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Re: NIH GTR Comments

The Society for Inherited Metabolic Disorders (SIMD) appreciates the recent informative public hearing and this opportunity to comment on the planned Genetic Testing Registry (GTR). We have been watching with interest the initial phases of planning for the GTR and in particular have been interested to know whether biochemical genetic testing (abbreviated hereafter as "BGT" and referring to non-DNA based testing for inborn errors of metabolism) would be included in the GTR. We now understand that BGT will be included and therefore offer the following comments in hopes they will increase the future value of the GTR.

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

- The clinical laboratory directors and staff who provide BGT, which is the first line of diagnostic evaluation for many genetic conditions, including most newborn screening follow-up, and
- The physicians and other clinicians who use BGT for diagnostic evaluation and management 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.

Prompt diagnosis and treatment can be lifesaving for those with inborn errors of metabolism; for a number of conditions diagnosis must be achieved within hours to assure best outcomes – requiring access to local expert laboratories whenever possible. We who provide care and the patients and families we serve depend on BGT for diagnosis (including confirmation of diagnosis after abnormal newborn screen or in patients with symptoms) and for monitoring of therapy, to assure adequate treatment and to avoid over-treatment (both for pharmacologic and for nutritional management).

Whether BGT is to be done in local laboratories for rapid turnaround for emergency management, or in national reference laboratories for relatively common or for highly rare conditions, information about the availability of appropriate and high quality biochemical genetic testing is critical to the provision of care for diagnosis and management of inborn errors of metabolism. The SIMD supports all efforts to improve both the quality of biochemical testing and the availability of accurate information about testing to help with the selection of proper testing for each individual and family. We expect that the inclusion of information about BGT in the GTR will help with access to information about test availability and assist those less familiar with BGT's role in diagnosis and treatment of genetic disease so that they might better understand the role of BGT in evaluation and management.

While we look forward to the opportunities offered by the GTR to improve the value of information about BGT, we do have some concern that GTR development efforts have to date narrowly focused on issues particular to DNA testing. While DNA testing has a role in the diagnosis of inborn errors of metabolism, BGT is by definition not DNA based testing. Biochemical testing is defined in a recent Clinical Laboratory Improvement Advisory Committee (CLIA) report (found at: <http://wwwn.cdc.gov/cliac/pdf/Addenda/cliac0210/Addendum%200.pdf> ) and involves the measurement of metabolites, proteins or enzymes, often on samples collected invasively. Samples are also often collected during acute illness or as timed samples. The CLIA report identifies a number of other ways in which BGT differs from other testing. Due to the unique characteristics of BGT, characterization of the quality of a biochemical genetic test using criteria appropriate for molecular genetic testing is not universally appropriate.

To illustrate this point: “sensitivity” and “clinical validity” may be definable for the measurement of a single amino acid or a single fatty acid metabolite for a specific condition under specific circumstances – e.g. in the context of newborn screening. However, for a panel of blood amino acids or an acylcarnitine profile, “sensitivity” and “clinical validity” may not be definable. For example, in the evaluation of an individual with acutely altered consciousness, blood amino acids and acylcarnitine profile are indicated to search for evidence of inborn errors of metabolism, and the results of testing are used for decisions about management. The use of the BGT in this circumstance resembles more the diagnostic use of electrolytes, liver function tests, ammonia levels, complete blood counts, cultures of body fluids and imaging than it resembles testing of DNA for a specific suspected condition. We do not ask for the “sensitivity” or the “clinical validity” of electrolytes in this setting.

It is also relevant to note that in many cases – in fact for most inborn errors of metabolism – results from BGT constitute the primary source of information leading to decisions about when or whether to use molecular genetic testing. In addition, BGT is typically the “gold standard” for diagnosis of inborn errors of metabolism against which the sensitivity and specificity of DNA testing for those conditions is defined.

Due to the remarkable differences between BGT and molecular genetic testing, the SIMD suggests that special attention will need to be given to BGT as the development of the GTR progresses. Decisions about specific types of information expected to be attached to each test included in the GTR must take into account the special issues of BGT. Success in this effort will avoid the unintended consequence of conveying to GTR users that BGT is somehow lacking in validity compared with molecular genetic testing. With appropriate consideration of the special issues of BGT, we hope that the GTR will prove to be the powerful resource for access to information about BGT testing that we have needed for some time. The SIMD looks forward to the opportunity to help assure that the GTR appropriately addresses BGT. To that end we hope to continue this conversation and we offer our services in the process of developing the resource.

Thank you again for this opportunity to comment, and please let us know in what ways we can be involved in and support ongoing efforts in development of the Genetic Testing Registry

Sincerely

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