Clinical Chemistry

Closing the Gaps in Pediatric Laboratory Reference Intervals: A CALIPER Database of 40 Biochemical Markers in a Healthy and Multiethnic Population of Children

Bob Barrett: This is the podcast from *'Clinical Chemistry'*. I am Bob Barrett. Proper medical assessment and care of children are widely dependent on both the availability of accurate laboratory tests and reliable reference intervals to help guide test interpretation. Although, the concept of reference intervals and their application appear straightforward, the process of establishing accurate and reliable reference intervals for a pediatric population is complex.

The development and growth of children profoundly influence normal circulating concentrations of biochemical markers and thus the respective reference intervals. Biochemically speaking, children are not just young adults and there are substantial gaps in our knowledge of the multiple influences of age, sex and ethnicity on reference intervals

In a paper published in the May 2012 issue of clinical chemistry, Dr. Khosrow Adeli, Head of the Clinical Biochemistry Department at the Hospital for Sick Children at the University of Toronto reported a comprehensive covariate-stratified reference interval database established from a healthy non-hospitalized and multiethnic pediatric population. The establishment of the new comprehensive database of pediatric reference intervals is part of the Canadian Laboratory initiative in pediatric reference intervals, the CALIPER Project.

Dr. Adeli joins us on this podcast. Doctor, what are the major aims of the CALIPER Project and just how did the CALIPER program get started?

Dr. Khosrow Adeli: Well, there was an understanding by the Canadian Society. There's a society here in Canada called the Canadian Society of Clinical Chemistry and similar to AACC, but there has been a realization over the past few decades in the US, in Canada and elsewhere that there are huge gaps in the what we have available as to what is actually healthy and normal in children when it comes to medical testing and biochemistry testing.

This is not so widely unfortunately recognized and so the gaps haven't been addressed for a long time and so this really led to meetings at the annual conferences here in Canada and eventually I proposed this national project to our Canadian colleagues and seven children hospitals here in Canada began working together and we submitted grant applications to them.

We have a NIH like system here called CIHR and we got some funding. We also discussed with industry and got some funding and support. The diagnostic industry colleagues also understand the really essential need for these reference intervals.

So, because of the need there was a lot of ground work done to begin the project back I would say about 5 years ago, but the actual work didn't start until about 2 to 3 years ago. Initially there were a lot of discussions. We had workshops in Toronto and in Vancouver and Victoria and those workshops eventually lead to the work that was started.

Now, I should mention that the work has so far been done mostly in the Toronto region, but there are activities now that are starting in other sites in Canada.

So, the major aims of the CALIPER Project are to develop a comprehensive database of what is healthy and normal in children and youth invariants at their groups in terms of the diagnostic testing and we've been looking at dozens of different clinical chemistry tests and so far have completed about 40 tests and others are being completed.

So, that was the major aim to determine a database, to develop a database and this database is to assist labs across the board in helping with the reporting of test results and that would of course helped the clinicians in the interpretation of test results. So, that's the major aim.

We were also aiming to look at ethnic differences among various ethnic groups. So far the only data available in literature has been mostly in Caucasian population, so another aim of this study has been to look at differences among ethnic groups.

Of course, there are differences between sexes, the males and females and most importantly perhaps how the values change as the child grows from a new born all the way to teenager years, how do these values change every year and we've been basically looking at those changes and in light of those changes determine what are the normal cut-offs or referred to as reference intervals.

Bob Barrett: So, what is the significance of this study?

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Dr. Khosrow Adeli: So, the major significance of this study is that it would ensure a appropriate interpretation of test results and as you would imagine this is really important because inappropriate interpretation would lead to misdiagnosis as well as inappropriate diagnosis that can lead to other expensive tests if the diagnosis is incorrect and such as for example if a Clinical Chemistry test is inappropriately interpreted, it can lead to for example more complicated and more expensive procedures like MRIs and that can be very expensive to the healthcare system.

So, having appropriate reference intervals or normal values is critical in ensuring appropriate and correct interpretation. Another key significance, that it can basically reduce medical errors in terms of missing diagnosis of various conditions that affect children and youth. So that's the major significance.

Bob Barrett: What are the current gaps in our knowledge of laboratory reference values in children and youth?

Dr. Khosrow Adeli: Surprisingly, we actually have known a little about how values and markers or tests changed in children of different ages as children develop and become young children and then young teens and then later in teen years many of these markers change.

We have had incomplete information in the literature and available to labs and to clinicians and so the aim of our project has been to try to address these gaps. And these gaps are quite significant in the sense, as I mentioned we also don't have data on other ethnic groups' data, limited data available is mostly on Caucasians.

And other issues are for example we don't know always what the gender differences are, also the effect of various factors such as body weight for example or BMI or body mass index, the effect of for example obesity or overweight, which is now very common in children and how those affect these normal values.

So, there're a significant number of areas where we have gap of information that needs to be completed.

Bob Barrett: What risks do these gaps pose when assessing and monitoring children with medical concerns?

Dr. Khosrow Adeli: As I indicated earlier we certainly have major risks associated with these gaps in a sense that currently many actually labs have either limited reference

intervals or normal values for children or they have none and for some test there's nothing available. And also in some of the smaller hospitals in the smaller settings actually they're just simply using adult values because they have no access to pediatric or childhood values.

So, the risks are therefore significant in a sense that they're using adult values and that can of course lead to misdiagnosis as I indicated or diagnoses of a condition that may not be present and that can lead to expensive follow-up tests and is very costly to the healthcare system and lead to over-utilization of scarce health-care dollars. So, there're risks both in terms of medical errors but also risks in terms of financial burden to the system.

Bob Barrett: Okay, so what were the major findings of the current study?

Dr. Khosrow Adeli: So, the current study is the first major report where we have established the comprehensive database for 40 of these tests. 40 of these tests, these are the most common tests that are done on children and youth when they have medical concerns and are seen by pediatricians either in a hospital setting or they go to their family pediatrician.

These tests are commonly done on children and so we focused, the first report in this study focused on those 40 tests and those 40 tests are being extensively studied on over 2000 children that we recruited. These are healthy children that we approached through their parents and ask for of course informed consent and if they consented to participate then a blood sample was selected and in these cases we go to schools, we go to community centers where the children are because we of course want to look at healthy children and not hospitalized children. So, we have been going out to the wider community and accepting children.

So, this report is based on over 2000 of those healthy children participating, donating blood samples and then these blood samples were tested extensively and the data is published in this current report. We also report in this study not only the basic reference intervals but we also show graphs of how these numbers change as children grow in both males and females and we have also looked at differences among ethnic groups.

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So, there're forty fairly comprehensive reports of these 40 common tests in children.

Bob Barrett: Well, let's get into these findings. How do the reference interval results differ between genders?

Dr. Khosrow Adeli: So, if you look at these 40 different tests, you can see that for some tests there are major differences in the sense that males or females might be quite different at certain ages. So, one test that is done for kidney disease, if children are suspected of kidney disease, this test is done is called creatinine.

And this creatinine and if you look at the graphs, you can see that there little difference in children or between sexes early on, but then as the children grow you can see the males have higher values than females, especially male teens have higher values than female teens and that is because of the muscle mass because this particular test is an indicator of the amount of chemical made in the muscle and therefore it indicates basically that as children grow and males have higher body muscle mass, they have higher creatinine values.

So, that's an example of where we can track these children as they grow and determine when they have differences and when they don't.

Bob Barrett: Well, let's talk about ethnic groups. What major differences did you find among different ethnic groups?

Dr. Khosrow Adeli: This study, another advantage it's on a multiethnic population because in Toronto area we have a large number of immigrant populations coming from around the world. We have basically over a 120 different countries, people from 120 countries living in this region. So, this allows us to look at a variety of different groups.

So, the main database is on the Toronto population, but I should say that to make sure that this is representative of a large North American city population, we're still having a large percentage of Caucasians over 66% and the rest are non-Caucasian populations from different regions of the world, mainly Chinese, Canadians and South Asian Canadians from India, Bangladesh, Pakistan.

So, what we did is we actually looked at the three major groups within our population which were Caucasians or European, Western European origin

and then we compared the data to South Asians and Chinese origin participants and interestingly many of the tests did not differ in the sense that they were similar and that's again an information that is not available, but what we found is that all of the 40 tests, seven of them showed significant differences among those three different groups and so we are reporting the differences and showing the differences in this report.

Bob Barrett: Well, developing such a comprehensive database is novel and very impressive, what are the implications of your findings and how would medical laboratories benefit?

Dr. Khosrow Adeli: So, I think the benefits are immediate in the sense that many groups have already contacted us because they were aware of the CALIPER studies ongoing and they've been waiting for this database to be published, so that they can use it in their labs and in their hospital communities. So, the benefits are immediate in a sense that many labs can start using these reference intervals.

The additional implication is that once the labs adapt some of these reference intervals it can be used by the pediatricians and help the pediatricians to improve their diagnosis and monitoring of children with various medical concerns. So, the benefits are significant and immediate and implications are, we're hoping that we would improve diagnosis and monitoring and it would reduce medical errors.

Bob Barrett: How the medical practitioners and pediatricians use the CALIPER database?

Dr. Khosrow Adeli: Well, there're two major ways. One is that through their labs in the sense that if let's say a hospital in New Jersey is the lab, the hospital laboratory decides to use this database then they would be indirectly helping their clinicians and indirectly their clinicians will receive these reference intervals and would benefit from them.

Another approach is that we are developing a website and the website is actually already available, but the data is not live yet, but the database that's in the article would also be published on the website and clinicians can access the database online by going to the website.

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But there's an additional tool we're developing is an application for a smart phone like iPhone, Blackberry where a pediatrician in any office can directly by entering information on the child they are seeing, their age and their gender and ethnic origin, they can download directly the normal values. So, they would have direct access through their smart phone. So, this is an additional tool we're developing to allow very rapid access directly to the clinicians in addition to their labs that are providing them.

Bob Barrett: Well, how about children and families? How do they benefit from the results of this study?

Dr. Khosrow Adeli: Well, of course, children benefit by basically being monitored by labs and clinicians who have more accurate data or an information and they benefit by having a more informed lab results and more accurate interpretation of these lab results and so we believe that the ultimate benefit is to the children and families in the sense that they would be more assured of a better diagnosis and better monitoring of their medical issues.

Unfortunately, this is not well understood or recognized that gaps do exist. Most families and children think that these values probably already exist for the last several decades, but the truth is that there've been many major gaps and these values need to be better established and this is a one major effort in this direction.

Bob Barrett: Well, finally doctor, what the next steps in the CALIPER Program and what other activities that are in progress or being planned?

Dr. Khosrow Adeli: The next steps are that we are continuing our campaigns. We're going to schools and community groups and we're collecting more samples. So, so far actually we have collected close to 4800 samples and so we're continuing to collect samples because there are many more tests that need to be studied.

I mentioned this report is reporting 40 different markers and reference intervals for those, but we're just about to complete another study of 23 hormones and other tests that we call amino acids or endocrine tests and the major gap for these tests as well. So, a second report hopefully should come out this year where we would be adding an additional 23 assays or tests to the database.

So, our efforts for the future, our current aims are to continue to add to the database to make sure that all of the tests that are needed for proper monitoring and diagnosis of children are available and tested and are available in the database.

We are also I should mention other activities are to look at additional questions such as, as I mentioned the effect of BMI or body mass index, the effect of ethical origin and various questions even the effect of time of the day and so on, on these values, markers or medical tests. And so there are many questions still to be e answered, but the main goal is to establish the initial database that can be used immediately by pediatricians and labs worldwide.

Currently, the database is developed on a particular system called Avid Architects system, but we are now doing these validation and transparency studies to ensure that this database is validated for other lab systems, so that no matter what lab system any hospital in North America or elsewhere is using they can benefit from the database.

So, the database is being expanded to other systems because currently hospitals don't all use the same laboratory systems to do the testing and this can result in differences from hospital to hospital. So, our aim is to do these so-called validation and transparency studies to ensure that the database eventually becomes useful to all hospitals.

Bob Barrett: Dr. Khosrow Adeli is the Head of the Clinical Biochemistry Department at the Hospital for Sick Children at the University of Toronto. He's been our guest in this podcast from *'Clinical Chemistry'*. I'm on Bob Barrett. Thanks for listening.

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