Pediatric reference intervals: current and future application in laboratory testing

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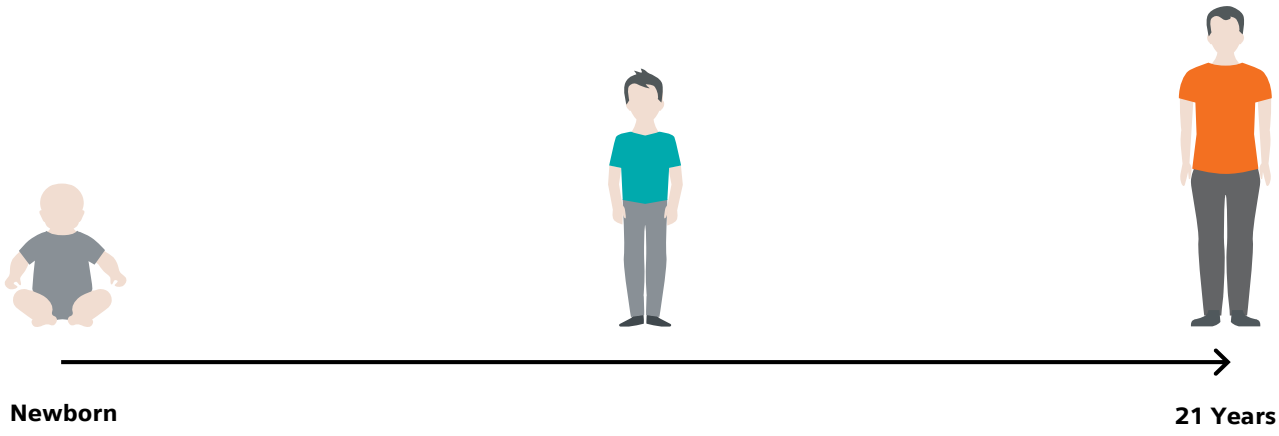
Reference intervals are essential tools used by clinicians to interpret laboratory tests results to determine whether a patient is healthy or unhealthy. Recognition that separate reference intervals are needed for children and adolescents versus adults has presented many challenges for laboratory scientists.

Laboratory tests provide key information that forms the basis for many clinical decisions taken in prevention, diagnosis, treatment, and management of disease in adults and children.[1] Over 80% of clinical practice guidelines for diagnosing or managing disease recommend laboratory testing,[2] and approximately 13 billion laboratory tests are performed in the U.S. annually[3] by over 260,000 hospitals and commercial laboratories.[4] Specialist clinicians in the U.S. have reported that 60–70% of clinical decisions are affected by laboratory test results, within and outside the hospital setting.[5]



Reference intervals

The reference interval (RI) is one of the most important tools in clinical decision making, representing the upper and lower limits of a range of laboratory test results that would be expected in a healthy population. Provision of appropriate RIs for the local population served is a major responsibility of clinical laboratories.[6,7] Detailed guidelines for defining, establishing, and verifying reference intervals are provided by the Clinical and Laboratory Standards Institute (CLSI)[8] and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).[9-15]

A reference interval (or reference range[16]) is usually defined as a statistically derived set of values representing a specified central percentage, usually 95%, of the distribution of test results from reference individuals sampled from a single healthy population.[8-15] By this definition, the 2.5th and 97.5th percentiles represent the reference limits that exclude individuals with the highest and lowest test results. Results that fall outside the reference interval may be interpreted as "abnormal," indicating the need for additional medical follow-up and/or treatment.

Reference intervals differ from decision limits, which are threshold values that have prognostic value or form criteria for diagnosis of a specific disease, e.g., hemoglobin A1c, cholesterol, glucose, and vitamin D.[17]

The preferred method for establishing a reference interval is by direct sampling of 120 healthy individuals selected specifically for that purpose.[8-15] However, indirect sampling from a database previously established for another purpose may be preferable when sufficient numbers of healthy individuals cannot be recruited; it is also easier and less costly, and new studies using indirect sampling are encouraged by the IFCC.[18,19] All reference intervals should be periodically reviewed and updated to keep up with novel methodologies and tests.[7]

Conducting studies to establish reference intervals with 120 samples can be complex, time-consuming, and expensive for individual laboratories, so many laboratories rely on verifying valid reference intervals established elsewhere. As recommended by the CLSI, this requires samples from only 20 individuals, which may be easier to achieve in children.[6,8,19,20] Prior to this strategy recommendation, approximately half of all laboratories adopted reference intervals supplied by instrument manufacturers without verifying them in healthy individuals on-site.[21]

Pediatric reference intervals

The expression "children are not small adults" is frequently applied in differentiating pediatric from adult clinical practice, and it is equally applicable to laboratory testing. Pediatric reference intervals need to reflect changes in growth and development and physiologic function at different ages, particularly during the first year and during puberty.[6,22-25] For example, levels of sex and growth hormones are low in infants, but increase during and after puberty. Biomarkers of bone metabolism (e.g., alkaline phosphatase) and muscle mass (e.g., creatinine) are elevated in infancy and puberty, then decrease with cessation of bone growth and increase in muscle mass.[25,26] Pediatric reference intervals should also reflect differences in gender, body mass index (BMI), sexual development (Tanner stage), and ethnicity. Partitioning of the reference population may be necessary when there are significant differences between these subgroups.

It has been widely documented that the use of inappropriate pediatric reference intervals, i.e., those that do not account for the effects of age, sex, or ethnicity on analyte concentrations, can result in misdiagnosis, delayed diagnosis, inappropriate treatments, and increased healthcare costs,[27-29] as well as having the potential to compromise the results of clinical trials. Despite the widespread recognition that adult reference intervals are inappropriate for pediatric patients, often the adult reference intervals continue to be used to interpret test results for children. In addition, reference intervals derived from hospitalized pediatric populations or outdated technologies that no longer meet current clinical performance expectations may also remain in use.[6,28]

Challenges in establishing pediatric reference intervals

Establishing statistically relevant pediatric reference intervals is still regarded as one of the foremost challenges in pediatric laboratory medicine.[30-32] Many currently available pediatric reference intervals were developed decades ago on outdated instrumentation, and many used hospitalized infants and children as reference individuals.[22,30] The main difficulties involved in establishing new pediatric reference intervals include recruitment of sufficient numbers of, and collection of adequate sample volume from, children defined as "healthy," and the understanding of inherent physiological changes in biomarkers with age.[25,28,31] Recruiting appropriate children, especially neonates, may be limited by ethical concerns and the need for parental/guardian consent. As a result, many laboratories determine reference intervals using residual or leftover samples from children already tested, for whom parental consent is not required, to establish or verify RIs, but since the children were tested because of a medical concern, they may not represent an appropriately "healthy" or sufficiently large population necessary for reference interval calculation.

To ensure that pediatric RIs reflect physiologic dynamic changes throughout childhood and adolescence, they are traditionally separated into groups based on characteristics such as age, sex, and pubertal status, as recommended by the latest CLSI guideline.[8] However this does not reflect the changes in biomarker concentrations that occur throughout child growth and development.[25] Continuous age- and gender-specific reference intervals for laboratory biomarkers have been established for a number of tests,[32-37] but to date consensus has not been achieved on the preferred statistical method for estimating continuous RIs, and guidelines are needed. Meantime, although continuous reference intervals are generally accepted as most appropriate for children, uptake has been limited by the current inability of most laboratory information systems (LIS) to process continuous reference ranges.[6,31]

Another potential limitation of producing standardized pediatric reference intervals is that the use of different analyzers and methods for analyte measurement results in values that are inconsistent among laboratories.[38-39] For example, values for alkaline phosphatase have been reported to vary by up to 300% among different commercial platforms.[40] Even among clinical laboratories using the same instrumentation and reagents within the same geographical area, large variations in RIs have been reported.[18] Continuing advances in technology must also be accommodated.

Because of all these challenges, it is likely that only larger testing laboratories or those that are dedicated to pediatric testing will have sufficient resources to establish pediatric reference intervals. Large-scale initiatives to establish and verify pediatric reference intervals will ensure that appropriate, updated RIs become available for use by smaller and less-specialized laboratories.

Global resources

A number of national and regional initiatives have been launched to establish pediatric reference intervals using samples prospectively collected from population-based studies.[6,25,28,31,41] Some of the groups involved have made their data publicly accessible by posting them online, most notably the most extensive database produced by CALIPER.[42]

Canada

The Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER), led by *Professor Khosrow Adeli, senior scientist, molecular medicine and head of biochemistry, pediatric laboratory medicine, at the Hospital for Sick Children, Toronto,* is the largest and most influential national pediatric reference interval project.[43] Developed and launched in 2008 by Dr. Adeli and colleagues at the Hospital for Sick Children and the University of Toronto,[44] to date (January 2021) CALIPER has collected blood samples from over 12,000 healthy children and adolescents from birth to 18 years of age recruited by 17 hospitals throughout Canada. Age and gender partitions are statistically determined, outliers removed, and reference intervals calculated using CLSI C28-A3 guidelines.[8] The database, which is regularly updated, currently consists of 200 blood tests, including biochemical, endocrine and fertility, vitamin, cancer, metabolic, and hematologic markers, accessible online[42] and via a mobile app (https://caliperproject.ca/caliper/database/#about-the-database). Some of the CALIPER data have also been included in a recently published manual, Pediatric Reference Intervals (8th edition, 2020, sponsored by the American Association for Clinical Chemistry [AACC]), of which Dr. Adeli is a co-author.[40]

The first CALIPER data[27] were extended, through a series of transference and verification studies, to multiple other commonly used analytical platforms in order to expand the utility of the database nationwide.[38] Samples have been analyzed on instrument platforms from Abbott Diagnostics, Beckman Coulter, DiaSorin, Ortho Clinical Diagnostics, Roche, and Siemens Healthineers, as well as by liquid chromatography and tandem mass spectrometry techniques. Analytical methods are controlled according to manufacturers' instructions via preventive maintenance and function checks, calibration, and quality control. All tests are subjected to automated interference analysis for hemolysis, icterus, and turbidity.

CALIPER has produced numerous publications on pediatric reference intervals that have contributed significantly to improving the clinical diagnosis and interpretation of pediatric test results.[45] The most recent reports include age- and sex-specific reference intervals for hematology parameters established on multiple analytic platforms for children from birth through age <21 years[46-48] and reference intervals for 11 critical point-of-care analytes in the CALIPER cohort.[49] Ongoing studies addressing other evidence gaps include establishment of reference intervals for trace elements in whole blood and plasma using inductively coupled plasma mass spectrometry (ICP-MS), and for cytokines and autoimmune markers.

CALIPER reference intervals have been adopted and implemented by hospitals across Canada and the United States, as well as globally.[44] Most children's hospitals in North America are using CALIPER data as well as major reference laboratories. The CALIPER team also aims to disseminate study results to the pediatric healthcare community worldwide using novel translation strategies (see below). CALIPER is also working with the Canadian Society for Clinical Chemistry (CSCC) to develop harmonized pediatric reference intervals, viewed as a key priority in laboratory medicine,[50] across Canada.[51]

United States

In the United States, the *Children's Health Improvement through Laboratory Diagnostics (CHILDx)* program, begun in 1999, is an initiative sponsored by ARUP Laboratories, a large commercial reference laboratory, in collaboration with the University of Utah.[52] To date, over 6000 blood and urine specimens have been collected from children and adolescents aged 6 months though 17 years, and reference intervals have been published for more than 35 analytes for children aged 6 months to 6 years and for over 65 analytes for those aged 7–17 years.[53] The *National Children's Study (NCS),* launched by the National Institutes of Health (NIH) in 2000, originally included establishment of pediatric reference intervals; however, the study was canceled in 2014.[41,54] Data and samples from around 5000 children who were followed from 2009 to 2014 in the NCS pilot (Vanguard) study, were made available through the NIH Data and Specimen Hub (DASH).[55]

Europe

In Germany, the *German Health Interview and Examination Survey for Children and Adolescents (KiGGS)*[56] has made available data for a number of parameters used in routine laboratory investigations as well as reference intervals and cutoff values for analytes of interest for children aged 0–17 years based on a sample size of more than 14,000 blood and serum samples.[57,58] Also in Germany, the multicenter The *Next-Generation Pediatric Reference Intervals (PEDREF)* project, based at the University of Erlangen,[59] is using an innovative indirect statistical approach to retrospective laboratory data (mining hospital LIS) to create next-generation pediatric reference intervals.[60] In the *COPENHAGEN Puberty Study,* conducted 2006–2008 in Denmark, blood samples from 1429 healthy Danish children aged 5–19 years were collected to establish reference intervals for 21 common biochemical properties.[62] In the Swedish *Falun Project*, blood samples were obtained from 701 healthy children aged 6 months to 19 years and used to define age- and gender-specific reference intervals for approximately 50 general clinical chemistry, hematology, and endocrine components.[62] The Danish and Swedish data were later combined to create a database with increased sample size and a broader age span.[63]

Australasia

The *Lifestyle Of Our Kids (LOOK)* study, an Australian community-based longitudinal study, followed a cohort of 852 healthy children and reported RIs for 37 analytes at age 8, 10, and 12 years.[64] In 2014, the *Australasian Association of Clinical Biochemists (AACB) and the Royal College of Pathologists of Australasia (RCPA)* endorsed harmonized pediatric RIs for nine biochemical analytes derived from data from over 200,000 test results from 15 laboratories for use in the region.65 The *Harmonising Age Pathology Parameters in Kids (HAPPI Kids)* study at the Royal Children's Hospital Melbourne (RCH), launched in 2015, has collected approximately 5000 pediatric blood samples from premature infants, term infants, and children aged up to 18 years and aims to publish age- and sex-specific reference intervals for common hematology and immunology analytes.[66-68]

Following a lack of accurate pediatric reference intervals available for China, many groups are now starting to publish data obtained locally. One of the largest is the *Pediatric Reference Intervals in China (PRINCE)* study, which recruited 14,646 healthy children aged 0–19 years from the 10 children's hospitals around China between January 2017 to August 2018. It aims to establish and verify pediatric RIs for 31 analytes. A pilot study in 602 children revealed potential difficulties in recruiting children aged under 3 years.[69]

International initiative

As current president of the IFCC, Dr. Adeli is bringing together representatives from around the world to form a consortium that will produce an international database of pediatric reference interval data. The first web page is expected to become available in 2021, with links to all major reference interval studies from different regions globally. "Over the coming year, I'm hoping that IFCC will be able to assemble and merge reference interval data, which is a bigger challenge. An IFCC task force is also being established to analyze and compare data from populations and various ethnicities across the world," Dr. Adeli explained. "Our ultimate goal is for every hospital and every clinician and every lab professional in every country to have access to one major resource accessible through, the IFCC web site, so that they can get all the data they need," he stated.

Role of governments and manufacturers

Over the past few years, the American Association for Clinical Chemistry (AACC) has been campaigning to improve and expand pediatric reference intervals within the United States[1,29,32,70,71] and lobbying Congress for federal funding for the establishment of a national repository of specimens from healthy children aged 0–18 years.[72,73] The AACC argues that most U.S. laboratories are unable to obtain enough samples from healthy children to determine their own accurate pediatric reference intervals and proposes that specimens be collected and stored by the Centers for Disease Control and Prevention (CDC), via the National Health and Nutrition Examination Survey (NHANES). The Environmental Health Laboratory would perform testing on these samples to generate pediatric reference intervals based on age, stages of development, race, ethnicity, and gender. The data would be disseminated to laboratories jointly by the CDC and the AACC. Manufacturers and clinical laboratories would be required to report back the reference intervals generated from repository samples and the methods used to determine them, and these reference intervals would be accessible to the public. The AACC's campaign is supported by 34 "PRI partners," including professional medical organizations, children's hospitals, and laboratory instrument manufacturers.

Assay manufacturers also have a responsibility to help support development of pediatric reference intervals. Siemens Healthineers is highly supportive of the efforts of AACC and CALIPER. In addition, Siemens Healthineers has led the way in establishing pediatric reference intervals for certain clinical chemistry, infectious-disease, thyroid, and reproductive assays (including Tanner stages as appropriate) in their portfolio, integrating these reference intervals into assay-specific instructions for use. Through these efforts, Siemens Healthineers has demonstrated its commitment to the delivery of a higher level of patient care and improved outcomes for our pediatric population across the globe.

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