Response to Comments Received During the 30-day Public Comment Period

The Office of Management and Budget received four comments during the 30-day public comment period from November 23, 2011, to December 23, 2011. NIH's response to those comments follows. Each of the four comments is provided in its entirety following NIH's response.

Coalition for 21st Century Medicine

Several of the Coalition's suggestions (e.g., adding common test name, clarifying the definition of "test performed in-house") have been addressed in the Genetic Testing Registry (GTR). Suggestions for additional data fields and categories for GTR menu options (e.g., gene expression testing and protein expression testing to the data field for laboratory types of services) will be considered in consultation with GTR clinical advisory groups. The National Institutes of Health (NIH) notes that gene and protein expression tests are generally somatic tests, which are outside the scope of the initial phase of the GTR, but will be added in subsequent phases. Regarding the comment to revise "internal test validation method description" to include a field for reference value/intervals, this field is in the GTR. NIH will clarify the instructions and note that reference values can be included. The Coalition expressed concern that requesting information about arrays and instruments could reveal proprietary information. At the November 2011 public stakeholder meeting and in subsequent presentations, NIH explicitly stated that it will not request proprietary information. This point also will be made clear in instructions for submitters. The Coalition pointed out that definitions for "precision" and "accuracy" were reversed; the definitions have been corrected. Regarding the option to describe the test methodology, submitters can choose "other" from the menu list and provide the test methodology or can provide this information in the text field for "Description of test procedure/protocol." NIH will consider the Coalition's suggestion to incorporate additional data fields for validation studies at a later date. Regarding the estimated burden, after the 60-day comment period, NIH recalculated the cost burden using a mean hourly wage more appropriate for experience laboratory personnel ($30.63 instead of $22.85). NIH re-evaluated the time burden and decided that it remained valid.

Robert Cook-Deegan, Duke Institute for Genome Science & Policy

NIH shares Dr. Cook-Deegan's concern about avoiding duplication with other government databases and has engaged in interagency discussions to ensure that the GTR does not duplicate other information collections. Before NIH's March 2010 publicly announcement of its plan to develop the GTR, it met with the Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS) to discuss whether such a registry would be useful to these agencies. Avoiding duplication and minimizing reporting burden were important elements of this discussion. Once GTR development began, NIH held two broader trans-agency meetings that included FDA, CMS, the Centers for Disease Control and Prevention, Health Resources and Services Administration, and Federal Trade Commission. The objectives of these meeting were to demonstrate GTR prototypes and gather feedback, discuss approaches that would reduce reporting burden for laboratories, and learn of federal activities relevant to the GTR.

In developing the GTR, NIH was sensitive to Dr. Cook-Deegan's concern about the burden to provide certain data repeatedly (e.g., quality control programs, contact person, laboratory certification). GTR submitters will be able to use time-saving features such as a copy function and bulk submission of data. His suggestion that GTR integrate with resources/tools such as OMIM and MESH categories has already been implemented. The suggestion to link to mutation databases such as Human Variome and MutaDATABASE will be done through ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), a companion database to the GTR that will be available later this year.

With regard to Dr. Cook-Deegan's recommendation to include patent and licensing information in the GTR, the primary purpose of the GTR is to enhance the transparency of information about the scientific and clinical basis of the test, and NIH does not plan to request data elements that do not relate directly to this goal. At the same time, the database will continue to evolve after its launch and as it matures and gains greater stakeholder support and wider utility, NIH will consider adding data elements that have other public policy purposes.

Human Genetics Society of Australasia (HGSA)

Several of HGSA's comments have been addressed in the design of the GTR (e.g., presenting information in tiers, providing pull-down menus to complete data fields, collecting accreditation information from international laboratories). HGSA expressed concern about the detail of some data fields (e.g., platforms, instrumentation, gene variants). These data fields are optional; submitters can choose not to complete them. HGSA suggested that test price and turnaround time be added to the information collection. Based on the collective feedback from extensive stakeholder engagement prior to the public comment periods required by the Paperwork Reduction Act, NIH decided not to include test price or turnaround time in the initial phase of the GTR. It will reconsider these data elements in later phases of the GTR. HGSA also suggested that NIH facilitate the importation of data from databases in addition to GeneTests. Using a bulk upload option, laboratories can place data held in personal or other databases onto a standard form for import into the GTR.

National Society of Genetic Counselors (NSGC)

NSGC requested that NIH implement a structured peer-review process to safeguard against false and inaccurate data. Absent this process, NSGC would like a notice that NIH, or other government entity, does not endorse the information in the GTR. NIH has taken a number of steps to address this concern, including an explicit disclaimer that states NIH or the U.S. government makes no endorsements of tests or laboratories listed in the GTR. Data fields suggested by NSGC (e.g., CLIA certification, common or commercial name of each test, and target population) have already been included in the GTR. NSGC also recommended that GTR focus on a primary audience. At the public stakeholder meeting in November 2011, NIH clarified that it will focus initially on health care providers as the primary GTR audience and will expand to other audiences in subsequent phases of the Registry. This point has been made in subsequent presentations and will continue to be made in the future.

December 23, 2011

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.

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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).

22 December 2011

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Dear Dr. Patterson,

Thank you for the opportunity to comment on the proposed form that will be used to generate the Genetic Testing Registry (GTR), per *Federal Register* notice of 23 November 2011 (Vol. 76, No. 226, pp. 72424-5).

The test registry could replace genetests.org as the first place to go to determine who is offering genetic testing for a particular condition or locus. The OMB notice appropriately focuses on the potential burden on those submitting data. Only data essential to make sense of the list and not available more readily elsewhere should be included.

I have several concerns based on reviewing the proposed fields and mock-up entry. One is overinclusion of information for which the GTR is not the appropriate archival resource, and therefore not a good use of time for those submitting entries; another concern centers on patent and licensing elements that bear directly on the availability of tests but would not be included. My final comments will focus on overlap and coordination with the regulatory data required of testing services, so that the NIH database is integrated with rather than separate from data required for those tests (now and in the future) that will be regulated by the Food and Drug Administration (FDA; both Laboratory Developed Tests and In-Vitro Diagnostic Multi-Index Assays) and for regulation, coverage and reimbursement by the Centers for Medicare and Medicaid Services (CMS) under federally funded health programs and the Clinical Laboratories Improvement Amendments. There is a danger that three agencies will set up somewhat different databases for their different purposes and with extensively overlapping data requirements that are nonetheless not coordinated, so that those submitting data have to comply with these and any state and private health plan data needs separately. Explicit explanation of how data submitted to GTR will be used by FDA and CMS would be most welcome, so the system is not an added data burden but instead a single database serving multiple purposes and so streamlining federal data submission on genetic tests.

Overinclusion and redundancy

While it makes sense to list participation in proficiency testing and quality control national programs and to designate a contact person, the level of detail seems unduly high. The nature of quality control programs is constantly changing; moreover, many programs relate to multiple tests or by laboratory rather than by individual tests. Asking for exactly which QC program is used for each test will require a substantial effort centrally to generate an up-to-date set of pull-down items to select, and redundancy test-by-test for those submitting data. This test-by-test data entry format will be particularly burdensome for laboratories that do many tests; for them it would seem to make better sense to instead link to a page they make public that shows how they are complying with proficiency testing and CLIA certification requirements, which are done laboratory-by-laboratory rather then test-by-test. A single

entry per laboratory noting which QC programs it subscribes to might be more logical, obviating repeat entries for the laboratories that offer multiple tests. This suggests the option of organizing the data according to test and according to laboratory, with ability to connect between them, rather than only test-by-test.

Regarding the contact person, the level of specificity about certification, licensing, and specialty seems beyond the need of a list focused on what tests are available, and items associated with personnel are sure to require regular updating and thus often be out of date and inaccurate. I don't think I would use GTR to find an individual's medical certification, but I would use it to find out who is the laboratory director. Beyond an initial contact, however, I do not think GTR is the right place to list genetic counselors, physicians, or others except to the degree they are the primary contact for information about a particular test.

Regarding the details about which tissue samples, how samples are submitted, how linkage to counseling services is maintained, and exemplars of negative, VUS and positive reports, a central database seems a poor way to try to capture the information both because it will be constantly changing, and because in many cases, the same procedures will be used for multiple tests. Another option would be to require each laboratory offering a test to have a site that explains these details, and perhaps specify the data that must be available, but not to require data entry test-by-test. That is, require a link to a document that supplies stipulated information, but not directly incorporate the information centrally in the database. This would leave the control of updates in the hands of the laboratories, and require central management only of links rather than the constantly changing data.

The section on the condition tested (currently called "disease," but that is probably going to encounter some confusion for some testing, for example pharmacogenomic tests or broad screening tests). The option for detail here is welcome, but GTR seems unlikely to be the place that information about acronyms, mode of inheritance, disease mechanism, or prevalence are documented. A link out to OMIM, where possible, would be much more logical, but it does not appear that OMIM categories are cross-referenced here, so the data are apt to be redundant with OMIM, which is an actively archived and curated dataset and more likely to be current with the literature than GTR will be (as a database about what tests are available not about what is known about the diseases being tested). Explicit attention to MESH categories and OMIM categories might reduce the amount of data entered and also connect users to the relevant database. Finally, the information on individual mutations will be accumulating at databases such as MutaDATABASE, Breast Cancer Information Core, Human Gene Mutation Database, and Human Variome database. Linking to these rather than duplicating the information in them seems a wiser strategy, and these databases are much more appropriate archives for the basic data on which interpretation of tests will be based, whereas GTR will be the database of clinical tests and testing services.

In the section on "method," this seems likely to be especially fast moving and liable to change, and the categories will be shifting to a degree that may make a central database hard to maintain. And yet this information is exactly what someone contemplating ordering a test will want to know. My comments here are not apt to be as useful as those from active laboratory directors, but this does seem both very difficult and yet essential to have in a useful database. I will say that some of the level of detail implied by the mock-up (down to the level of reference sequences and which variants) seems impractical. In thinking of CF or BRCA testing, for example, there would be thousands of variants listed and it seems

unreasonable to expect that list to be maintained and up to date in a central database unless the database maps directly to one that is operational at the testing service, and automatically updated as test methods change. For sequence-based tests, the "all variants" item would work, but for multi-allele methods, there are many tests now that have dozens or even hundreds of variants. Is GTR the right place to try to keep track of this? The answer may be yes, but it may also be no. One solution might be to require a link to a page that would describe the test method that would be under control of the laboratory doing the testing, with specifications of the level of detail that those offering tests are expected to provide, but not trying to keep all this information in the central database.

The information about how VUS and other categories of interpretation would be most welcome to know, but seems more likely to arise more from other databases like the variome database, Mutadatabase, and human gene mutation database than from GTR. The part that would be essential to capture is how the lab bases its interpretation, and how to find the data and algorithms on which the interpretation is based. If there is an interpretive algorithm, then link to where that can be found. The questions about whether additional family members are invited for analysis (although right now, the only option is "without charge") seems excellent, as well as information about recontact if interpretation changes. These answers of course have legal ramifications, but this seems like a reason to include, rather than exclude them.

There will surely be a debate, however, about whether GTR should be the place where such information is archived and documented. These are generally not laboratory-specific features, but about the nature of the test in general, and of course answers to such questions entail liability and spill over to regulatory compliance (under FDA, CLIA, New York State, etc.). The information about performance characteristics and clinical validity and utility are welcome, in part for these very reasons. Asking each laboratory to state utility and validity and cite the basis for it would go a long way towards accountability. These items would also mean the federal government would be able to readily note the conditions under which tests are being offered, including medical claims.

Missing elements about patents and licensing

Huys, et al., in their analysis of genetic testing for 22 commonly tested conditions, found at least one blocking claim in patents associated with genes for 16 of the conditions (*Nature Biotechnology* 29: 903-909, October 2009). Only a small fraction of claims were blocking, and most that were hard to work around were method claims, many of which may be invalid under shifting jurisprudence in the United States. But nonetheless, one fair interpretation of their findings is that patenting and licensing could affect availability of 73 percent of Mendelian conditions commonly tested.

Cho, et al., surveyed laboratories offering genetic tests a decade ago, and found that 65 percent had been contacted about patent enforcement (*J Molec Diagnostics* 5: 3-8, February 2003). Indeed, their sampling strategy started from genetests.org, indicating that GTR is the logical locus for identifying when intellectual property considerations might be relevant. In eight case studies of genetic testing for ten clinical conditions prepared for the Secretary's Advisory Committee on Genetics, Health and Society, the evidence about effects of patenting and licensing on clinical access to tests was complex and often equivocal; but the evidence that patenting and licensing matter to which laboratories offer which tests was overwhelming and unequivocal. This work was summarized (*Nature* 458: 405-406, 26 March 2009; and *Nature Biotechnology* 28: 784-791, August 2010) and the case studies published (*Genetics in Medicine* 12 (Suppl): S1-S211, April 2010).

It is thus quite clear that one reason a test may or may not be offered is patent rights. Moreover the locus of responsibility for managing it will be at the level of laboratories. Just as other items on the list seem intended to assist in establishing accountability in genetic testing, it seems odd to leave licensing status entirely off the list of GTR data items.

The GTR is not the logical place to gather the detail information about patent status of relevant genes, or terms of licensing. It does seem appropriate to have an acknowledgement of and link to further information (where relevant) and patents and licensing. A simple check-box about whether patent rights are licensed, with a link to a laboratory-maintained page that lists patenting and licensing status when the box is checked (e.g., the list of patents, or public statement about licensing status) would both be simple to submit, would require only disclosure of information that a service offering a test should know about without undue research, and would greatly increase transparency and inconsistency in reporting that directly affects which tests are available from whom.

Since the function of intellectual property, like property, depends on defining metes and bounds, it seems remiss to leave out any mention of patents and licensing rights in a database of genetic tests given the evidence that such rights directly affect which tests are available from which laboratories. Indeed leaving such information out seems to signal acquiescence to patent-holders not disclosing their patents and laboratories continuing to indulge in wink-and-nod avoidance of intellectual property conditions for some genetic tests. At the least, if the decision is not to include such a check-box and link to further information, then an explicit reason for not doing so seems warranted, and this letter is an invitation to provide that justification.

This has obvious implications for infringement liability, but many other items being included in the database also have liability implications. The patenting and licensing situation for some tests can be murky, but this is in no small part because of failure in transparency for which GTR could be a partial remedy. To the degree that intellectual property considerations operate in the shadows, it breeds uncertainty and inefficiency. Patenting and licensing are at least as relevant to genetic testing as many other items on the list, and demonstrably relevant to whether genetic tests are available from a given laboratory. Moreover, if the legal regime under which genetic testing is to operate is to be both transparent and also respect intellectual property rights where they exist, the logical place to effect the transparency is where the test is publicly offered, i.e., the GTR. If a decision is made not to include this information, the reasons for the decision should be explicit and public.

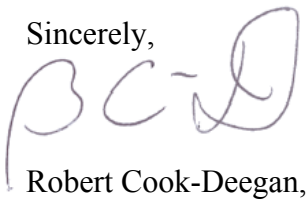
Coordination with other federal (and state) agencies that require data submission

CLIA certification seems essential. But presumably such CLIA certification comes with certain information submitted to CMS; will GTR be linked to such data, reducing the need to submit redundant information and keep it updated in two places? Regarding state licensing, it is not clear whether the information requested is for the lab or the lab director or both. And of course, the special requirements of New York State introduce yet another potential data redundancy. GTR could become the repository of relevant information for the federal government, serving this function for CMS as well as NIH, but it could also simply link to a separate CMS database (or the laboratories' own records of CLIA certification), but it would be good to avoid outright duplication.

The information about FDA status also seems essential, analogous to CLIA certification. The same issues of coordination arise. Asking if the test is FDA-approved as a kit, an IVDMIA, or (in the future) LDT or is under investigational use or is research use only is a core element, and should be required. For tests that a laboratory administers but was not responsible for FDA review, however, there needs to be an option (e.g., if they offer a kit test manufactured elsewhere).

Again, thank you for the opportunity to comment. I can be reached at gelp@duke.edu; 919 668-0790 if I have been unclear or if you have questions or need more information.

Sincerely,



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RCPA
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NIH GTR RFI Comments,
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Office of Management and Budget,
Office of Regulatory Affairs
6705 Rockledge Drive,
Bethesda, MD 20892.

OIRA_submission@omb.eop.gov

December 23, 2011

Dear Sir,

Re: Comments on the practical utility of proposed data collection for the Genetic Testing Registry

The Human Genetics Society of Australasia (HGSA) is grateful for the opportunity to further comment on the development of the Genetic Testing Registry (GTR). The HGSA is the peak Australasian professional body to provide a forum and, in some instances, certification for the various disciplines related to human genetics in Australia and New Zealand. As with our previous comments regarding the GTR, we are submitting this response with another Australasian organization with a professional interest in genetic testing, the Royal College of Pathologists of Australasia (RCPA). The RCPA is the peak body representing pathologists and scientists in the delivery of medical testing in Australasia, has a major role in developing accreditation standards for laboratories, and is a partner in the assessment of medical testing laboratories in Australasia.

We applaud the concept of the GTR as a resource for patients, referrers, laboratories, and (potentially) funders to guide the utilization of useful, cost-effective, high-quality genetic tests in healthcare. The Australian Government has commenced a discussion on similar issues, and we are following the development of the GTR story with keen interest.

The broad range of stakeholders in genetic testing, and the variety of genetic competencies within each category of stakeholder, makes it challenging to provide a resource that will be useful and contemporary for everyone. This challenge is compounded by the GTR being a repository of data that is provided on a voluntary basis by laboratories.

The PDF screenshots of the proposed interface indicate that a lot of detailed information will be provided by each laboratory for each test. We are concerned that many laboratories will not volunteer to provide this level of detail, and that the detail will render the information inaccessible to many potential users. The use of free-text to describe a test and its utility provides freedom of expression and allows a laboratory to provide detail or nuances, but free text can obscure the very facts that the user is seeking. And the facts that one user seeks may be different to those sought by another.

We submit that GTR would be enhanced by the following:

- The target audiences need to be clearly defined. Rather than having one interface meeting all needs, it may be appropriate to have interfaces for both the professional and the consumer
- Information needs to be presented in different tiers, with the principal information being on the surface and more detailed information below. The screenshots already have this structure, with the overview providing a “one screen” summary. But the language in this overview is too dense for most non-experts (consumer and professional alike).
- Where possible, the key message for a field should be selected from a list, thereby ensuring ease of reading (consistent layout and language) and searching. This summary statement could then be linked to more detailed free-text statement that captures the detail.

- There should be a central resource of statements regarding the validity and utility of certain tests that any laboratory can utilize. If a gene test for a certain mutation is offered by a number of laboratories, the validity and utility of the test should be independent of the laboratory providing the test (assuming that each laboratory has appropriate Clinical Laboratory Improvement Amendments (CLIA) certification). But the proposed screenshots indicate that each laboratory needs to draft its own statement regarding these parameters. It seems inefficient to have each laboratory replicate this task.

The considerations above are "high level". We have the following more specific comments.

- We appreciate that not all options on drop down boxes or lists are visible, making it difficult to determine the utility of the information collected and the burden of data entry on the respondents. We have assumed the full list of options is as described in GTR Proposed Field Definitions V 0.25.

- It appears the Personnel, and Licensure and Accreditation fields are built around North American qualifications and certifications. It would be a pity not to collect accreditation information from International laboratories, especially since ISO15189 accredited labs are required to ensure referral laboratories and consultants are competent to perform requested examinations. We note over 1/3rd of the laboratories in Gene Tests are outside the USA and an International resource such as the GTR should capture accreditation information from non-CLIA labs.

- The Ordering information fields are difficult to follow and not intuitive, they refer to URLs for detailed ordering instructions in several places but in reality there is probably only one URL for the laboratory which is required.

- Under the Methodology section, collection of detail on platforms and instruments would appear to be unnecessary for users of the GTR. Multiple instruments may be used for some testing. The section on listing all relevant gene variants and clinical significance of each would be impossibly arduous unless it was automatically filled from locus specific databases.

- The interpretation fields include policy on reporting Variants of Unknown Significance. This could be extremely complex and take a great deal of time for high level personnel to complete. It is unclear what is meant by the final field in this section. We are also uncertain whether this will be useful. The experts who would understand this section would only rely on it if they could be assured that it was current and comprehensive. Given the voluntary nature of submissions, this is unlikely and the experts will contact the laboratory directly. Non-experts could simply be confused by this section.

- The whole section on Performance Characteristics is very complex and often likely to be context-specific. Clinical validity and utility seems to be targeted at Direct-to-Consumer Testing. Clinicians using the GTR should already have their reasons for ordering the test and what they want to do with the results.

- Potentially useful information not in the proposed collection includes price and turnaround times.

- Import of at least minimal data sets from existing databases should help to reduce the burden of data entry, however, we suggest there should be ability to import from other national or regional databases of genetic tests.

Overall the HGSA and RCPA continue to support the concept of the GTR as a resource for clinicians, laboratory staff, researchers and the public. However, the burden of completing many of the optional fields appears to outweigh the utility of this information for users. We submit that it would be preferable to have simpler resource of consistent high quality than something more ambitious of variable quality.

Thank you for considering our views.

Yours Sincerely

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National Society of Genetic Counselors

December 22, 2011

NIH GTR Comments
National Institutes of Health
Office of Science Policy
6705 Rockledge Dr., Room 750
Bethesda, MD 20892

Dear GTR Staff,

The National Society of Genetic Counselors (NSGC) is responding to the National Institutes of Health's (NIH) November 23, 2011 request for comments on the practical utility of the proposed collection of information for the Genetic Testing Registry (GTR).

NSGC supports efforts to enhance access to information regarding the availability, validity, and utility of genetic tests. Additionally, NSGC appreciates the previous work that NIH has conducted on accessibility and we encourage NIH to continue to seek out genetic counselors and NSGC for expertise in fine-tuning the GTR. Further, we respectfully request that NIH consider the following comments and recommendations of NSGC.

General recommendations:

- NSGC requests that NIH safeguard against false or inaccurate GTR data by implementing a structured peer-review process.

  While the GTR seeks to increase transparency by establishing a general clearinghouse for genetic data, more information is not always better. The volunteer-based submission criteria make the GTR vulnerable to erroneous and false data that can be misconstrued as valid and accurate information. If the GTR links to marketing materials on a company or laboratory's website, there should be disclosure that the viewer is being directed to an external website.

  Further, NSGC is concerned that tests that have little or no clinical validity will gain credibility simply by being listed on the GTR. The increased transparency and information available should be weighed against the quality of the data submitted through a peer-review process. If formal peer-review is not feasible, then NSGC recommends that NIH enable providers and other laboratories to submit external comments to all publicized data within the GTR. In the absence of oversight of the information presented, there should be notice that NIH, or any other government entity, does not endorse the information presented on the GTR.

- NSGC recommends that the GTR provide adequate information on all tests.

  The GTR should also include Clinical Laboratory Improvement Advisory Committee certifications, as well as the common and commercial name for each test. Issues such as unique product identifiers would help to identify and compare tests, though no current regulations exist that mandate such standards. An example of useful information that should be included is population or demographic data to ensure that tests are appropriately applied to those populations.

- NSGC recommends that the GTR focus on the audience that will benefit most from the GTR.

  It is not possible to create a resource that is equally valuable to all audiences. While consumers, researchers, providers, payers, and policy makers may have some overlapping needs, many are distinct. For example, clinicians may value and correctly interpret accuracy and analytical sensitivity/specificity, but consumers may misinterpret these data elements as clinical validity. Even genetics professionals and non-genetics professionals have substantially different needs. Genetics providers will likely use this service as they used GeneTests – a resource for genetic test availability and application. Non-genetics providers and the public may use the GTR to infer validity.

  Payers could find the GTR helpful if it addresses clinical validity in addition to analytical validity, as they seek guidance on covering certain genetic tests. However, the GTR, in its current form, will not be sufficient for payers' purposes because it cannot assess the circumstances under which testing should be offered and covered on a case-by-case basis.

NSGC appreciates the opportunity to provide comments. We look forward to collaborating with NIH to ensure that the GTR is a valuable tool for genetics professionals.

Sincerely,

Karin M. Dent, MS, LCGC
President