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The SIMD is composed of physicians, laboratory professionals, research scientists, and other professionals working in the diagnosis, treatment and management of patients with inborn errors of metabolism (IEM). While the IEM as a group affect a significant number and percent of babies, individually most of the IEM are rare disorders. SIMD members provide essential clinical services to patients and families in the United States to prevent death and disability for those with IEM, including IEM which are detected by newborn screening (NBS). The SIMD supports efforts to improve the quality of laboratory testing including biochemical genetic testing (BGT), but is also cognizant of the risk of decreased access to currently available high quality testing.

Prompt diagnosis and treatment for IEM can save lives and prevent permanent disability. For the symptomatic patient or the baby with abnormal NBS, rapid access to results of appropriate BGT is needed to make diagnosis and initiate lifesaving therapy. Management of IEM depends on the availability of BGT for monitoring of therapy, and results need to be available in time to make appropriate adjustments to management. For the growing child, adjustments need to be made in days, and for the acutely ill individual adjustments may need to be made in hours. Therefore monitoring BGT requires access to local expert laboratories wherever possible. Reduction of access to testing would compromise current success in prevention of death and disability, and reduce the effect of the important public health newborn screening programs.

With this in mind, the SIMD is highly concerned about the U.S. Food and Drug Administration’s (FDA) intent to exert regulatory oversight of Laboratory-Developed Tests (LDTs), as currently defined by the FDA. Most laboratory tests used for the diagnosis and treatment for patients with IEM would meet the FDA definition of LDTs. This includes relatively high volume screening tests and complex BGTs, as well as molecular tests. While molecular genetic testing is critical to the diagnosis of many IEM, the SIMD can speak most specifically to the BGTs that are performed by some SIMD members and used by other SIMD members as key clinical information that is critical to our practice of medicine.

The FDA cites concerns about the quality of LDTs as the primary impetus for developing its guidelines and believes that LDT related errors are common and have caused patient harm. The FDA asserts that this additional oversight
will assure safety and quality. We are aware of no data to support the premise that FDA oversight of LDTs will improve quality of BGT.

All clinical laboratories are already regulated and must have CLIA or other appropriate certification, must participate in proficiency testing programs and must have robust quality systems and controls programs in place. CLIA also requires full analytical validation of LDTs (determinations of accuracy, reproducibility, and other test-performance characteristics) in order to assure reliable and safe test results; this applies to BGTs. Laboratory personnel must be accredited by state agencies, and some by national level agencies such as the National Accrediting Agency for Clinical Laboratory Science. In addition, clinical Biochemical Geneticists are (by definition) board-certified by the American Board of Medical Genetics and Genomics (ABMGG) and must maintain certification through continuous education, peer review, and repeat examination.

The SIMD is concerned that the guidelines proposed by the FDA will result in greater harm than benefit to our patients. Most BGTs are highly specialized and complex tests, requiring interpretation to be provided as part of the report. Determination of clinical validity and clinical utility of BGT presents unique challenges including:

- the individual disorders are rare;
- there are groups of conditions with overlapping clinical and biochemical features
- levels of and patterns of analytes vary between individuals with the same condition
- levels of key analytes in a single individual vary with clinical status, so that testing done at different times can have widely different results; in fact, samples from an affected individual can in some circumstances be indistinguishable from those of an unaffected individual,
- some testing, including some testing of analytes and some functional BGT, can be done only on samples collected by invasive means such as skeletal muscle and cerebro-spinal fluid.

It is not possible to define test sensitivity and specificity for many BGTs, even as applied to a specific condition, without attention to the clinical condition of the patient at the time of collection (fasting or fed and with what diet; sick or well). This is a serious obstacle to any randomized clinical trial to determine clinical validity and clinical utility of BGT. Even if the problem of costs of such trials could be surmounted, such trials would take decades. For many tests and conditions, the need for invasively collected samples would be a challenge for human subjects protection and ethics.

BGT is done in both commercial and academic laboratories. SIMD membership includes the directors of both academic laboratories and of the BGT sections of the largest commercial laboratories in the United States. There is a collegial relationship between the large commercial laboratories with relatively limited menu/high volume services, and their sister academic laboratories. The FDA proposal would adversely affect all types and sizes of laboratories performing BGT, but would likely have more adverse effect on the majority of BGT laboratories that are hospital-based and university-affiliated. While there is excellent BGT in some large commercial laboratories, the commercial laboratories do not offer the full range of testing that is now available in the current network of commercial and academic laboratories, and the academic laboratories perform much of the diagnostic testing for the most rare conditions. Furthermore, the academic/hospital-based laboratories provide rapid turnaround for BGT for management of the acutely ill patient and for diagnosis of critical conditions detected by NBS (as addressed in SIMD's position statement "Identifying abnormal newborn screens requiring immediate notification of the health care provider", found at http://www.simd.org/Issues/SIMD%20NBS%20Critical%20Conditions%20policy%20statement.pdf.) Access to the large commercial laboratories performing BGT requires shipping; adding at least one to three days to the turnaround time for testing results and causing harm to patients and families. The academic laboratories that would be most severely impacted by the FDA proposal serve a national need by providing local and rapid access to quality testing, as well as unique specialization and expertise for diagnosis of rare conditions.
The cost of clearing new tests or test modifications through the FDA-proposed process is significant and would:

- markedly increase the testing fees or prevent labs from even developing critically needed tests;
- limit if not abolish the abilities of laboratories to be innovative;
- stifle the development of new tests that take advantage of new scientific and medical findings,
- hinder development and implementation of modifications to existing assays to enhance quality and performance.

The SIMD agrees with the FDA that clinical validation (including determination of clinical sensitivity and specificity of a test) is critically needed for physicians to properly use test results. CLIA regulations currently only require analytical validation and not clinical validation. Whether or not further regulation of laboratories with respect to clinical validation is needed is a subject for further discussion; it has been pointed out that this may cross the line into regulation of the practice of medicine. In addition, as noted above, it is not possible to define clinical sensitivity and specificity of some BGT; this is the reason that quality BGT includes expert interpretation of laboratory values for clinical application. It is possible that a more appropriate response to some of the concerns of the FDA would be to focus on the marketing claims of LDTs. The FDA’s current proposal would add inappropriate oversight by another by another federal agency. Having multiple agencies involved in reviewing laboratories is not in the best interest of the patient and adds cost to the health care system. Implementation of the FDA’s currently stated intent and guidelines for LDTs will significantly delay the goal, articulated most recently by the President in the State of the Union address, of better and affordable healthcare for all citizens through “precision” or “personalized” medicine.

Overall, implementation of the FDA-proposed guidelines will lead to fewer tests being developed by fewer laboratories and thus have a negative impact on laboratory access for all patients. This limited access to needed laboratory tests will significantly reduce the quality of care received by patients. Fewer testing facilities will result in less competition and increase health care costs.

The SIMD believes that high-quality testing can be achieved through judicious application of current or any future CLIA requirements, and by implementation of robust quality systems as required by accrediting agencies such as the College of American Pathologists (CAP). Involvement by additional agencies will only lead to confusion, redundant regulatory requirements, and increased costs.

The SIMD also believes that many or all of these points also apply to molecular genetic testing.

We recognize and respect that it is the intent of the FDA to improve the quality of medical testing for people in the United States. However, we expect there would be a serious adverse impact on biochemical genetic testing if the current proposal goes forward. We of the SIMD therefore respectfully and strongly suggest that there should be substantial reconsideration of the FDA proposal, including attention to the serious adverse effects on the ability to perform BGT, and the consequent adverse effects on the population's health.

For any questions, please contact:
Carol L. Greene, MD
SIMD Public Issues Committee Chair and SIMD Past-President