CHILDREN'S HOSPITAL ASSOCIATION

600 13TH ST., NW, SUITE 500
WASHINGTON, DC 20005
p | 202-753-5500
f | 202-347-5147

16011 COLLEGE BLVD., SUITE 250
LENEXA, KS 66219
p | 913-262-1436
f | 913-262-1575

WWW.CHILDRENSHOSPITALS.ORG

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The Honorable Bill Cassidy
Ranking Member
Senate HELP Committee
United States Senate

Dear Senator Cassidy,

The Children's Hospital Association (CHA) and many of its member hospitals' physician Chiefs of Pathology and Clinical Laboratory Services thank you for this opportunity to respond to your request for information (RFI) on the Regulation of Clinical Tests. We share your goal of protecting American's health by assuring the safety and effectiveness of diagnostic tests, especially for children with serious or complex medical needs. We believe it is essential to understand the unique pediatric considerations of any approach to regulate diagnostic tests, particularly the regulation of laboratory-developed tests (LDT). **It is imperative that actions to regulate these vital diagnostic tools protect children's access to life-saving and timely health care.**

Children are not just little adults. They are constantly growing and developing, and their health care needs and the delivery system to meet those needs are different from those of adults. Pediatric health care requires specialized medications, diagnostics, tests, therapeutics, and equipment that the nation's children's hospitals provide. **LDTs fill a critical gap in the practice of pediatric medicine as they allow for accurate, timely, accessible, and high-quality testing for many pediatric conditions for which no commercial test exists or where an existing FDA-approved test does not meet current pediatric clinical needs or is not validated for use in children.** They are essential to children's hospitals' ability to provide timely, cost-effective, and high-quality diagnostics and care for all children, and particularly for children in need of treatment for rare and difficult-to-diagnose pediatric disorders. LDTs developed and used in pediatric health care settings account for all stages of childhood development, from newborn through adolescence and young adulthood, and address numerous genetic and heritable diseases, pediatric cancers, and acquired conditions that are not well-represented in adult health care practice.

We are pleased to provide our perspective on the unique aspects of the use of LDTs in the provision of pediatric health care that must be considered as you explore ways to improve regulation of clinical tests in the United States.

FDA Regulatory Framework for Diagnostics

#1. How well is FDA's medical device framework working for the regulation of diagnostic products? Are there improvements that should be made?

FDA-approved tests for pediatric diseases frequently do not exist. Furthermore, the smaller population size and unique aspects of studying children are barriers to commercialization of tests for pediatric diseases. Similar to the development of new pharmaceuticals, which are usually developed for adults, children are

often left behind in the development of commercial testing—given the small market, the highly specialized nature of pediatric diseases, liability concerns, and volume limitations.

The needs of our nation's children have not always been adequately met by the current regulatory structure at the FDA, which the agency recognizes in its May 2023 "Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations." As a result, FDA has lagged in approving drugs that can appropriately and effectively be used for children. For example, we respectfully note that, over time, the FDA has had to contend with updates and modifications to the regulations that guide drug development for children to account for the unique aspects of studying children and creating health care devices that support their needs. As we note above, the commercial testing industry has not—and is not likely to in the future—stepped in to fill this market gap, given the small population and highly specialized nature of pediatric diseases.

Children's hospitals' laboratories fill the gap in the availability of FDA-approved tests by either developing their own LDTs for their patients or performing the extensive validation work needed to demonstrate that an FDA-approved test for adults can safely and reliably be used for children. In the event the proposed FDA rule on LDTs goes into effect, we believe that FDA will likely be overwhelmed by the sheer volume of applications and its capacity (staffing, pediatric expertise, etc.) to complete the necessary reviews of pediatric-related LDTs will be inadequate. **As a result, needed diagnostics may no longer be available, impeding children's access to timely care.**

We are also very concerned about the impact of the FDA's proposed regulatory framework for LDTs on children's hospitals' resources. Under the proposed rule, most pediatric-related LDTs will likely be graded as Class II and III devices due to their clinical importance. As a result, the regulatory requirements related to the approval process will be the most resource intense. It is important to note that these tests have already been developed and validated in children's hospital laboratories that are tightly regulated and further accredited under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), individual states, the College of American Pathologists (CAP), or the Joint Commission—in accordance with the CLIA regulation. The financial resources and staff needed to pursue the large numbers of FDA submissions that would be required under the proposed rule would be in addition to resources already used to meet the current, stringent regulatory and accreditation requirements. The additional resource needs makes it even more challenging for children's hospitals to meet the rule's requirements. In the end, there will be fewer tests to use for children and those with diseases that predominantly affect pediatric patients.

Furthermore, Medicaid, on average, provides health insurance coverage for half of children's hospitals' patients, and for some children's hospitals patient mix, closer to three-quarters. This makes children's hospitals among the largest Medicaid recipients, and Medicaid is a critical funding source for the care they provide to our nation's children. However, Medicaid reimburses children's hospitals, on average, only about 80% of the cost of providing care.[1] The additional resource demands of the proposed rule will impede timely treatment and management of conditions affecting our pediatric patients, hinder innovation by jeopardizing children's hospital laboratories' ability to integrate the latest scientific discoveries into clinical testing and strain the capacity of children's hospital laboratories to meet the needs of children today and over the long-term.

[1] Annual Benchmark Report, FY 2022. Children's Hospital Association

#4. Are the regulatory pathways intended to evaluate diagnostics for special populations (i.e. rare diseases or genetic disorders) working?

According to the GAO, half of the estimated 30 million people in the U.S. with a rare disease are children,[2] and for many pediatric-related diseases and diagnoses there are no FDA-approved tests. LDTs are critical to children's hospitals' ability to provide timely, cost-effective, and high-quality diagnostics and care for children in need of treatment for all conditions, as well as for those that are particularly difficult to diagnose. Children's hospitals develop and validate LDTs, following requirements specified by CLIA, in laboratories tightly regulated and further accredited under CLIA and by their states, CAP, or the Joint Commission—in accordance with the CLIA regulation. These existing regulatory measures ensure the quality of this testing, which is usually developed in partnership with pediatric clinical providers to meet well-defined clinical needs.

In fact, current LDTs are often the "gold standard" for rare pediatric disorders. There are FDA-approved tests that have known analytical weaknesses compared to the "gold standard" LDT test for the same analyte for children. For example, the most used, FDA-approved liquid chromatography, tandem mass spectrometry testing is the "gold standard" for diagnosis of vitamin D deficiency in infants and children, and is a pediatric-focused LDT.

Children's hospitals' LDT test menus include numerous FDA-approved tests that the children's hospital laboratories validate as an LDT for use in children because the FDA did not provide the manufacturer with a pediatric age range claim. This includes tests that could potentially be used for children but are not validated for such use, as well as approved tests that do not include pediatric reference (normal) ranges that our hospitals derive and determine using their high-quality processes under CLIA. Further, numerous genetic and heritable diseases, pediatric cancers, and acquired conditions that are not well-represented in adult health care practice are diagnosed using LDTs.

Pediatric LDTs are also used when there are no FDA-approved alternatives available for time-sensitive tests to enable pediatric specialists to make immediate clinical decisions for children. These include the test used to diagnose childhood leukemia, which may be individualized within different children's hospitals' laboratories for the specific child. The curative treatment for children with leukemia is bone marrow or stem cell transplantation, and the genetic test used to monitor the state of the bone marrow transplant after it happens is also an LDT.

Furthermore, there are numerous situations in which the instructions for use for an FDA-approved test do not include the parameters needed to use the test in the pediatric population. Children's hospitals routinely develop different reference ranges to inform age-appropriate clinical decision-making. For example, FDA-approved tests are available for testing of blood, plasma and serum, but testing on other types of body fluids or specimens that are needed to care for children's specific needs are not approved. Other examples include Thromboelastographic testing, which is used to determine bleeding risk in surgical patients of all ages, but is not approved by the FDA for use in patients under the age of 18 years.

In addition, many pediatric hospital laboratories develop their own genetic test panels that prioritize the types of genetic abnormalities that are seen in children and can lead to severe forms of inherited and rare diseases in children and many types of pediatric cancers. They do so because developing assays to diagnose these rare conditions is often out of scope for manufacturers because of the low volume of testing and consequent low monetary returns.

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[2] See GAO-22-104235, Accessible Version, Rare Diseases: Although Limited, Available Evidence Suggests Medical and Other Costs Can Be Substantial (October 2021).

LDTs allow children's hospitals' laboratories to develop genetic tests specific to pediatric populations, modify testing rapidly to include additional genes that are newly implicated in childhood disease, and adopt more efficient and sensitive testing platforms and methodologies.

#5. Are there regulatory hurdles to expanding the settings in which diagnostics are performed, i.e. point-of-care (POC) tests performed in patients' homes?

As you explore expanding the settings for diagnostics, **we strongly caution against any policies or requirements that result in the centralization of tests to certain locations, or any requirements that care and tests be conducted at the same physical location.** Given the regionalization of pediatric specialty care, it is not uncommon for children to travel long distances to receive specialty care at a children's hospitals because the services they need are not available close by. These children will then receive follow-up and continuing care from local providers to allow them to stay in their homes, communities, and schools, reducing stress and burden on their families and overall well-being.

However, when a test is sent out to a centralized laboratory, decision-making is delayed and the length of stay for that child increases, leading to additional stress on the child and family, worse outcomes, and higher costs. In addition, centralization to just one or two labs in the country greatly endangers patient care, as there is no resiliency in the system if these labs suffer issues that compromise testing. For example, a test that measures a blood level of a chemotherapeutic drug to assess organ toxicity must be performed and resulted rapidly to help the clinician determine whether a change in the drug dose is warranted to prevent organ damage. Waiting days for a result would render the test medically unusable. Tests performed on site are always preferred for faster results and therefore better patient care.

In addition, a "same physical location" requirement does not realistically reflect the way pediatric specialty care is practiced and could impede timely diagnoses and care for our sickest children. It is common practice for children's hospital providers to swab (sample collection) at a variety of children's hospital locations (including outpatient primary care and specialty centers) that are near a child's home and then send those samples for testing at a laboratory located at the children's hospital main campus. While a "same physical location" requirement might be appropriate for diagnostic tests in the inpatient setting, it will not support clinical pediatric care in the outpatient setting, including testing to diagnose rare or uncommon pediatric conditions.

#8. In considering reforms to FDA's risk classification framework for diagnostics, what types of IVDs should be exempt from premarket review?

It is essential that any regulatory reforms ensure that all children continue to have access to life-saving diagnostics and timely care. LDTs fill a critical gap in the practice of pediatric medicine as they allow for accurate, timely, accessible, and high-quality testing for many pediatric conditions for which no commercial test exists or where an existing test does not meet current clinical needs. They are critical to children's hospitals' ability to care for all children, particularly for children in need of treatment for rare and difficult-to-diagnose pediatric disorders.

Given the expected impact of the proposed FDA rule on the practice of pediatric medicine, **we have strongly recommended that the FDA modify its proposed rule and continue its current general enforcement discretion approach for all hospital and health system LDTs.** At a minimum, enforcement discretion should continue for the following pediatric-related LDTs, which will enable children's hospitals to meet the specialized needs of the children.

- Tests for diseases/diagnoses that are related to infancy or childhood.
- Tests that must be altered or modified for pediatric off-label use.
- Tests for pediatric rare and orphan diseases.
- Tests that cannot be done by adult-focused laboratories.
- Tests that are run in hospitals for immediate patient care.

We urge Congress to focus on better regulating LDTs developed by commercial laboratories, as there have been examples of those laboratories marketing LDTs—most commonly geared towards adults and for more common diseases—with unproven clinical validity to providers and patients. In particular, we support the oversight of manufacturers and commercial laboratories that sell and distribute test kits, rather than on LDTs developed and used by children's hospitals that rely on those tests to meet the specialized health needs of children.

Pediatric-related LDTs offer the flexibility and nimbleness that children's hospitals' accredited laboratories need and use to perform pediatric diagnostics. It is critical than any changes to the current regulatory structure do not lead to additional barriers to innovation in pediatric diagnostic testing that would limit advances in treatment and lead to less favorable outcomes for children and higher health care costs.

#10. Do the proposed reforms to FDA's device framework warrant the establishment of a new regulatory pathway specific to diagnostics? If yes, what are the principles that should guide such a new framework, as it would be applied to diagnostics currently subject to FDA premarket review?

As noted above, pediatric-related LDTs must be protected and exempted from additional, extensive administrative requirements that do not improve outcomes for our pediatric patients. We urge you to address the unique implications of any new framework for children's hospital laboratories' development and use of LDTs. Children's hospitals must be able to modify, develop, and rapidly deploy a broad array of LDTs—as they do now—by meeting the stringent regulatory and accreditation requirements under CLIA, CAP, the Joint Commission, state and related standards.

CLIA provides a robust framework for the oversight of laboratory testing, including LDTs, based on stringent standards developed by CMS, with public input. As currently regulated, LDTs can only be created in laboratories that have Certificate of Accreditation from CLIA/CMS as a High Complexity Laboratory. All High Complexity Laboratories must have a leadership team and staff that meet the requirements for CLIA laboratories.[3] Those standards include rigorous personnel requirements, and quality assurance programs that include robust validation for all new tests that assess the new test's accuracy and precision; quality control, and proficiency testing requirements for every test performed; regular inspections by specialists in the field; and required corrective actions, when necessary.

CLIA Regulatory Framework for LDTs

#1. What updates to the clinical laboratory regulatory structure under CLIA should Congress consider to reflect the latest scientific practices and safety standards?

[3] See Laboratories Performing High Complexity Testing (§§ 493.1441 - 493.1495)

As previously stated, children's hospital laboratories' LDTs are developed and validated following requirements specified by CLIA in laboratories that are tightly regulated and further accredited under CLIA, by CAP, their states or the Joint Commission—in accordance with the CLIA regulation. These existing regulatory measures ensure the quality of this testing, which is usually developed in partnership with pediatric clinical providers to meet well-defined clinical needs. We believe that CLIA, in combination with its companion programs, provides a robust framework for the oversight of laboratory testing given the stringent standards for personnel, quality assurance, quality control, and proficiency testing requirements; regular inspections; and required corrective actions, when necessary.

We also recognize that updates to CLIA may be warranted to reflect the latest technologies and advancements to further strengthen its effective oversight function. We look forward to working with Congress and CMS on updates that reflect the unique nature of pediatric diagnostics and care.

#2.What compliance challenges would legislative reforms to CLIA create? How should new regulatory requirements apply to tests currently available to patients?

It is critical that any reforms to CLIA or any other regulatory structure for LDTs include grandfathering provisions for current pediatric-related LDTs to ensure that children continue to have access to the specialized clinical diagnostics and care that children's hospitals provide. In the absence of a grandfathering provision, it is likely that some, if not many, children's hospitals' laboratories would be unable to make the substantial administrative and financial investments that would be required to prepare for the review of the range of LDTs currently in use. As a result, they would have to make extremely difficult decision to consider abandoning existing effective pediatric-related tests, thereby putting their child patients at risk.

Furthermore, we know that the commercial sector will not step in to make tests for rare pediatric and orphan diseases as the market is too small. As a result, absent a grandfathering protection, many needed tests for children—including those with rare, uncommon and often life-threatening, diseases—would no longer be available with significant negative implications for their overall health and wellbeing.

However, a grandfathering provision will not fully ensure that children have access to the tests and health care they need. In addition to a measure to protect tests currently in use, measures must be put into place to support the ability of children's hospitals to continue to develop—and innovate with—new diagnostics that are safe and clinically effective and drive pediatric cures and treatment.

Thank you for the opportunity to provide our feedback to your RFI. It is critical that the regulatory structures to review, approve and monitor diagnostics address the unique role that LDTs play in pediatric health care and ensure that children continue to have access to life-saving diagnostics and timely care. We look forward to working with you to meet the health care needs of the nation's children. If you have any questions about our comments, please contact Jan Kaplan at 202-753-5384 or jan.kaplan@childrenshospitals.org.

Sincerely,

Leah Evangelista
Chief Public Affairs Officer
Children's Hospital Association

Mark Fleming, MD, PhD
Pathologist-in-Chief
Boston Children's

Elizabeth P. Weinzierl, MD, PhD
Interim Division Chief, Pathology and Laboratory Medicine
Children's Healthcare of Atlanta

Jennifer Black, MD
Chair, Pediatric Pathology
Children's Hospital Colorado

Alexander R. Judkins, MD
Pathologist-in-Chief
Children's Hospital Los Angeles

Stephen R Master, MD, PhD
Division Chief and Director of Metabolic and Advanced Diagnostics
Children's Hospital of Philadelphia

John David, L. Nolen, MD, PhD
Chair, Department of Pathology & Laboratory Medicine
Children's Mercy Children's Hospital

Meghan Delaney, DO, MPH
Chief, Pathology & Laboratory Medicine
Children's National Medical Center

Amy L. Treece, MD
Chief of Pediatric Pathology
Children's of Alabama

Sarangarajan Ranganathan, MD
Division Director and Endowed Chair, Pathology and Laboratory Medicine
Cincinnati Children's Hospital Medical Center

Irene Castañeda-Sánchez, MD
Medical Director, Pathology and Laboratory Services
Cook Children's Medical Center

Paul Herrmann, MD, PhD
Chair, Department of Pathology and Human Anatomy
Loma Linda University

Jeffrey D. Goldstein, MD
Chief of Clinical Pediatric Pathology
Mattel Children's Hospital and Ronald Reagan UCLA Medical Center

Shamlal Mangray, MB, BS
Chief, Pathology & Laboratory Medicine
Nationwide Children's Hospital

Lili Miles, MD
Chair, Department of Pathology
Nemours Children's Hospital, Florida

Sean C. Murphy, MD, PhD
Director, Clinical Microbiology Division, Department of Laboratories
Seattle Children's Hospital

David Ellison, MD, PhD
Chair, Pathology Department
St. Jude Children's Research Hospital

James Versalovic, MD, PhD
Pathologist-In-Chief and Chair, Department of Pathology
Texas Children's Hospital

Christine Schmotzer, MD
Vice Chair and Medical Director, Department of Pathology
University Hospitals Cleveland and Rainbow Babies & Children's Hospital

Amy Davis, MD
Director of Pathology and Laboratory Medicine
Valley Children's Healthcare