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Via Electronic Mail Submission to: OIRA submission@omb.eop.gov; gtr@od.nih.gov

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RE: Submission for OMB Review; Comment Request Information Program on the Genetic Testing Registry, 76 Fed. Reg. 72,424 (Nov. 23, 2011)

Dear Dr. Patterson:

On behalf of the Coalition for Twenty-First Century Medicine (the "Coalition"), we are pleased to submit comments in response to the above-captioned request for comments from the National Institutes of Health (the "NIH") on the proposed Genetic Testing Registry ("GTR"). As we emphasized in our July 31, 2010 letter to Dr. Francis Collins responding to the NIH's request for information on the development of a genetic testing registry (the "July 31, 2010 Letter"), our Coalition strongly supports the NIH's efforts, and we appreciate the opportunity provided through this request for comment to discuss further the implementation of the GTR.

The Coalition represents diagnostic technology companies, clinical laboratories, researchers, and other relevant industry stakeholders who work together to improve the quality of healthcare by encouraging research, development, and commercialization of diagnostic technologies in order to improve patient outcomes and reduce healthcare costs. Through its diverse membership, the Coalition seeks to ensure that innovative diagnostic and therapy management tests are available to patients and their physicians, and consistent with this mission, the Coalition applauds the NIH on its development of the GTR, which is designed to serve as a public resource for information about the availability and scientific basis of genetic-based tests. As a representative of a wide range of industry stakeholders, the Coalition is well-positioned to provide comments on the development of the reporting fields in the GTR.

The Coalition generally supports the majority of the proposed fields developed to collect the information for the GTR and believes these fields will effectively assist the NIH in achieving its goal of increasing access for the public to information about genetic-based tests. However, we have included below comments and concerns for specific proposed fields where certain definitions of the terms of the field will likely cause significant confusion to the laboratories reporting these data. Within these comments, we also provide considerations for additional data fields that NIH may want to consider including in the GTR at a future date. Finally, we address concerns with regard to the estimated burdens on laboratories to compile and complete submissions to the GTR.

I. Comments on Specific Genetic Testing Registry Fields

A. Laboratory Definitions

The Coalition generally supports the reporting fields under the “Laboratory Information” category. With regard to the field for “Laboratory Types of Service,” however, the Coalition is concerned that the types of testing performed by its members are not included in the list of possible types of services. The majority of the laboratories that are members of the Coalition perform gene expression or protein expression testing used to (i) assess the risk of progression or recurrence of an underlying disease, or (ii) evaluate the potential benefits of therapy for a specific disease. In their article *Developing the Blueprint for a Genetic Testing Registry*, Javitt, *et al.* specifically define a genetic test to include an analysis of DNA, RNA, chromosomes, proteins, or metabolites to detect levels of gene expression in a human sample.¹ The decision tree developed in this article for inclusion of tests in the GTR would also support the conclusion that the types of tests offered by the Coalition’s members would be included in the GTR. Moreover, the Coalition’s laboratory members are single-source providers of the tests performed, and therefore it is important that their types of services be represented in the options for this field. Insofar as the NIH uses the Javitt, *et al.* article as a reference for creating the “Laboratory Types of Service” field, we recommend that NIH add two categories entitled “Gene Expression Testing” and “Protein Expression Testing” to the proposed list under “Laboratory Types of Services,” and we also request that the NIH make the corresponding additions to the “Test-Specific Laboratory Services” field.

B. Test Information

As the Coalition requested in its July 31, 2010 Letter, the NIH has provided a field for laboratories to list the “Laboratory Test Name.” The Coalition appreciates the NIH’s inclusion of this field, but requests that the NIH also provide a field for the laboratory to list the common name for the test (which may be a proprietary name or a non-proprietary name), which will assist individuals – particularly researchers and other industry stakeholders – with another way to identify the test.

With regard to the field entitled “Test Performed In-House,” the Coalition has two primary concerns. First, the Clinical Laboratory Improvement Amendments of 1988 (“CLIA”) uses the term “in-house testing” to refer to the development and performance of laboratory-developed tests.² In contrast, we understand the purpose of the GTR data field “Test Performed In-House” to be limited to data regarding the performance of different portions of the reported test. Accordingly, we would strongly recommend that the NIH provide a clarifying definition of “in-house” so as to avoid confusion for laboratories as they submit information for this field.

In addition, if the Coalition is correct to assume that “in-house testing” refers exclusively to information regarding the performance of a test (and not to its development), the Coalition is concerned that the options in this field may not accurately capture how a test is often performed by the laboratories. By way of example, for many diagnostic tests, specimen preparation may take place both at the performing laboratory and the referring laboratory. This may occur because certain steps always occur at both locations (e.g., retrieval of blocks always performed at the referring laboratory and review of specimen slides to confirm the adequacy of the sample performed at the performing laboratory) and/or because certain steps may be performed at the referring laboratory on some occasions and at the performing laboratory on others (e.g., cutting of blocks to prepare slides for analysis). As drafted, however, these

¹ Javitt, *et al.* *Developing the Blueprint for a Genetic Testing Registry*. *Public Health Genomics* 2009; 13:95-105.

² 42 C.F.R. § 493.1253(b)(2).

fields do not provide an opportunity for the laboratory to explain these multiple preparation steps when completing this field.

Given the complexity of advanced diagnostic testing and the variability as to the location of where steps of a test are performed, the Coalition requests that the NIH revise the category “Test Performed In-House.” We recommend that the NIH keep the fields “Entire test performed in-house” and “Entire test performed externally,” but if a test does not fall into either of these categories, then the fields for specimen preparation, wet lab work, interpretation, and report generated would contain an open text field to allow the laboratory to explain where each of these steps occur. This will minimize confusion as the laboratory completes this portion of its submission, while also ensuring that the GTR contains the most accurate description of the performance of the test.

C. *Indications for Use*

Consistent with the Coalition’s recommendations in the July 31, 2010 Letter, the NIH proposes to include a field in the GTR for the laboratory to identify the indication(s) for use of the test. While the Coalition appreciates the NIH’s efforts to develop this field, many of the Coalition’s members perform tests that are designed to (i) assess the risk of recurrence or progression of a disease, or (ii) predict the benefit of a particular treatment. However, these types of tests do not fit into any of the options listed in this proposed data field. The Coalition recommends that the NIH add the categories “Disease Progression” and “Treatment Benefit Assessment” to this field in order to allow laboratories to identify appropriately the type of test being reported.

On a similar note, the NIH has proposed to include under the “Indications for Use” category several fields related to the disease for which the test has been developed. The GTR would require the laboratory to list the “Condition for which test is offered,” defined as the name of the disease/syndrome/drug response for which the test can be ordered, and the “Description of the Target Population,” defined as the segment of the population that should be tested for this disease. The Coalition is concerned that it will not be clear to laboratories completing the fields how to differentiate between the condition for which a test is offered and the population that should be tested, when both describe the category of individuals who should be offered the test.

The MMWR article included as a reference for the proposed GTR definition of “Description of the Target Population” uses patient population as the basis for reporting the intended use of the test.³ In contrast, the Logical Observation Identifiers Names and Code (“LOINC[®]”) database identifier referenced for purposes of the field “Condition for which test is offered” focuses on the “Genetic Disease Assessed.” The inclusion of both categories may demonstrate an attempt by the NIH to capture the fields recommended by each source, but these fields would appear to measure the same population and are therefore somewhat duplicative in nature. As such, the Coalition urges the NIH to remove one of these reporting fields from the “Indications for Use” category in order to streamline the submission process, or, in the alternative, provide clarification and examples to demonstrate the data requested for these two categories.

³ Chen et al., *Morbidity and Mortality Weekly Report (MMWR): Good Practices for Molecular Genetic Testing for Heritable Diseases and Conditions* (2009), available at <http://www.cdc.gov/mmWR/preview/mmwrhtml/rr5806a1.htm>.

D. *Test Methodology*

Although the Coalition supports the NIH's efforts to include information in the GTR regarding test methodology, we are concerned generally with the level of detail that would be required from laboratories under this field. Moreover, the Coalition urges the NIH to consider that these fields may provide only limited benefit to users of the GTR, most importantly the general public, while creating significant confusion for laboratories attempting to submit these data.

1. Test Methodology: Pull-Down List

With regard to the field for the test method used in the assay ("Test Methodology"), we would note that developers of the LOINC database have specifically stated that LOINC distinguishes tests by the type of methodology only "if a given type of method has an important effect on the interpretation of the result."⁴ Moreover, the LOINC database does not include broad categories of test methodologies which potentially encompass a wide range of laboratory tests and for which multiple categories might be appropriate for a specific test. Instead, the LOINC database permits laboratories to spell out the test method fully in the LOINC identifier.⁵ Creating distinct requirements under the GTR as compared to the LOINC database may create substantial confusion for laboratories when determining under which, if any, category the test methodology should fall.

By way of example, certain diagnostic tests developed by the Coalition's members target specific genes in order to assess the risk of disease recurrence or progression; other tests analyze specific genes in order to assess the likely benefit of certain therapies; other tests are designed for both purposes. The Coalition is concerned that its members would be unable to determine whether their tests would fall under the "gene expression profiling" category, the "GeneID" category, or would be appropriately reported under both categories in the proposed GTR. In order to avoid confusion and to provide consistency with the processes used in the LOINC database, the Coalition requests that the NIH instead allow laboratories the option – but not the requirement – to describe the methodology for a test in the GTR. As an alternative, the NIH should provide examples of the relevant sub-categories it would include under each method category.

2. Platforms: Laboratory-Specific Pull-Down List; Instrument(s) Used During Testing: Pull-Down List

With regard to the proposed fields for Platforms and Instrument(s) Used During Testing, we understand that the NIH anticipates that laboratories would submit the names of specific manufacturers whose assays and/or instruments are utilized by the laboratory to perform the test. The Coalition urges the NIH to consider that requiring laboratories to list arrays and instruments with manufacturer-specific information may raise significant proprietary concerns. By providing this information, laboratories would run the risk of disclosing confidential data with respect to the procedures used to perform their highly unique testing. This is especially important for the Coalition's members insofar as they are single-source laboratories, and disclosure of their assays and instruments would reveal proprietary information as to how the specific test conducted at their laboratory is performed. Moreover, the Coalition seeks clarification as to how to differentiate between the general field "FDA-Approved tests" and the fields listing specific manufacturer's arrays, and whether the laboratory would list one or both in describing a certain array used to perform the test.

⁴ McDonald et al., *Logical Observation Identifiers Names and Codes (LOINC®) Users' Guide* 17 (June 2011).

⁵ *Id.* at 39.

Overall, the Coalition is also confused as to the utility of requiring laboratories to report this information in the GTR. Specifically, if the goal of the GTR is to provide access to the public for information regarding tests offered by laboratories, then requiring laboratories to complete fields that will not be available to the public provides little, if any, benefit to the public. In addition, the risk of disclosing proprietary information – especially in the context of single-source laboratories – outweighs any minimal benefit to submitting this information. As such, although we agree with the NIH’s decision to prevent the public from viewing this field, the Coalition strongly urges the NIH to remove this field entirely in order to minimize proprietary concerns and further streamline reporting procedures under the GTR.

E. *Quality Control and Quality Assurance*

1. Observations on Performance Specification Fields

The Coalition supports the NIH’s inclusion of fields for laboratories to submit data regarding precision and accuracy consistent with the recommendations in our July 31, 2010 Letter. We would note, however, that the definitions of “accuracy” and “precision” appear to be reversed. Specifically, “precision” is defined as reproducibility or repeatability, meaning the degree to which the results are the same when reproduced under the same conditions, but this definition is included under the heading for “accuracy” in the proposed GTR definitions. In contrast, “accuracy” is customarily defined as how close the quantitative results of a test are to the actual (true) quantitative value, but this is the definition for “precision” under the proposed GTR definitions. We would therefore request that the NIH revise the definitions for these fields accordingly.

In addition, the Coalition supports the NIH’s decision to include “Analytical Sensitivity” and “Analytical Specificity” fields to describe a test’s performance specifications, and believes that these are important data for purposes of demonstrating how laboratories validate the results of the tests which they perform. With regard to validation methods, however, the Coalition is concerned that the NIH has not provided a field for laboratories to report the reference intervals, or normal values, for the test. NIH has relied on CAP.MOL.31245 “Reference/Reportable Range” for purposes of creating the field to list the reportable range in the GTR. It is important to note that CAP.MOL.31245 also suggests that the laboratory be required to report the reference value (normal versus abnormal result). The Coalition believes this information is especially pertinent for healthcare professionals so as to understand better the results received from a particular test, and therefore we urge the NIH to revise the Internal Test Validation Method Description to include a field for laboratories to submit the reference value for the test.

2. Additional Clinical Validity Fields

Finally, the Coalition encourages the NIH to consider expanding the GTR at a later date to incorporate additional fields regarding validation studies for the test reported by the laboratory. Because many tests reported under the GTR have an intended use which includes a claim of clinical meaning or usefulness of the analytical result, the Coalition urges the NIH to add a field to the GTR that permits laboratories to submit primary and secondary endpoint measures for the test, including the value for each measure, and the results of any tests measuring the statistical significance of these endpoint measures. These data are significant for purposes of providing healthcare professionals with important clinical details about a test, and publishing these data in the GTR provides an opportunity for healthcare professionals to have quick and easy access to these measures after they receive results from the laboratory.

The Coalition also believes that researchers, health care professionals, and the general public would benefit from more information regarding clinical studies conducted to establish the clinical validity of a test. The NIH should consider creating a field for laboratories to submit a synopsis of the study protocol

so that health care professionals and researchers will be able to interpret and evaluate the results of the studies accurately. This information would be reported by creating additional optional fields under the “Quality Control and Quality Assurance” category, so long as the NIH determines that inclusion of these studies would not be misleading or promotional in nature. Although these fields would require additional reporting by laboratories, the Coalition believes this provides the public with access to important information regarding the test. Moreover, postponing implementation of these fields until a future date will permit laboratories to adjust to the fields currently proposed for the GTR before requesting that laboratories complete additional fields.

II. Observations Regarding the Burden on Laboratories to Report Data

In the original Request for Comments published in the July 27, 2011 *Federal Register*,⁶ the NIH estimated that it would take laboratory personnel – at a mean hourly wage of \$22.85 – an average of three hours to complete each submission to the GTR. Although the Coalition appreciates that the NIH has made efforts to streamline and simplify the reporting procedures for the GTR, the complexity of the data to be reported necessitates that a Laboratory Director review, verify, and complete many of the fields proposed for the GTR. The participation of Laboratory Directors in the GTR submission process will therefore significantly affect the NIH’s previous estimates by substantially increasing the three-hour completion time to review the data, as well as increasing the mean hourly wage estimated by the NIH. Accordingly, the Coalition would urge the NIH to reconsider its proposed estimates with regard to the financial burden on laboratories to participate in the GTR.

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We appreciate the opportunity to submit comments on the Genetic Testing Registry and we hope that you have found the information and suggestions in this letter to be helpful. If you have any questions about our comments, please contact Paul Radensky at 202-756-8794 or pradensky@mwe.com.

⁶ National Institutes for Health, Request for Comments Under the Paperwork Reduction Act, Section 3506, 76 Fed. Reg. 44,937 (July 27, 2011).