American
Clinical Laboratory
Association

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VIA E-MAIL (GTR@od.nih.gov)

Francis S. Collins,
Director
NIH GTR RFI Comments
National Institutes of Health
Office of Science Policy
6705 Rockledge Drive, Room 750
Bethesda, MD 20892

Re: Request for Information on the National Institutes of Health Plan to Develop a Genetic Testing Registry

Dear Dr. Collins:

On behalf of the American Clinical Laboratory Association (ACLA), I am pleased to submit these comments on the proposed National Institutes of Health (NIH) Genetic Test Registry (GTR). ACLA represents national, regional, and local laboratories across the country, many of which offer extensive menus of genetic tests. As a result, we have a direct interest in the development of the registry.

At the outset, ACLA wishes to express its appreciation for the work being undertaken here by the NIH. We believe that the growth of personalized medicine provides great opportunities for improving the health of patients. Further, we believe that a registry that will provide easy access to information about genetic tests and could increase the understanding of users, including patients and providers, about the valuable information these tests offer. At the same time, we are mindful that a registry will be only as good as the information that goes into it. It is therefore important to ensure some level of oversight so users and submitters can have confidence in the accuracy and reliability of the information. We believe that a non-curated registry may not achieve the fullest potential of this kind of research tool, as a higher likelihood of inaccurate or outdated information could lead to less reliance on the registry as a source of useful and important information.

Below, we provide comments in response to the questions posed in NIH's Request for Information (RFI):

1. Are there any types of genetic tests that should not be included in the GTR?

The definition of "genetic test" for purposes of the GTR will dictate which tests are included. The GTR should be limited to tests on human genes and gene products that play a role in promoting health; in predicting, preventing, diagnosing, or treating disease; or in determining a patient's prognosis. This would include pharmacogenetic tests and tests for inherited conditions and cancers. All analytes (DNA, RNA, proteins, metabolites, etc.) that are used in tests for

diagnosis, treatment, follow-up, and prognosis should be included. Non-medical testing, such as forensic testing or paternity testing, should not be included; as such testing is not used for promoting health or diagnosing or treating disease. Genetic tests for infectious agents should also be excluded at this time. These include tests for some form of pathogenic DNA or RNA to detect the presence of an infectious agent. The focus of the GTR should be *human* genes and gene products.

2. What are the potential uses of the GTR for (1) researchers, (2) patients/consumers, (3) health care providers, (4) clinical laboratory professionals, (5) payers, (6) genetic testing entities/data submitters, (7) policymakers, and (8) electronic health records?

We anticipate a number of uses of the GTR by clinical laboratories. Beneficial uses include obtaining information about genetic tests and identifying tests available for certain conditions. The GTR also may create opportunities for laboratories to provide useful information to other health care providers, including other laboratories that may need to make a referral or locate a specialist. We also anticipate that laboratories and researchers will be able to use the GTR to compare different methodologies.

While we cannot anticipate all potential uses of the GTR, we are concerned about potential efforts to use the GTR to gain a competitive edge based on information in the registry. We hope that the NIH will work to ensure that the GTR is designed as a scientific resource rather than as a platform for advertisement or a mechanism for companies that wish to gain proprietary information about their competitors. The GTR will be most useful if it remains a scientific resource.

3. What data elements are critical to include for use by (1) researchers, (2) patients/consumers, (3) health care providers, (4) clinical laboratory professionals, (5) payers, (6) genetic testing entities/data submitters, (7) policymakers, and (8) electronic health records?

Critical data elements for inclusion are discussed under question number 6, below. Our comments reflect the perspective of clinical laboratories.

4. What are the potential benefits and risks associated with facilitating public access to information about the:

a. Availability and accessibility of genetic tests?

Greater information and improved educational opportunities for professionals and patients will benefit the rapidly evolving specialty of genetic testing, a 21st-century resource that promises to change the nature of healthcare through tailoring care for each patient individually through use of that patient's genetic information combined with family history and other personalized data.

b. Scientific basis and validity of genetic tests?

Obviously, educating the public about the uses of genetic tests will promote the understanding of genetics and the opportunities that genetic testing can afford. However, information about the scientific basis and validity of genetic tests that is made available through the GTR can be useful only if it is accurate. If the accuracy of the data published through the GTR is not verified, or otherwise subject to some minimal editorial oversight, then the usefulness of such information will be diminished. Oversight to ensure that information included in the GTR is consistent and relevant is essential. If no such "curation" is provided, the GTR could become

cluttered with useless entries. NIH should take steps to promote reliability such as providing links to GeneReviews and published literature where available. We urge NIH to consider how to provide such oversight and editorial curation of the information in the GTR. If such oversight is not provided, the GTR should include an appropriate disclaimer.

c. Utility of genetic tests?

Information on the utility of genetic tests will be most beneficial to the public and to laboratory professionals if it is supported by published data. References to peer-reviewed articles, where available, or cross-links to such literature, would be an optimal way to ensure that users are able to find third-party support for posted information regarding utility. If information on utility is provided without support, there is a risk that the utility of tests will be misunderstood by patients and practitioners alike.

Ideally, well-supported and accurately reported utility information would enable patients and physicians to make the most informed decisions when choosing a test. Such information also could help to clarify which tests provide results that factor into immediate clinical decision making and which tests have utility more appropriately associated with longer term decision making.

5. What is the best way to distinguish between data fields left blank because of an absence of data/evidence and those left blank for other reasons? How important is this distinction for enhancing transparency, including for the purpose of identifying research opportunities?

We recommend giving submitters three options to indicate why a field is left blank: "no information available," "not applicable," or "no information provided." As a default, blanks would be filled in with "no information provided." Laboratories would have the option of indicating that the requested information is not available or not applicable for the test in question.

6. To describe adequately and accurately a genetic test, which of the following data elements should be included in the GTR? Are there other data elements that should be added? What information is necessary to represent adequately each data element?

Many of the data elements suggested by NIH in its request for comments are appropriate for inclusion in a GTR. Others present serious risks and should not be included.

a. Contact information (e.g., location, name of the laboratory director and contact information for the laboratory performing the test)

Contact information should be provided. While "location" need not include an address for every laboratory of a corporation, at least the location of the company's headquarters should be included. In addition, submitters should designate an individual, with telephone or electronic contact information, who will serve as a point of contact for inquiries regarding each test listed in the GTR. This person need not be the Laboratory Director. Submissions lacking this information should not be included in the GTR.

b. Laboratory certifications (e.g., Federal or State certification of the laboratory that performs the test)

This information is appropriate for inclusion. Presumably this will include whether a

laboratory is accredited by an outside accrediting organization, such as the College of American Pathologists or JCAHO, and what state licenses the laboratory holds.

c. Name of the test (e.g., common test name, commercial name, marketing materials about the test and/or genetic testing entity, standard identifier (e.g., CPT codes, LOINC))

Tests listed in the GTR should be identified by their common name. To avoid confusion, the name listed should be the name used in the laboratory's directory of services. We do not believe that CPT codes belong in the "name of test" field. CPT codes are not intended for this purpose, and most genetic tests use more than a single code for billing purposes. While LOINC uses names for test observations, LOINC names are not used typically to identify the test and are not useful as part of a "name of test" data element. Since the same test may be performed differently by different laboratories, and different tests may be represented by the same codes, the use of CPT and LOINC codes in the GTR would likely create more confusion than it would resolve.

d. Regulatory clearances (e.g., for tests reviewed by the Food and Drug Administration, the 510(k) or premarket approval (PMA) number)

We agree that this data element is appropriate, but it is important for the GTR to recognize that not all genetic tests may require regulatory clearance, or that some tests may not have required FDA clearance at the time they were first offered. We recommend allowing submitters to select from several options to fill this field, including: "regulatory approval not currently required;" "PMA"; "510(k)"; "RUO;" and/or "IUO." The GTR should include a general explanation of these terms, as well as explanation concerning whether and why FDA clearance may not be required for some tests.

e. Intended use of the test (e.g., diagnosis, screening, drug response)

While it is important for patients, practitioners, and other users of the GTR to be able to determine how tests are used, we recommend that the term "intended use" be replaced by another term that does not have a long-used and well-understood definition in current law and regulation. We are concerned that information called "intended use" could be construed as a health claim and, in the case of tests regulated by the FDA, be considered a labeling claim. In either case, this could lead to confusion because the phrase "intended use" is commonly linked with FDA-cleared or approved products, but not all tests included in the GTR will necessarily fall into this category. We recommend replacing "intended use" with "potential use" or another phrase that describes more clearly the type of information provided.

f. Recommended patient population

Since the selection of a laboratory test is based principally on the individual circumstances of the patient, "recommended patient population" may be an overly generalized descriptor that could be misleading to users of the GTR. We believe that it would be more appropriate to include this type of information as part of the "potential use" of a test (see "e" above).

g. Limitations of the test (e.g., is the test validated only for certain subpopulations or limited to particular uses such as screening but not diagnostic testing?)

For this to be a useful data element for inclusion in the GTR, NIH must provide clear

guidance on what is meant by test "limitations." As with "intended use," the word "limitations" may be misleading and confusing out of context. To the extent that limitations exist for a particular test, these would be captured by other data elements, such as intended or potential use.

h. Test methodology

General descriptions of test methodology are appropriate for inclusion in the GTR. More specific descriptions of testing methods, such as the gene sequence identified, may be proprietary. We recommend that NIH develop a list of high level, standardized test methodology descriptors, (e.g., amplification) to be used in connection with this element. In conjunction with this type of high level description, laboratories could cite to methods described in published literature.

i. Analyte(s)--What is being measured in the test (e.g., genetic sequence)

As discussed above, information provided on the analyte or analytes targeted by a specific test must be kept high level to avoid requiring disclosure of proprietary or competitive information. The actual gene sequence or location should not be published.

j. Specimen requirements (e.g., blood, saliva, tissue samples, amniotic fluid)

It is appropriate to include this information in the GTR.

k. Availability (e.g., is the submitter the sole provider of the test or are there multiple providers?)

Information on the "availability" of a test should not be included in the GTR. We believe such information goes beyond the scope of the science-based nature of the proposed GTR and relates more to product advertisement. The availability of a test may change over time as laboratories choose to add or subtract tests from their available services. A sole provider may later decide to license a test to additional providers, making availability dynamic. Further, a submitter may not know of all locations where a test is provided, such that the accuracy of information submitted on this data element would be questionable. Incomplete and stale information on test availability would cause confusion. The GTR itself will serve as a source of information on availability of genetic tests, without the necessity of representations by submitters.

Based on recent discussions, we understand that NIH is interested in circumstances where various components of a test are performed at different entities. While more than one entity may perform parts of a test, only one entity offers the test.

l. Accessibility (e.g., accessible through a health provider, public health mandate, and/or direct-to-consumer)

As with test availability, laboratories submitting information for the GTR may not have complete information on the accessibility of a test at the time a submission to NIH is made. Not only is this information dynamic, but it also depends on a patient's location and governing state laws related to the ability of consumers to order their own tests. Patients would benefit more from a consistent instruction within the GTR to contact laboratories for additional information about the availability and accessibility of tests.

m. Performance characteristics:

i. Analytical sensitivity
ii. Analytical specificity
iii. Accuracy
iv. Precision
v. Reportable range of test results
vi. Reference range
vii. Method used for proficiency testing (e.g., formal PT program, alternative assessment) and score

Regulations implementing the Clinical Laboratory Improvement Amendments (CLIA) currently require laboratories to establish and verify performance specifications. Specifically, "before reporting patient test results, [each laboratory must] establish for each test system the performance specifications for the following performance characteristics, as applicable: (i) Accuracy. (ii) Precision. (iii) Analytical sensitivity. (iv) Analytical specificity to include interfering substances. (v) Reportable range of test results for the test system. (vi) Reference intervals (normal values). [and] (vii) Any other performance characteristic required for test performance." 21 C.F.R. § 493.1253(b)(2). The CLIA regulations further require that laboratories make these performance specifications available to clients upon request. 21 C.F.R. § 493.1291(e).

We believe that the existing list of CLIA-required performance characteristics is sufficient and appropriate for inclusion as part of the GTR to provide assurance of test accuracy. As such, we recommend that the GTR include only the information required by CLIA. This will make it easier for laboratories to submit information and will make the information provided more reliable, given the scrutiny of CLIA oversight. We further recommend inclusion of confidence intervals around analytical validity parameters.

Even with the assurance provided by CLIA standards, it is important that performance characteristics reported through the GTR are comparable from one test to another. Keeping the performance characteristics listed on the GTR consistent with CLIA requirements will further this goal.

We are opposed to inclusion of "[m]ethod used for proficiency testing . . . and score" as a test performance characteristic. Proficiency testing score relates to how well a laboratory performs a test, and does not have an impact on the underlying validity or utility of the test. Since the purpose of the GTR is to provide information about laboratory tests, not laboratories, proficiency testing scores are irrelevant, particularly to genetic testing, for which there are no particularized proficiency tests.

n. Clinical validity:

i. Clinical sensitivity
ii. Clinical specificity
iii. Positive and negative predictive value
iv. Prevalence
v. Penetrance
vi. Modifiers

Clinical validity information should generally be supported by literature cites, which can be included in the GTR. Published articles may or may not address each of the elements of clinical

validity listed above, but we believe that references will provide the most complete and accurate information available. There may be instances where a test is valid despite the lack of availability of data in each of these fields.

o. Utility (e.g., clinical and/or personal utility) or outcomes

i. Benefits
ii. Harms
iii. Added value, compared with current management without genetic testing

Citations to literature are also the best source of information on genetic test utility. Moreover, while laboratories can show the analytical validity of the test (i.e., that the test consistently detects the same genetic variables) and the clinical validity (i.e., that the test has proven useful for a particular clinical purpose), it is far more difficult for laboratories to demonstrate clinical utility (i.e., how the physicians use the test in their care and treatment of the patient.) This is because clinical utility must be shown by actual experience in clinical settings, which is an area to which laboratories typically do not have access. As a result, the physician community, rather than the laboratory community, is best situated to make determinations about clinical utility. Therefore, laboratories submitting information to the GTR may be unable to provide information beyond citations to literature. GeneReviews conducted by NIH also play an important role and should be cited where available.

p. Cost (e.g., price of the test, health insurance coverage)

Cost information should not be included as part of the GTR. Such information is not only irrelevant to the goals of the GTR, but is also very difficult to define. Because the types of insurance vary, the cost to the patient for any particular laboratory test also will vary.

7. What types of information might be difficult for test providers to submit and why?

Proprietary information is inappropriate for inclusion in a public database. Test providers have confidentiality obligations in their license agreements and must protect their intellectual property. In addition, if information is not presented in a standard format, it will be difficult for a submitter to know exactly what information to include in certain sections. As discussed in other sections of these comments, NIH can mitigate these concerns by eliminating fields that would require the submission of proprietary information, by providing clear definitions of terms, and by using data fields that are consistent with existing CLIA requirements. We also urge NIH to use the ACLA test compendium, discussed below, as a template for providing this information.

8. What are the advantages and disadvantages of collecting and providing information on the molecular basis of genetic tests, such as detailed information about what the test detects and the specific methods employed?

In general, such information seems to be beyond the scope of the GTR. While some information about methods may be useful to practitioners, it seems less likely to be relevant for patients, and may be confusing. With regard to what the test detects, this information is very likely to be proprietary and not appropriate for a publicly accessible database. We believe that literature citations will provide sufficient access to this sort of scientific information.

9. In addition to the data elements, would it be helpful to reference other resources, and if so,

which ones (e.g., published studies, recommendations from expert panels such as the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, U.S. Preventive Services Task Force, or Evaluation of Genomic Applications in Practice and Prevention Working Group)?

GeneReviews is essential and needs to be maintained. Links to these reviews should be provided to the extent that they have been completed. In addition, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative, the Agency for Healthcare Research and Quality (AHRQ), and other agencies and organizations play an important role in identifying areas where additional studies need to be performed. The National Cancer Institute (NCI) website is a critical resource for information on cancer, and this model could work well for genetics. This could include enhancing the Online Mendelian Inheritance in Man (OMIM) database based on the current state of research. It may be useful to provide a field in which submitters can reference outside information available on specific tests, but this is, to a certain extent, secondary to the main purpose of the GTR.

10. As the GTR is being designed, what are the important processes to consider to make the submission of data as easy as possible for the data provider (e.g., the capability of linking to information that has been submitted to other agencies, such as the Food and Drug Administration and the Centers for Medicare and Medicaid Services, or a master file of data common to particular tests)?

ACLA has created several tools that may serve as useful models as NIH considers how to collect data for the GTR. We believe our online test compendium would be a useful template for data submission and format for the GTR.

ACLA developed a framework for its Laboratory Test Compendium to provide the ability electronically to exchange the Directory of Services (eDOS). This development effort aims to simplify the exchange of data related to test Directories of Services and associated orders, while increasing their functionality and value within compatible electronic medical record (EMR) systems. Although it was developed for a different purpose, using the Compendium framework would make submission of data for the GTR easiest for laboratories.

ACLA's eDOS is intended to provide a simple and low-cost vehicle so all clinical laboratories can share their eDOS with their clients and enable electronic medical record (EMR) systems to support all order codes used by the laboratories that the physician selects and uses. It is our belief that the clinical laboratory industry is naturally suited to define the standards for sharing and distributing the eDOS, which is a laboratory resource that is unique to each laboratory. Development of a standard Laboratory Test Compendium Framework addresses and defines how information that differs from laboratory to laboratory, such as the following, easily can be exchanged among all provider laboratories used by a client and the client's EMR system:

- The codes used to order laboratory tests and the description of the laboratory tests
- The nature of the test (profile, single observation, etc)
- The potential reflex observations
- The specimen requirements
- The processing priorities (ability to order as stat, routine, or other priorities)
- A list of analytes included in the Lab Order Code
- The additional clinical and useful information required at the time of ordering

The draft ACLA Test Compendium Framework is available at: http://www.clinical-labs.org/issues/technology/documents/ACLA_LabTestCompendium.pdf. We would be happy to discuss this template with you further.

11. Which potential benefits and risks would be most likely to affect the decisions of researchers, test developers, and manufacturers on whether to submit data to the GTR, and what factors will best encourage submission of complete and accurate data?

As discussed above, to the extent that submitting information for the GTR requires reporting proprietary business information or trade secrets, or if there are no checks in place to provide assurance of the accuracy of information, laboratories will be less likely to participate. If too much detail is required, laboratories may find submitting data too time-consuming or too risky. Factors providing assurance that information will be presented fairly and accurately will minimize the level of these concerns.

12. What are the most effective methods to ensure continued stakeholder input into the maintenance of the GTR?

A key issue is whether patients could be harmed by the posting of unverified performance characteristics that could lead a physician to choose a test that is not appropriate for a patient. Patient safety should motivate submitters to keep information current. As stated throughout these comments, we recommend that NIH find ways to ensure that the GTR data are verifiable and not distorted or biased, or include an appropriate disclaimer.

13. For what purpose(s) would you use the Registry to support your professional efforts?

As discussed above, we anticipate that laboratories will use the GTR to identify relevant tests and the providers of those tests. This will facilitate appropriate referrals to reference laboratories.

14. Are there any other issues that NIH should consider in the development of the GTR?

In addition to the points above, it is important that users of the GTR be able to sort the data and make valid comparisons. The user should have the ability to sort the data for all assays for a particular purpose. In addition, NIH may wish to consider asking whether the laboratory offers genetic consultation, which can help physicians better understand and interpret a laboratory's test results.

ACLA appreciates the opportunity to comment on the proposal. We look forward to working with NIH as it continues this process. If you have additional comments, or need further information, please do not hesitate to contact us.

Sincerely,

David Mongillo
V.P. Policy and Medical Affairs