ADLM Association for Diagnostics & Laboratory Medicine™
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Advancing Children's Health Through Pediatric Laboratory Medicine: *The Unique Healthcare Needs of Children*

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The Unique Healthcare Needs of Children

Pediatric laboratory medicine is integral to the healthcare of infants, children, and adolescents [1]. Over 22 percent of the U.S. population is under the age of 18 [2]. Annually, youths account for over 5.2 million hospitalizations and about 171 million outpatient visits, in addition to annual well-patient visits. Approximately three billion pediatric laboratory tests are performed in more than 320,000 Clinical Laboratory Improvement Amendment (CLIA)-certified laboratories in the U.S. [1, 3, 4, 5, 6].

As essential members of the healthcare team, pediatric laboratory professionals ensure high quality and timely test results that can have different implications depending on the child's developmental stage, gender, ethnicity, and age. Lab professionals can help healthcare providers interpret and better understand lab results. With this information, pediatricians, family practice, and other related providers assess health, diagnose disease, and plan and monitor treatment for the patients under their care.

Pediatric laboratory professionals continually assess and adapt to today's complex, changing healthcare environment and offer their vital professional expertise to providers. Young patients and their families receive accurate diagnoses and treatment every day for common and rare childhood illnesses partly thanks to the resources provided by pediatric laboratory medicine experts.

About Pediatric Laboratory Professionals

Pediatric laboratory medicine teams produce essential, objective test results for healthcare providers. They work in a variety of public and private settings, including hospitals, academic institutions, physicians' offices, and independent facilities. The laboratories might or might not serve solely pediatric patients; however, pediatric laboratory specialists emphasize pediatric healthcare regardless of the overall setting in which they work.

In U.S. hospitals, most newborn blood draws are performed by phlebotomists, who have at least one year of specialized practical experience in addition to a high school diploma or equivalent. Phlebotomists use specialized techniques to draw small-volume blood samples from young patients with minimal pain or discomfort.

Medical laboratory scientists run laboratory tests on standard equipment following protocols and procedures for small-volume samples that ensure reliable results. These well-trained professionals typically have two- and/or four-year degrees in a relevant scientific discipline with hands-on professional pediatric training and applicable certification. With at least a bachelor's degree, specialist certification, and years of experience, laboratory managers or supervisors are responsible for daily laboratory operations, including quality control and other regulatory compliance activities.

Pediatric laboratory directors oversee clinical and operational aspects of the laboratory. These individuals are Board-certified pathologists with medical degrees (MD or MD/PhD) in pathology, pediatric pathology or a related specialty, or Board-certified clinical chemists (PhD) and other PhD-level scientists in related fields or CLIA accepted directors.

They ensure the laboratory complies with all quality standards and regulatory requirements while meeting the clinical needs of patients. This includes verifying the accuracy and precision of FDA-approved tests. Many of these tests are designed for adults instead of children. Pediatric laboratory directors address these gaps by creating laboratory developed tests (LDTs) that better suit their patient population. They also ensure the completion of quality assurance testing on laboratory equipment.

Regularly, they evaluate the process of clinical testing, from when the test is ordered and the sample collected, to when the result reaches the provider. Laboratory directors use the findings of these assessments to improve laboratory procedures. They also work with providers to make test utilization and results interpretation efficient and effective.

With their advanced degrees and scientific expertise, laboratory directors often conduct research, working to translate scientific discoveries into clinical care. Additionally, they generate and contribute laboratory data to clinical practice guidelines and evidence-based medicine and work with providers to integrate and maximize the usefulness of informatics [1].

Together, laboratory professionals play an integral role in providing high quality patient care.

At academic institutions, laboratory directors are faculty members, responsible for educating students and doctors in training. Pediatric laboratory directors undertake these activities with an emphasis on children's health.

Pediatric Lab Tests

Diagnostic and screening tests are integral components to pediatric healthcare in all stages of childhood. In the U.S., newborn screening tests begin within 48 hours of birth for approximately four million infants per year. Pediatricians, family practice, and other relevant healthcare providers rely on laboratory tests to ensure the health and well-being of their patients from birth through adolescence [7, 8, 9, 10].

For instance, a test might be ordered on infants who appear jaundiced. Often bilirubin, the naturally occurring by-products of the normal breakdown of red blood cells, build up in the blood can result in the characteristic yellow skin and eye discoloration of jaundice. Most two- to four-day-old newborns have mild jaundice, but as the liver matures this naturally resolves within one to two weeks [11, 12]. If untreated, very high levels of this compound can cause brain and central nervous system damage that can result in seizures and permanent hearing loss. Thus, testing can help determine whether blood levels are sufficiently high to warrant treatment.

During annual wellness visits, pediatricians may request children (0 to 12 years old) be screened for diabetes, obesity, high cholesterol, tuberculosis, iron deficiency anemia and lead poisoning, depending on determined risk. According to the CDC, about 250,000 children between one and five years old have detectable blood lead concentrations [13]. Additionally, the prevalence of childhood obesity has more than doubled in children and tripled in adolescents in the U.S. during the past 30 years, increasing the number at risk for cardiovascular disease and diabetes [14].

With providers' discretion and risk assessment, teenagers (13 to 18 years old) may be screened for some of the same conditions as younger patients at annual visits. The CDC also recommends testing for certain sexually transmitted diseases, like human immunodeficiency virus (HIV).

Although the annual number of HIV infections has decreased among persons aged 13–24, they account for 20% of all new HIV diagnoses as of 2020 [15, 16].

Common or routine lab tests at different ages

Newborns (0-5 days)
- Newborn Screening
- BilirubinTesting

Children (0-12)
- Diabetes
- Obesity
- Cholesterol
- TB
- Anemia
- Lead Poisoning

Adolescents (12-18)
- Childhood Screening
- STD Testing

The Impact of Pediatric Laboratory Medicine

In support of children and their families, pediatric laboratory professionals use their unique expertise to help pediatricians and other caregivers improve health outcomes.

Public Health and Prevention

Pediatric public health policies are designed to meet the unique health needs of children to ensure their physical, mental, and social well-being. Clinical laboratory testing plays a vital role in public health and disease prevention programs, with a focus on identifying diseases, either within an individual or within a population. The major aim of these programs is to prevent the diseases from causing harm to the individual or spreading to others. Children may be tested because they meet specific criteria for being at risk for a disease or condition. Alternatively, all children, despite risk, may be screened for specific diseases or conditions that meet certain criteria of population screening. The early detection of diseases or conditions through lab tests allows for timely treatment before permanent damage occurs, which is especially crucial in children to prevent long-term complications like cognitive or physical impairments.

Screening children for lead exposure is an excellent example of the significant impact of lab testing on public health outcomes. Lead is a toxic metal that is found in the environment as a result of the historical use of leaded paints and gasoline, and aging plumbing and infrastructure.

Children are particularly vulnerable to lead toxicity as their bodies are not fully developed to effectively eliminate the toxin from their bodies. Exposure to lead can slow growth and development. High lead exposure can cause permanent damage to the brain and nervous system.

"Lab tests can detect diseases or conditions before signs and symptoms occur, allowing for intervention before physical or mental damage is permanent."

Young children are also more likely to be exposed to lead because they play and crawl on the floor and have tendencies to place hands in their mouths and other non-food objects, like leaded paint chips in older houses. Ingestion of one lead-based paint chip in a toddler can result in significant lead toxicity. The impact of lead poisoning on the brain and overall development may not become apparent until long after exposure. However, clinical laboratory testing can detect lead in a child's blood, enabling the initiation of treatment to remove lead from their system and the elimination of lead sources from their environment.

Newer data suggests that there is no safe blood lead level. Even a very small amount of lead in blood in a child can have negative impact on cognitive development. With that in mind, pediatric laboratory medicine professionals have developed the capability to detect very low levels of lead in a child's blood. As a result of the expertise and diligence of laboratory professionals, low-level lead testing is now widely available in hospitals, physician's offices, and mobile health centers.

Although lead toxicity is one example, other conditions where lab tests are integral to public health and prevention programs for children include newborn screening for several metabolic and genetic disorders, cholesterol and lipid screening, and iron deficiency screening. These early screenings in children help identify and treat various conditions for improved health outcomes by preventing long-term complications.

Newborn Screening

In 2008, George W. Bush signed into law the ADLM-backed legislation, the *Newborn Screening Saves Lives Act*. The law has provided resources to identify and evaluate conditions for screening, assists states in improving and expanding their programs, and ensures the quality of the laboratory testing.

Difference between Screening and Confirmatory Testing

Screening tests are typically conducted on large populations, independent of symptom status. Screening tests may detect diseases or environmental exposures. Abnormal screening tests are typically followed with confirmatory testing that is more sensitive and specific.

Confirmatory testing is also known as diagnostic testing and clarifies the significance of the abnormal screen result. Diagnostic confirmatory testing may be ordered if clinical symptoms are present, without performing a screening test first [19].

Newborn Screening

Newborn screening (NBS) is the nation's premiere public health program intended to identify at-risk newborns with genetic disorders for whom early diagnosis and treatment will be beneficial. NBS identifies approximately 15,000 affected children and their families in the U.S. each year. Each state runs its own NBS program and determines what conditions are included in the panel. The federal Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) generates a list of recommended genetic disorders that meet criteria for public health screening including more than 30 conditions [19, 20]. This list is referred to as the RUSP (Recommended Uniform Screening Panel) and is regularly updated as disorders are nominated, reviewed, and approved for population screening.

If a screening test yields an abnormal result, NBS coordinators from the state's health department will contact the infant's healthcare provider with recommendations for further action. The healthcare provider will then arrange for additional, specialized testing, typically conducted at a hospital or reference laboratory. Additionally, more accessible chemical testing may be recommended to assess the risk of critical illness and determine if immediate medical intervention is required.

NBS started in the 1960s when **dietary management** was demonstrated to change long-term outcomes for individuals affected by Phenylketonuria (PKU). PKU occurs when the body is unable to breakdown excess phenylalanine, an amino acid found in protein-based foods. If untreated, PKU can lead to irreversible brain damage, mental disability, seizures, and other adverse outcomes. Early diagnosis and implementation of a protein-restricted diet can enable individuals with PKU to lead healthy, normal lives.

In the early 2000s, there was a significant expansion of **metabolic disorders** covered by NBS. One of the great success stories is that of early identification of medium chain acyl-CoA dehydrogenase (MCAD) deficiency. MCAD deficiency is the most common inborn error of fatty acid oxidation, with population incidence of 1:1,300 to 1:1,9000, and typically manifests with severe hypoglycemia that can rapidly progress to coma and death [21]. Therapy includes frequent feedings and vigilance for symptoms concerning for low blood sugar. Early diagnosis of MCAD through the expansion of NBS has reduced the mortality rate from 50% at first presentation to 3.5% when its captured early. Increased identification of individuals affected by disorders of fatty acid oxidation also resulted in a dramatic decrease in sudden infant death (SID) cases of about 5%.

Most **genetic diseases** detected by NBS are based on the presence of elevated or missing metabolites. For some disorders on the RUSP that do not result in metabolic changes, alternative technologies must be employed. Disorders of hemoglobin, such as sickle cell disease, are screened with a test that specifically detects these protein molecules. Additionally, screenings for heart conditions (like pulse oximetry) and hearing are routinely conducted shortly after birth.

In the area of **DNA testing**, early detection and intervention for several disorders are now possible. Current NBS programs test for disorders like galactosemia, biotinidase deficiency, and cystic fibrosis, then utilize highly targeted DNA tests to confirm the results. Other conditions, such as spinal muscular atrophy (SMA) and severe combined immunodeficiency (SCID), necessitate DNA analysis for a precise initial diagnosis.

Furthermore, **therapeutic advancements** like gene therapy for SMA and bone marrow transplantation for SCID have revolutionized the expectations around disease progression and outcomes. While broad DNA sequencing (exome or genome sequencing) is not yet a standard part of NBS, ongoing studies have explored its cost-effectiveness and diagnostic efficiency. Despite current limitations in laboratory infrastructure, this strategy holds promise for the future, potentially expanding the range of identifiable genetic diseases.

NBS programs play a critical role in identifying many congenital conditions. When left untreated, these disorders can lead to severe health complications, including seizures, loss of muscle tone, failure to thrive, coma, and even death. For policymakers, the focus on early and accurate laboratory diagnosis emphasizes the importance of supporting and expanding these programs as a key strategy in infant health protection and intervention [17, 18].

Diagnoses and Management of Childhood Illnesses

Childhood illnesses are often different from adult disorders. specialized laboratory tests are required to accurately diagnose, treat, and manage these diseases. Many childhood illnesses are caused by infectious agents. Although vaccinations have tremendously decreased the incidence of previously common infectious diseases, infections still remain the leading cause of childhood illnesses.

Children and teenagers with cancer, poisonings from unintentional ingestion of toxic materials, and intoxications from harmful drugs like fentanyl, also require laboratory testing to monitor drug concentrations and help clinical teams to effectively treat them and prevent toxicity.

"Children are not small adults."

Common childhood infections include respiratory syncytial virus (RSV) infection which may cause airway inflammation and pneumonia, and streptococcus bacterial (strep) infection that is a leading cause of sore throat. Since children, particularly newborns, do not have fully developed immune systems, prompt diagnosis is needed to treat these patients. To diagnose these and other infections, laboratory professionals generally use rapid screening tests that provide quick preliminary diagnosis for early patient management.

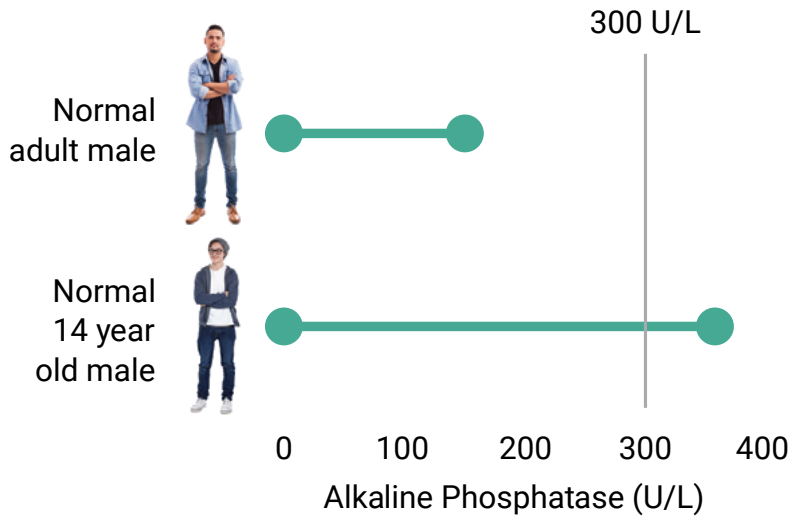
Definitive tests are used to confirm the results of screening tests. For example, a rapid strep test can provide results within a few minutes from a patient throat swab. If the test is positive, the clinician prescribes antibiotics and treatment can begin immediately, minimizing disease duration and the risk of the patient spreading the infection to others. If the screen is negative, the laboratory will perform a culture from the throat swab sample to confirm the negative preliminary results. If the throat culture turns out to be positive, the laboratory professional contacts the ordering provider so the patient can be prescribed antibiotics at that time [26].

Children are also increasingly affected by chronic illnesses [28]. An estimated 27% of children between the ages of 2 to 8 years in the U.S. have chronic diseases [28]. To successfully manage these conditions, continual clinical and laboratory assessments are needed.

A common, chronic disease that requires consistent management in children is Type 1 diabetes. In this disease, a child's body cannot make a hormone called insulin. Insulin is needed to process the sugar glucose, which is a primary source of the body's energy. Patients with Type 1 diabetes have increased glucose in the blood and urine resulting in increased thirst and urination. Since the body cannot appropriately utilize glucose, the pediatric patient experiences extreme hunger and increased food intake. If untreated, Type 1 diabetes can lead to serious complications, such as heart, kidney and eye disease. Thus, laboratory professionals play an important role in the diagnosis and treatment of diabetes.

Obesity among children and adolescents is also on the rise. Obesity is defined as increased body weight relative to one's height. Genetic factors, certain disorders, sedentary and dietary behaviors contribute to the development of obesity. Obesity increases the risk of developing hypertension, stroke, and heart disease and is important to monitor. The laboratory plays a key role in the clinical assessment and management of children with obesity. Sometimes, obesity is caused by treatable underlying diseases like hypothyroidism or Cushing's disease. These can be identified by laboratory assessments that measure the concentration of thyroid hormones. Tests that explore how well the other organs like kidney, liver and bones are functioning are also often performed.

Normal Alkaline Phosphatase Intervals



Reference intervals in healthy children and adults can be different.

Pediatric Reference Intervals

To interpret laboratory results, providers rely on reference intervals developed by laboratory medicine professionals. Reference intervals, historically called the "normal" range, is the spectrum of values for a given lab test that would be expected for a healthy person. If a patient's test result falls outside a reference interval, it can provide valuable insight regarding potential disease in the patient. Without precise reference intervals that accurately reflect the healthy range, clinicians may misdiagnose a condition, which could result in patient harm and increased healthcare costs [27].

"The establishment of robust pediatric reference intervals is critical to ensure accurate diagnosis and treatment of children."

Pediatric laboratory professionals have long recognized that reference intervals in children differ from adults, but also at different developmental stages. Other countries have established specimen biobanks for the purposes of establishing pediatric reference intervals. However, many of these countries do not have the diversity of the U.S. so it is difficult to utilize their pediatric reference intervals. There are also gaps in many of these ranges from birth to 1 year where developmental changes can occur that may alter the reference interval rapidly, depending on the test.

Testosterone, a steroid sex hormone that is an indicator of various clinical conditions including infertility, cancers, and precocious puberty, has dynamic reference intervals based on puberty, preterm delivery, sex, and daily variation. In adult males, testosterone levels are relatively stable with a slow decline with age. However, there can be rapid changes in males during puberty that is specific to pubertal status of the individual. Newborns and preterm individuals can also experience rapid changes in reference intervals. Therefore, accurate and dynamic reference intervals that reflect the individual at the development stage they are in, are required to deliver the best clinical care.

Alkaline phosphatase, an enzyme found at high levels in both the bone and liver, provides a classic example of how reference intervals in healthy children and adults dramatically differ. Many adult reference intervals for this enzyme lack a lower bound, whereas for children, reduced activity of alkaline phosphatase is a marker of the hypophosphatasias, disorders of bone formation. In adults, increased levels of alkaline phosphatase typically indicate liver or bone disease. In children going through puberty, it is normal to have high levels of alkaline phosphatase in the blood, due to bone growth. During growth spurts, levels may reach particularly high levels. A standard reference interval for alkaline phosphatase in a healthy adult male is 53-128 U/L1. However, an appropriate reference interval for alkaline phosphatase in a healthy 14-year-old boy is 54-369 U/L1. Therefore, a result of 300 U/L could trigger a misdiagnosis in a 14-year-old boy if the clinician relies on the reference interval for a healthy adult male [21].

Pediatric laboratory professionals strive to provide precise reference intervals to best assess the children under their care. The most robust reference intervals are those established using blood samples from healthy children. Unfortunately, the development of more precise pediatric reference intervals is hindered by the limited access to blood samples from healthy children. In addition, limitations of laboratory information systems can impede best practices with reference intervals. The establishment of robust pediatric reference intervals is critical to ensure accurate diagnosis and treatment of children [23].

"Children are our future. Clinical laboratory tests serve as the voice for young children who can't speak for themselves and manage their healthcare. We must guarantee children access to high-quality, accurate testing to lead happy, healthy, productive lives."

– ADLM President Dr. Octavia Peck Palmer

Future Directions

Pediatric laboratory medicine is a vital, dynamic, evolving field. Pediatric laboratory professionals continue to innovate by developing laboratory developed tests for rare diseases to identify and diagnose medical conditions and diseases affecting children more quickly. Through their dedication, skills, and expertise, they have become an integral part of the team that cares for children and saves lives.

Many children are born with metabolic disorders that can be treated if the disease is identified early enough. Not very long ago, many of these children died or suffered from life-long debilitating conditions because there was no way to diagnose them. Thanks to the collaboration of the laboratory and medical communities, screening tests and treatment plans were developed, and now virtually all newborns are screened for more than 30 diseases/conditions ensuring earlier life-saving treatments. This number is likely to grow as laboratory professionals, medical researchers, and clinicians partner to advance children's health.

"Pediatric laboratory medicine is a vital, dynamic, evolving field."

Today, several point-of-care molecular tests exist for the detection of infectious agents. These tests are faster and more precise than their predecessors and allow pediatricians to personalize their patients' care. Laboratory experts continue to develop new and unique molecular tests to promote even more efficient and effective treatment of common childhood infections and diseases.

Advances in pediatric laboratory medicine enable healthcare providers to better assess the risks and benefits to their patients of various care options and choose a plan of action to optimize outcomes [25, 26]. As laboratory medicine continues to advance and increase in promise and complexity, the collaborative development of clinical practice guidelines will be critical to ensure diagnostic advances are appropriately applied. Guidelines provide vital information and direction for diagnosing and treating their patients, and laboratory tests are often critical components of decision-making. When laboratory professionals inform the recommended testing paradigms, they enhance the effectiveness of clinical guidelines in improving patient care and reducing overall healthcare costs.

Pediatric laboratory professionals are increasingly at the center of the rapidly changing healthcare delivery system and contribute to advances that make healthcare equitable and accessible to all. Despite these advances, care gaps remain. Some children are affected by rare genetic diseases for which formal diagnoses are unavailable. Whole genome sequencing, a technique by which the sequences that make up a person's genetic makeup is mapped, is being adopted by laboratory professionals to help diagnose rare diseases. Also, children with conditions like cancer who require regular drug monitoring may live in places with limited access to laboratory testing and may have to travel significant distances to be tested. Laboratory professionals are exploring the possibility of remotely obtaining blood samples for laboratory testing. This promises to ease the time and cost burdens of pediatric patients with chronic conditions who have to travel long distances for testing [30].

Timely, accurate test data is necessary for providers to make faster, more effective patient care decisions. The most vulnerable population is children, many of whom are unable to adequately describe their ailments. Laboratory professionals are the voice of their patients, providing clinicians with the information they need. Pediatric laboratory professionals go to work each day knowing they are helping countless infants, children, and adolescents lead healthier lives.

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