Commentary

SIMD commentary on FDA oversight of laboratory-developed testing

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1. Introduction

An ad hoc committee of the Board of Directors of the Society for Inherited Metabolic Disorders (SIMD) developed the following commentary in response to the Food and Drug Administration’s request for comments at a public meeting held on July 19–20, 2010 in Hyattsville, MD on FDA oversight of laboratory-developed testing (LDT). The Board recognized the importance of being heard on this very important topic of interest to all who are stakeholders in LDT. The President of the SIMD, Georgirene D. Vladutiu, gave a brief presentation at the open meeting both as an individual stakeholder and as a representative for the SIMD. The following is a summary of her remarks and is posted as part of the FDA docket for comments on August 15, 2010.

The SIMD is composed of physicians, laboratory professionals, research scientists, genetic counselors, nutritionists and nurse practitioners who all are invested in the diagnosis, treatment and management of patients with inborn errors of metabolism, many of which are rare disorders.

These varied SIMD members provide essential clinical services to patients and families in the United States to prevent death and disability for those affected by inborn errors of metabolism, including those detected by newborn screening and those with conditions for which newborn screening does not exist. In either case, prompt diagnosis and treatment can be lifesaving; for a number of conditions diagnosis must be achieved within hours to assure best outcomes—requiring access to local expert laboratories whenever possible. Biochemical genetic testing also includes newborn screening utilizing programs based in individual States. The unique case of newborn screening combines biochemical testing principles with screening principles to identify those individuals at increased risk of having an inborn error of metabolism and therefore in need of diagnostic testing. Without clinical services for the diagnosis and management of inborn errors of metabolism, newborn screening cannot achieve its purpose.

The provision of care to those with inborn errors of metabolism, whether detected by newborn screening or not, depends upon the availability of biochemical genetics testing for diagnosis (including confirmation of diagnosis after abnormal newborn screen or in patients with symptoms) and depends on the availability of biochemical testing for monitoring of therapy, to assure adequate treatment and to avoid over treatment (both for pharmacologic and nutritional management). The SIMD supports all efforts to improve the quality of biochemical testing as well as genetic testing in general, but is also cognizant of the risk of decreased access to biochemical genetic testing that is currently available and that is required to maintain programs that prevent death and disability across the United States.

While DNA testing has a role in the diagnosis of inborn errors of metabolism, biochemical genetic testing is not DNA based testing. Biochemical testing is defined in a recent Clinical Laboratory Improvement Advisory Committee (CLIAC) report and involves the measurement of metabolites, proteins or enzymes, often on samples collected invasively. Due to the unique characteristics of biochemical genetic testing, strategies to regulate LDT primarily involving DNA testing, by the FDA or any other agency, are generally not universally appropriate for biochemical genetic testing. We are concerned that the FDA’s definition of genetic testing for the purpose of this meeting includes not only lab-developed complex DNA testing but also biochemical genetic testing.
Clinical Biochemical Geneticists are (by definition) Board-certified by the American College of Medical Genetics; the recent CLIAC document recommends such Board Certification for the technical supervisor of a laboratory carrying out complex biochemical genetic testing.

In New York State each laboratory director must have a Certificate of Qualification in Genetic Testing.

In New York State, the biochemical genetics laboratories must document assurance from referring physicians that they will provide for genetic counseling of their patients in the event of positive test results no matter where they are in the country. The recent CLIAC document for biochemical genetic testing makes general recommendations that laboratories engaging in biochemical genetic testing should provide information regarding any genetic implications of the testing as part of information available to health professionals ordering testing and as part of test reports.

Most biochemical genetics laboratories are highly specialized, working with complex tests, requiring interpretation to be provided as part of the report. While some tests are similar across many laboratories (e.g. amino acid analysis), many tests are laboratory developed. Testing is not done on cheek-swab samples, but on blood, urine and often on samples collected by invasive means such as skeletal muscle and spinal fluid. The recent CLIAC recommendations recognize the difficulty in collecting large numbers of abnormal control samples for rare diseases, and the difficulty also in collecting normal control samples for invasively collected samples, especially in children.

While some large commercial laboratories perform excellent Biochemical Genetic Testing, many Biochemical Genetic Laboratories (especially those performing diagnostic testing for rare conditions) are hospital-based and university-affiliated serving a national need due to their individual levels of specialization. This network of laboratories also provides the relatively local testing with rapid turn-around for diagnosis of conditions detected by newborn screening and for conditions with emergency presentations.

The market share of these academic laboratories is relatively small compared to large commercial laboratories but extremely important for the patients served; in the Biochemical Genetics world there is a supportive relationship between the relatively limited menu/high volume services of the large commercial laboratories that provide biochemical genetic testing and their sister academic laboratories (the SIMD membership includes the directors of the Biochemical Genetic sections of the largest commercial laboratories in the United States).

While DNA testing is included in many biochemical genetic testing laboratories, it will not replace biochemical testing due to the need for quantification of analytes and measurement of enzyme activity in various tissues to make diagnoses and to monitor therapies.

2. Concerns of the FDA Regarding LDT Testing

We understand the concerns of the FDA regarding the application of a risk-based oversight to LDT.

As diagnostic tests play an increasing role in clinical decision making it is possible that the development of these tests may not be properly validated for their intended use. There are also concerns that diagnostic test development may not provide reasonable assurance of safety and effectiveness.

New Guidelines for Clinical Biochemical and Molecular Genetics Laboratories


The FDA’s concerns are taken into account in guidelines developed by the CLIAC for good laboratory practices in biochemical genetic laboratories.

This document also provides guidelines for a Quality Management System (QMS) that overlaps with that of CLIA.

A similar document for clinical molecular genetics service laboratories has been published in the Morbidity and Mortality Weekly Report, June 12, 2009 also available at the CDC website as indicated.
We understand that the FDA is concerned that large corporations are using complex tests and algorithms that physicians may not understand.

LDT Testing: FDA Concerns

- Not all laboratories using LDTs are large commercial entities, therefore, it will be important to define which types of laboratories and which types of tests should be included in proposed new regulations not covered by other agencies.
- Biochemical genetic testing requires that physician specialists receive detailed interpretations of test results; regulation of the use of algorithms will not change the need for test-specific, patient-specific interpretation of results for biochemical genetic testing.
- In the end, it will be physicians who will control the success of genetic testing going forward depending on their ability to understand test results and be able to apply them to the diagnosis, treatment and management of their patients. There needs to be a concerted effort by genetic specialists combined with regulatory agencies, such as the FDA, to provide CME credit-based programs for internists, family medicine physicians, and others who are not routinely aligned with genetics specialties for proper training in advances in genetic testing, the benefits and the potential pitfalls.

As the FDA proceeds to consider a risk-based application of oversight there are several things to take into consideration.

First, the measure of risk will vary depending on the setting of testing, that is whether testing is prenatal, neonatal, in children or in adults, and whether the testing is performed in response to a symptom (or an abnormal newborn screen), or whether testing is presymptomatic or is to derive a perceived measure of risk. This latter consideration, depending on definition, may include newborn screening and we are not confident that it is really the intent of the FDA to include newborn screening – an already closely monitored system of testing – in this new regulatory oversight development. Another consideration will be whether “presymptomatic testing” would include testing the newborn sibling of a child affected with an inborn error of metabolism, for early diagnosis in order to receive life-saving therapy. Attention will need to be paid to the definitions developed for any new system of regulation to avoid unintended harm by restriction of currently available and necessary life-saving testing.

The predicted consequences of testing are more important than of the specific tests performed. That is, the implications of testing including the type of therapy implied must be taken into consideration. The implications of new regulation will also need to be considered.

Impact of New Oversight on Biochemical Genetic Testing

- Cost of test development will increase
- Disincentive to innovative
- Healthcare costs will increase
- Access to services will further decrease

The impact of any new regulation to biochemical genetic testing would definitely increase the cost of this specialized testing. This will be a disincentive to innovative test development. Access to specialized testing is already limited for many reasons, a number of which relate to cost, and access would only further decline. While we are concerned about the risks associated with limiting the development of new testing – including testing that is needed to match the new developments in newborn screening – we are also extremely concerned that we do not abruptly cut off access to existing services that are essential to maintain health for our patients and their families.

In summary, we ask that

- biochemical genetic testing not be lumped together with DNA testing for regulatory considerations.
- laboratories with LDT should be categorized according to a risk-based scale in order to assure safety, effectiveness, and applicability to a clinical diagnostic or predictive purpose.
- an advisory committee to the FDA should be made up of experts in the development and implementation of LDT at all levels of complexity.

The Society for Inherited Metabolic Disorders respectfully requests inclusion in further deliberations and development of next steps toward increased oversight of LDT.