients' samples such as urine, blood, serum, plasma, et cetera, and measure the concentrations of some specific analytes and finally, report the results of these analytes. For clinical decision, physicians need a reference data to interpret

the measurement results of analytes, and a digital reference data are usually referenced intervals or cut-off points. A patient's laboratory result has no meaning if appropriate reference interval for comparison is lacking. Therefore, reference data are needed for all laboratory tests because physicians compare patient's laboratory results with the reference intervals. If the patient's test results are located within the reference intervals they are accepted as normal, and if the patient's test results are outside of your reference intervals they are considered potentially pathological.

For example, the reference interval of serum glucose is generally accepted as 70 to 100 milligrams per deciliter by many laboratories. If the serum glucose concentration of a patient is within this interval, for example, 85 milligram per deciliter, it will be accepted as normal. Otherwise, it will be considered as pathologic. We can say that without reference intervals, physicians cannot make their decisions about patient's laboratory test results, which are necessary for the diagnosis and monitoring of diseases.

Bob Barrett: So, what are the main problems of current reference intervals, and what are the advantages of using personalized reference intervals?

Abdurrahman Coşkun: Well, the main problem is that the current reference intervals are derived from population data, and the population is not homogeneous. From the data of between subject biological variation, we know that for the same analyte, the homeostatic setpoints of different individuals are not the same. For most of analytes, the between subject biological variation is higher than the with subject biological variation. This means that, individuality is characteristic for more laboratory tests. For all these reasons, the population-based reference interval is not compatible for all individuals. And in this case, even if the patient's test results are located within the population-based reference intervals, it may be pathologic for individuals. On the other hand, even if the patient's test results are outside of the population-based reference intervals, it may be normal for individuals. This point is very important because it is about the patient's safety team. Unfortunately, we cannot say that the power of population-based reference intervals to distinguish sick individuals from healthy ones is at the desirable level.

In addition to all these problems, it is not easy to derive population-based reference intervals directly from population because we have to take samples from at least 120 reference individuals. Therefore, in many cases, laboratories use the reference intervals recommended by manufacturers, or use modified reference intervals obtained from literature, textbook, et cetera. This makes the population-based reference intervals more complicated. The main advantage

of personalized reference interval is that they are derived directly from the individual's own data and not from the population data. Although we have not sufficient data in hand, but we can say that by using personalized reference interval, it will be easy to separate sick individuals from healthy ones. For patient's safety team, this point is very important.

Bob Barrett: Do you think that personalized reference intervals will ever replace population-based reference intervals?

Abdurrahman Coşkun: No. I do not think so. In the future, probably a population-based reference interval and personalized reference interval will evolve in different directions. I think we will use personalized reference intervals for individuals and physicians will interpret patients' test results by comparing them with the patient's own reference intervals.

Population-based reference intervals will probably be used mostly from epidemiological and public health studies because population-based reference intervals are necessary to observe the general situation of the analytes in the population. But different scenarios are also possible; a combination of both reference intervals may be used on the same report for patients and physicians. I am very optimistic about the personalized reference intervals. One point is very important: if an analyte is being used in clinical practice for the first time, in the first step, the population-based reference interval of the analytes should be determined. And then in the second step, personalized reference intervals should be calculated when more results accumulate for the person.

Bob Barrett: So, what are the main parameters of personalized reference intervals, and how can personalize reference intervals be derived?

Abdurrahman Coşkun: Well, the personalized reference intervals can be derived easily from a few well-known parameters. These parameters are within-subject biological variations, analytical variation, and individuals' test results. We developed a very simple algorithm to derive personalized reference intervals by using only these three parameters. The critical point is that the individuals must be healthy and in steady-state condition. This point is very important. Additionally, he or she must not be taking any drugs that may change the levels of the analytes. If the individual is not in steady-state, then the calculated homeostatic setpoint of the analytes will be different, and in this case, the model cannot be used.

From a practical point of view, healthy individuals can have their own personalized reference interval calculated in a steady-state situation by at least three or more previously measured test results within-subject biological variation and

analytical variation of the test. Within-subject biological variation of the analytes can be found on EFL and biological variation database, and the analytical variation and individual test results can be obtained from laboratories and hospitals easily.

Bob Barrett: Well, finally doctor, what do you think about the contribution of personalized reference intervals to personalized medical applications?

Abdurrahman Coşkun: Well, personalized medicine has become the hot topic in the last decade. It presents better patient care, and also a unique challenge. The availability of modern biomedical technologies particularly the Omix Technologies, has enabled the identification of molecular variation among individuals, and this offers new opportunities for personalized medicine, but one point is very important, the success or personalized medicine depends on the availability of personalized reference intervals.

For example: if physicians apply personalized treatment or targeted drugs to cancer patients, they should evaluate the effect of treatment by comparing patients' test results with their own reference intervals, and not with the population-based reference intervals. So, it is clear that personalized reference interval is the cornerstone for personalized medicine, and persons that has to make reference intervals will be inevitable for personalized medicine in the future.

Bob Barrett: That was Dr. Abdurrahman Coşkun. A professor of medical biochemistry in Istanbul, Turkey. He has been our guest in this podcast on personalized reference intervals. He is a lead author of a paper describing a new model based on within-subject biological variation for determining personalized reference intervals that appears in the February 2021 issue of *Clinical Chemistry*. I am Bob Barrett, thanks for listening.