Editorial

Pediatric reference intervals for liver markers derived from healthy community-based subjects will improve diagnostic interpretation in children and adolescents

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The article "*New pediatric percentiles of liver enzyme serum levels (ALT, AST, GGT): effects of age, sex, BMI and pubertal stage*" by Dr. Bussler *et al.* (1) is a major advancement, and a good example of the development in pediatric reference intervals that has occurred over the last 5 years.

Liver enzymes are frequently requested laboratory tests. Such results should be accompanied by proper reference intervals to aid the clinician in differentiating between healthy and diseased populations. In children, these reference intervals should not only be derived from healthy subjects, but also reflect the different phases of physiological development from birth to adolescence. However, many pediatric laboratory tests are still inappropriately interpreted using reference intervals derived from either an adult population, hospitalized pediatric populations, or from outdated laboratory methods. The use of inappropriate reference intervals impacts clinical decision-making and has potential detrimental effects on the quality of patient healthcare including misdiagnosis, delayed diagnosis, inappropriate treatments, and patient risk.

From the beginning, reference intervals were often based on students or military recruits. The study subjects were usually around 20 years of age, and the values obtained were used for all age groups. The next step was to include adults of different ages, roughly in the 18 to 65 years of age range. This was easily done as laboratory and hospital staff could be included. During the last decade, we have been trying to fill out the gaps below 18 and above 65 years of age. Filling these gaps are both challenging and costly for the individual laboratory, especially in children. Pediatric reference values often change several times as the child become older, and puberty occurring at different ages causes additional difficulties. In contrast to adult reference intervals that may only require sex partitioning and possibly one or two partitions in the 18 to 65 years of age range, pediatric reference intervals may require multiple partitions. This calls for large populations of healthy children. Collecting hundreds of children at different ages is a project too demanding for individual laboratories.

Recent studies have revived the older approach with data mining and searches through laboratory information systems (LIS) to by-pass the need for blood sampling from healthy children by doing large scale LIS searches or using new statistical approaches (2,3). However, such retrospective LIS searches retrieve data from healthy as well as diseased children. Thus, when possible, blood sampling from healthy individuals is the preferred method (4).

Thus, there has been several recent initiatives to collect blood samples in healthy population-based pediatric cohorts. These projects include projects in Denmark and Sweden (5,6), the Canadian Laboratory Initiative on Pediatric reference intervals (CALIPER) in Canada (7), the KiGGS study in Germany (8), the CHILDx project in the United States and the present cohort. The possibility to compare values from several populations ensures that a reference interval from one of the studies is not flawed by a bias that could affect the test results. A limitation of the present initiatives is that they are from countries with

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Table 1 Recent pediatric reference interval studies on liver enzymes

Study, country	Age range (years)	Number of subjects	Source of data	References
KiGGS, Germany	0–18	14,000	Healthy subjects	Dortschy *et al.* 2009 (8)
CALIPER, Canada	0–18	1,604	Healthy subjects + leftover samples (<1 year)	Colantonio *et al.* 2012 (7)
Copenhagen, Denmark	5–20	1,419	Healthy subjects	Hilsted *et al.* 2012 (5)
Falun, Sweden	6 months–18 years	694	Healthy subjects	Rödöö *et al.* 2013 (6)
AACB, Australia and New Zealand	0–18+ adults	200,000	LIS search	Tate *et al.* 2014 (11)
Zierk, Germany	0-18	32,000	LIS search	Zierk *et al.* 2015 (2)
CHMS, Canada	3–18+ adults	5,930	Healthy subjects	Adeli *et al.* 2015 (12)
Loh & Metz, Australia	0–18	56,712	LIS search	Loh and Metz 2015 (13)
LIFE, Germany	11 months–16 years	3,131	Healthy subjects	Bussler *et al.* 2017 (1)

LIS, laboratory information system; CALIPER, Canadian Laboratory Initiative on Pediatric reference intervals.

fairly similar populations. Thus, we need more studies on pediatric reference intervals in other ethnic groups.

When reading these types of publication our first thought is: can we use this reference interval instead of developing our own unique reference interval? Publications that present reference intervals always raise the question about transferability. Is the study cohort similar to the one that may come to our hospital and could there be a bias between the method in the study and the method used locally? The analytes studied in this article are ALT, AST and GGT. The laboratory methods for ALT, AST and GGT are generally the same throughout the world with a few manufacturers producing the instruments. ALT, AST and GGT are well established methods that have been used for several decades. There are international reference materials and external quality assurance programs for all three analytes. The total interlaboratory coefficient of variation (CV) in the Swedish External Quality Assurance (EQA) program (Equalis, Uppsala; www.equalis.se/en/start/) show low total CVs for all three markers (ALT 4.5%, AST 4.0%, GGT 3.1%) regardless of the method used. The low interlaboratory CVs makes it possible to use the same reference intervals.

Another challenge in pediatric reference intervals are the toddlers. The present study has no children below 11 months of age. CALIPER do present data from children under 1 year of age, however these data derive from leftover samples at the laboratory, in contrast to the samples from children older than 1 year of age that come from blood sampling of community based healthy children (7). Gaps present a challenge for laboratories. The absence of flagging for certain age groups lacking defined reference intervals may mislead the clinician to think that the reported numbers are normal. Major age gaps are present in the NHANES study (9) and the paper from England *et al.* (10) cited in the Bussler *et al.* paper (1). *Table 1* summarizes recent studies that has no or only minor gaps between birth and 18 years of age.

To use the present data in everyday practice still remains a challenge for most laboratories. LIS and electronic patient records usually take care of discrete age groups when handling reference intervals. Thus, it will be an IT challenge to make use of these trajectories describing the changes in serum transaminases in healthy children. A compromise that has been suggested is to implement very narrow age partitions in the LIS, e.g., 12 months for each discrete step. In a study from Søeby *et al.* (3), that resulted in 32 discrete reference intervals for creatinine. This could be compared to supplementary tables 3–5 in the study by Bussler *et al.*

In conclusion, the study by Bussler *et al.* is a major advancement. Covering almost all age groups of children and adolescents it has included an unprecedented number of community-based healthy children and established reference intervals for ALT, AST and GGT, as well as presenting additional information on effects of puberty and BMI on the reference intervals.

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Footnote

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