AACC Better health through laboratory medicine.

Position Statement

Pediatric Lab Results: The Need for "Normal"

July 2016

Introduction:

Every day pediatricians and family doctors order laboratory tests on children under their care. The results from these tests provide the doctor with reliable, accurate information for diagnosing a child's condition and determining what, if any, medical intervention is necessary. When making this assessment, the physician must evaluate the result within the context of a reference interval—the range of normal values appropriate for the age, stage of development, ethnicity and/or gender of the child. Laboratory professionals play a vital role in creating and refining pediatric reference intervals and disseminating this information to the medical community. Without precise reference intervals physicians may misdiagnose a condition, which could result in patient harm and increased healthcare costs (1, 2). Unfortunately, scant access to samples from healthy children significantly hinders the establishment of pediatric reference intervals (1). A national repository of samples from healthy children would be an invaluable resource to the healthcare community in improving the health of America's children.

Background:

Establishing Reference Intervals

Medical device manufacturers and clinical laboratories develop pediatric reference intervals that assist clinicians in interpreting laboratory test results. Samples from individuals are collected, tested and analyzed to establish the 'normal' range of values for each substance being measured based on age, stage of development, ethnicity and gender. A test value within the normal range generally does not signal the need for medical intervention whereas an outlier may require a plan of treatment.

AACC POSITION:
High-quality reference intervals for children age 0-18 years are needed to ensure that pediatric patients are appropriately diagnosed and treated. AACC supports the creation of a national repository to collect and store pediatric samples from healthy children that can be used to develop more precise age, developmental, ethnic and gender specific reference intervals. The repository should also maintain a comprehensive database of existing pediatric reference intervals and make them readily accessible by healthcare providers and patients.

Use of Residual Specimens

Currently, many laboratories use residual or leftover blood samples from children who were tested for a medical condition to verify or establish reference intervals. Generally, informed consent is not required for the use of these samples, since they are used for quality improvement purposes and patient identifiers are removed. However, these specimens do not provide a normal range for a healthy patient population, as many of the children were ill, or had symptoms of illness, when their samples were drawn.

Current Initiatives

There are a number of ongoing efforts in place to improve the quality and accuracy of pediatric reference intervals. For example, the Children's Health Improvement through Laboratory Diagnostics (CHILDx) program—initiated by ARUP Laboratories and the University of Utah Department of Pathology—and the Canadian Laboratory Initiative in Pediatric Reference Intervals (CALIPER) are two programs seeking to enhance the quality of reference intervals for children. However, there remains a need for more extensive funding and access to sufficient

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samples from healthy children. Unfortunately, one potential source for such specimens, the National Institutes of Health's National Children Study, was discontinued in December 2014 leaving a void that has not been filled.

Considerations:

Age, Developmental Stage, Ethnicity and Gender Variations

Normal ranges can differ significantly between children and adults (3, 4). For example, a high level of alkaline phosphatase (ALP) in an adult can indicate bone or liver disease, while the same level in young children and infants may be normal and just represent growth and development. Reference intervals often change with age and in parallel with major shifts in physiology: shortly after birth, when an infant's body is adjusting to living outside the womb; early childhood, when children experience growth spurts; and adolescence, when growth velocity changes and there are large fluctuations in sex hormone levels (4). Similarly, there may be significant differences due to ethnicity and gender (2). Reference intervals that reflect these variations are needed to properly interpret laboratory values.

Availability of Specimens

Identifying a truly healthy group of children that is representative of an entire patient population is complex and demanding. For reference interval studies, large numbers of volunteers are needed in order to provide meaningful statistical power (1). Though large numbers of children are seen at healthcare facilities, the majority of them are ill rendering their blood samples unsuitable for normal range studies. Frequently, parents are reluctant to allow sample collection or examination of children who are otherwise healthy, thereby limiting access to suitable samples. In addition, there are limits on how much blood should be drawn from small children (4). The lack of specimens from healthy children is a significant challenge for laboratory professionals (1).

Informed Consent

Recruiting healthy children to obtain blood samples requires approval from an institutional review board (IRB) as well as informed consent from the parents and assent from the child (age of assent can vary among institutions). The IRB determines if permission is required from one or both parents based on a study's potential risk and benefit. Once approved by the IRB, the laboratory must identify eligible children, explain the importance of the study to the family, and seek informed consent. For many testing facilities this can be an administratively difficult and costly process.

Technological Changes

Pediatric reference intervals frequently change as a result of technological innovation. New test methods may detect previously unobserved substances or may enable the detection of lower concentrations of something already known to be present in higher abundance. The new data may necessitate that laboratories update the existing normal range for that test. The use of outdated reference intervals can lead to misdiagnosis and treatment (1).

Informatics

A sound informatics plan is essential for collecting and interpreting the data needed to calculate reference intervals and provide meaningful information with the test values. An often-underappreciated aspect of reference interval studies is the level of explanation required for each result. Such studies include information about the child and details about the sample and results. The collection of these meta-data is essential to generating clinically applicable, quality reference intervals to help clinicians interpret diagnostic testing results. Currently there is significant variation among laboratories in the data they collect to establish reference intervals and the information they report to physicians.

Need for a National Repository

Developing accurate pediatric reference intervals is administratively challenging and costly for medical device manufacturers and clinical laboratories. Each interval requires at least 120 specimens from healthy children and each medical condition, depending on the analyte, may necessitate the creation of several separate age-defined intervals for boys and girls alike, as well as for different ethnic groups, to cover the range of physiological changes that take place from birth through adolescence. The resources and level of coordination needed to achieve this objective will likely require a national approach, such as the creation of a central repository to systematically collect, store, and disseminate samples from healthy children.

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Positions:

AACC is concerned that the laboratory community does not have the resources necessary to establish and maintain pediatric reference intervals that reflect normal ranges in healthy pediatric populations. Policymakers have the responsibility to provide access to samples from healthy individuals of all ages, developmental stages, ethnic backgrounds, and both genders to ensure the health of the nation's children. Specifically, AACC recommends:

- Congress should mandate and fund a national repository of specimens from healthy children age 0-18 years to develop pediatric reference intervals.
- The samples in the repository must have been collected with informed consent and be available to in vitro diagnostic device manufacturers and clinical laboratories to establish appropriate reference intervals.
- Manufacturers and clinical laboratories should be required to report back the reference intervals generated from repository samples and the analytical methods used to determine them, and these reference intervals should be accessible to the public.
- De-identified residual specimens must continue to be available as they currently are, without informed consent, for quality improvement activities.
- Data that are gathered, analyzed, and reported with pediatric reference intervals should be standardized across the laboratory community.
- The laboratory community should collaborate in developing a process for sharing and transferring existing established pediatric reference intervals across clinical laboratories and evolutions of technology.

References:

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