

**Article:**

Mary Kathryn Bohn, Dana Bailey, Cynthia Balion, George Cembrowski, Christine Collier, Vincent De Guire, Victoria Higgins, Benjamin Jung, Zahraa Mohammed Ali, David Seccombe, Jennifer Taher, Albert K Y Tsui, Allison Venner, Khosrow Adeli. *Reference Interval Harmonization: Harnessing the Power of Big Data Analytics to Derive Common Reference Intervals across Populations and Testing Platforms* Clin Chem 2023; 69(9): 991–1008. <https://doi.org/10.1093/clinchem/hvad099>

Guest: Dr. Khosrow Adeli is from the Hospital for Sick Children in Toronto, Ontario, Canada.

Bob Barrett:

This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Among non-laboratorians, one common misperception is that clinical laboratory test results are interchangeable, regardless of the instrument or method used or the laboratory performing the test. For many analytes, laboratories may use different test methods and generate results that are not interchangeable. To compare a current result to a previous result, patients must have their testing performed at the same lab, which may not be convenient or even possible. For other analytes, different test methods generate equivalent results but the reference intervals vary, meaning a patient with unchanging values could be considered normal at one location but abnormal at a different one. When analytes show a good agreement across test platforms with minimal variation across patient populations, a single harmonized reference interval would reduce the need to use the same laboratory and eliminate the risk of result misinterpretation.

A new article appearing in the September 2023 issue of *Clinical Chemistry* takes steps in this direction by using big data from many hospitals throughout Canada to establish harmonized reference intervals for several common laboratory tests. In this podcast, we are pleased to welcome the article's senior author. Dr. Khosrow Adeli is a Professor and Division Head of Clinical Biochemistry at the Hospital for Sick Children in Toronto, Ontario, Canada and the president of the International Federation of Clinical Chemistry and Laboratory Medicine. Dr. Adeli, let's start with the basics. What do you mean by big data analytics in clinical laboratories and what are its potential applications?

Khosrow Adeli:

Well, thank you for that question. Clinical labs around the world, as you know, test thousands of patients every month and in some cases, tens of thousands of patients and many more every year. So they usually collect a lot of data, clinical lab data, and this is usually deposited in their databases called Lab Information System, or LIS. Every year, labs, including like our lab here in Toronto, collecting huge amount

of information on patients. So this is really big data, big data that's available to all clinical labs that perform testing and if you look at data over the past few years, in some cases, we're talking about millions and millions of data points. So this is what's referred to big data that's available to clinical labs readily and available for analysis. So it's been shown in the last decade or so, particularly, that there are many ways that laboratories and hospitals and clinical lab services can take advantage of this data to answer many questions in related to patient care and laboratory services, analytical questions, clinical questions. So a big data analytics is referring to analysis of patient data accumulated over many months or many years, and this data is readily available. And the analysis, once one becomes familiar with the statistical methods available, it's pretty straightforward and can be done at minimal cost. So there is now a lot of emphasis on the use of big data analytics in clinical lab arena, both by academic institutions but also by private reference labs around the world.

Bob Barrett: Is it really feasible to harmonize reference intervals when laboratories use different test methods and serve different patient populations?

Khosrow Adeli: So, in this *Clinical Chemistry* article that we just published, we have shown that in Canada, actually, this is a project going on now for over five years in Canada. We have actually used this big data analytics approach to try to harmonize reference intervals or reference ranges for many tests across different labs in Canada. This was a pilot project that has been fairly successful, showing the feasibility of harmonization. Now, why do we need higher harmonization is because there are many differences between, huge differences in some cases, between labs that report reference intervals for the same test. So if a patient goes to one hospital even in the same city, and then next month goes to the next hospital, even the next day, the testing could be done on the same type of instrument and same type of test, but the interpretation could be very different because hospitals are using variable reference intervals, reference intervals that are not evidence-based in many cases.

So therefore, this can lead to variation in interpretation and even diagnosis of disease and monitoring of disease in patients. So therefore, a lack of harmonization across hospitals, across labs, in the same city, in different cities, and different countries is a major issue. And so this approach of big data analytics has been useful to compare labs across different regions and show that it is feasible to harmonize, meaning that you could try to develop one reference range that can be used across different labs. Now, of course, this may not be feasible for all tests, but we have shown in this study that just got published in *Clinical Chemistry* that it is

feasible for a majority of tests. But there are some tests where the differences do exist across different instruments and assays, so we're not saying that this approach is feasible for all clinical or medical tests, but it is feasible for most. And so we should take advantage of this opportunity.

Bob Barrett: Okay, so how could this approach be utilized by other clinical laboratories?

Khosrow Adeli: We're hoping that this report will serve as an example of how to approach this reference range harmonization. So labs can easily access their data through their lab information system and start using some of the methods that we have proposed. Now, we're not the only one who have applied these methods. It's actually a statistical R program using this method called refineR. And this method actually was developed in Germany, and there are publications available on how to use this statistical method. Some background in statistics is of course required, but it is not too complicated to learn and use the codes, these sort of statistical codes, to calculate reference ranges for one's own hospital. So that's the other advantage of this approach is one can actually calculate a reference range for their local population.

Right now, many hospitals in the US, in Canada, and many other countries are using published data in the literature. But this could come from many sources and may not be that relevant to the population you're actually testing in your own city, in your own community. So the advantage of using this approach, big data analytics, is that you could use your own big data in your own hospital to calculate the reference range for your own population, and therefore you have data that's most relevant to you and to your patient population. So that's the advantage of each hospital using this method. But also hospitals across the city can get together and try to compare their reference ranges through this approach. So there are two ways to use this approach. One is calculating reference values or reference ranges for your own hospital. The second is to start comparing and harmonizing with other hospitals.

Bob Barrett: It makes so much sense. It really does. So what is the key take home message from this study that could help clinical labs everywhere?

Khosrow Adeli: I think the take home message is that every hospital is sitting on a huge amount of valuable data and that this data can be easily mined using these new statistical tools, and therefore, one should take advantage of that. The clinical lab scientists and clinical lab managers should learn these new methods and start using them. And it's not just for reference range calculation. There are many labs who are all using big data analytics to actually ask other questions related to analytical performance of the lab, related to quality assurance, related

to clinical questions. One could, for example, look at a specific test in a specific group of patients and try to ask specific questions. So there are many applications. Reference range calculation is important one, but potentially is quite high for applying this kind of approach to many other clinical laboratory-based questions.

So, therefore, my take home message is really try to start becoming familiar with these new approaches. There are lots of publications now. There is even an electronic tool available online through the group in Germany. And so, start using these approaches and, of course, start playing around with the data. And if you have questions, contact us or contact other groups working in this area.

Bob Barrett:

That was Dr. Khosrow Adeli from the Hospital for Sick Children in Toronto, Canada. He and his colleagues published a study describing the use of big data to derive common reference intervals in the September 2023 issue of *Clinical Chemistry* and he's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.