March 21, 2011

Genetic Testing Registry Staff
National Institutes of Health

Re: Genetic Testing Registry Draft Data Fields

The American Clinical Laboratory Association (ACLA) appreciates the opportunity to ovide comments on the draft Genetic Testing Register (GTR) data fields. ACLA represents national, regional, and local laboratories across the country. Members of ACLA are proud to be at the forefront of delivering innovative genetic tests in partnership with healthcare providers and the patients they serve. As a result, we have a direct interest in the development of the registry.

ACLA members would likely be among the laboratories that would input information into the GTR. Based on members' experience with describing the tests they offer, we have provided a number of comments below on the GTR Design Considerations and the Proposed GTR Field Definitions – Version 0.22.

I. General Comments

We remain concerned that the GTR Design Considerations and Field Definitions do not provide a definition of "genetic test." While NIH provides that "a Test is any separately orderable test offered by a laboratory," it does not provide guidance on which tests should be included in the GTR. We recommend that NIH provide clear instruction on which tests should be submitted.

A number of the requested data elements lend themselves to links to external databases or consensus statements, rather than submissions by individual laboratories. As discussed below, this includes information related to FDA-approved or cleared kits and fields addressing clinical validity and clinical utility where a consensus statement could be drafted by either professional associations or the NIH.

In general, we suggest that the NIH narrow the scope of the data requested through the GTR to better serve the needs of the intended audience. Our understanding is that the GTR is being developed to help practitioners and patients understand what tests are available and basic information about these tests. It appears that the level of detail and complexity of information proposed in these data fields is so involved that it may cause more confusion than increased understanding. Much of the information being requested is likely too technical to be readily

understood by the general public or even the intended provider audience. ACLA believes that NIH review the information requested and attempt to pare down the amount of required information. We think requesting significant amounts of "optional" information will further complicate this task, as those reviewing the information will simply not understand why certain information was not included. As a result, ACLA believes that many of the optional fields should simply be excluded. The required information should be minimal, including the following suggested fields:

- Laboratory name
- Mailing address
- Primary laboratory contact name
- Contact information (i.e. phone number, email address)
- Laboratory director name
- Name of test
- Where test performed (internal, external) (please note additional comments on this issue below)
- Indications for use/clinical utility (pulled from a central source, as discussed below)
- Primary/alternate specimen source
- Analyte information
- What the test measures
- Mutation(s)/analytes tested
- Test development/regulatory status (see comments below regarding appropriate options to list)

Other fields should either be removed from the GTR or made optional. Recommendations related to specific fields are included in the comments below. If a data element is optional, laboratories may wish to explain why no information is provided, and it may be helpful to include that language in the GTR, itself. We believe that NIH should consider this as an option.

We also have a general concern that the draft document makes a significant number of references to commercial sources. We are concerned that the data requested may be driven by commercial goals. It should be clear that the GTR is not intended to be used for commercial purposes.

Finally, as the GTR platform is developed, we hope that it will allow for general laboratory information to auto-populate for a laboratory that has previously entered such information for another test.

II. Comments on Specific Fields

Proposed data fields on which we are providing comments are listed below and underlined, with our comments or concerns following.

Name of Laboratory (page 12): NIH should clarify that this is the name of the laboratory on the CLIA license.

Mailing Fax Number: Text Field – Manual Entry – Optional (page 14); and Mailing Email Address: Text Field – Manual Entry – Required (page 14): NIH should clarify whether laboratories are being asked to set up new fax numbers and email addresses for this purpose.

Laboratory Types of Service: Pick from List Plus Ability to Suggest New – Optional (page 15): This field appears to be included to provide general information on the types of services a laboratory offers. NIH should clarify whether services selected in this field are intended to represent all services offered by the laboratory or just those services involved in the specific test being submitted.

Laboratory Services Order Code: Text Field – Manual Entry – Optional (page 15), Laboratory Unique Code: Text Field – Manual Entry – Optional (page 22), and Laboratory Test Order Code: Text Field – Manual Entry – Optional (page 24): It would be helpful for NIH to clarify how these fields relate or differ and what information is being requested in each. The field on page 15 seems out of place.

Laboratory Affiliations – Text Field – Optional (pages 15-16): The description of this field asks whether a laboratory is "linked to" other entities. The types of relationships that should be reported here are unclear. NIH should clarify whether this is the appropriate place to identify parent companies of fully owned subsidiaries.

Laboratory Participation in External Programs: – Select from List – Optional (page 16): "CETT Program" should be deleted as an option, as this program no longer exists.

Standardization Programs (page 16) and Data Exchange Programs (page 16): NIH should define and provide further examples of the types of programs it is interested in for these fields.

Primary Laboratory Contact: Yes/No Check Box – Required (page 16): In most cases, the Laboratory Director will not be the most appropriate point of contact for purposes of questions arising from the GTR. In fact, in a large laboratory, the individual who is the Laboratory Director will not have sufficient time or resources to triage these calls, so it may not be useful to include that individual's contact information. Laboratories should assign a more appropriate individual to triage questions and direct them to appropriate personnel within the lab, and we believe that this is the individual who should be listed here.

Person Genetic Certifications: Select from List (page 17): Per the comment directly above, it is important for this field to be kept optional, if maintained.

Regulations – Laboratory (page 19): This heading would be more appropriately changed to "Licensure and Accreditation – Laboratory," for clarity.

Default Specimen Source – Pull-Down List – Optional (page 20): This field appears to be part of the set of default values that will automatically populate unless a lab overrides them. Because specimen source differs for each test, it does not make sense to include it as a default value. Further, the list provided is incomplete. If this field is maintained, "other" should be added, with the option for the laboratory to describe the specimen source used for the test in question. Laboratories should also be able to define the containers acceptable for specimen collection. In this field, laboratories should be able to select more than one option, with an instruction for laboratories to "pick all that apply."

Default Sample Negative Report – Optional (page 21) and Default Sample Positive Report – Optional (page 21): Because laboratory reports are frequently updated, inclusion of a sample may not be useful and it may be difficult for laboratories to keep this field up to date. Moreover, the value of this criterion is somewhat difficult to understand. We recommend that this field be removed, given that similar fields (Sample Negative Report: Upload Document – Manual Entry – Optional and Sample Positive Report: Upload Document – Manual Entry – Optional) are also listed later in the draft document. We believe it is more useful for laboratories to include test-specific sample reports, as appropriate, than to maintain generic default sample reports in the GTR.

GTR Accession ID (Auto Assigned by NCBO with Versioning) – Required (page 21): We have several concerns related to this field. First, terms of use of the GTR should include a restriction on use of numbers assigned to tests for this field. These numbers should not be used commercially. Second, we believe that it is dangerous to make information on prior versions of a test publically available. The GTR Design Considerations document specifies that, while the newest version would be displayed by default, it will be possible to retrieve older versions. If data on prior versions is stored in the GTR, it should be viewable only by the submitting laboratory. Questions on prior versions of a test should be directed to the laboratory that offers the test.

Laboratory Test Short Name: Text Field – Manual Entry – Optional (page 22), and Other Names: Text Field – Manual Entry + Pull-Down list – Optional (page 22): NIH should provide clarification on how these fields should be used, and delete unnecessary fields. Multiple fields for test name may be confusing for laboratories trying to enter data and may lead to inconsistencies in the GTR. The "Short Name" field can likely be deleted. We believe it is important to identify aliases, which will permit a user to find all similar tests regardless of the name used by a particular laboratory.

Test Development – Pull-Down List – Optional (page 22): We have two comments on this field. First, the options provided in are incomplete. The following options should be added: LDT with ASR; LDT without ASR; FDA cleared or approved; Modified FDA cleared or approved; IUO; RUO; CE (Europe); FDA exempt; and other. Second, reflex testing should not be included in this field. We recommend inclusion of a separate field to capture reflex testing.

Informed Consent Required: Yes/No Checkbox – Optional (page 23): This field raises concerns if "No" is selected. Checking this box requires legal conclusions that may differ based

on state law. We recommend adding an option to indicate that informed consent requirements are determined based on applicable state law.

Testing Strategy/Sequence: Text + Citations – Manual Entry – Optional (page 24): Laboratories should be able to describe whether a test has a required reflex test. If this is the appropriate field in which to provide such information, clarification should be provided. The proposed approach does not provide a sufficient means of indicating whether a test has a reflex mechanism, and it is unclear whether each test component should be described. If a test is ordered, additional tests may be performed as necessary under certain circumstances based on initial results. Inconsistency in how this field is used could create the appearance that some laboratories perform only the base test and not the additional related tests based on results. In general, the GTR should include information parallel to what a laboratory lists in its directory of services.

If Test Performed Externally – Check Box – Required (page 25): A laboratory can identify what it does to perform a test, but it cannot certify to how a test is done in another facility. NIH should provide clarity on how this field should be used and how "external" is defined. For example, it is unclear whether a test performed at an outside facility owned by the same company would be considered to be performed "externally." Clarity is also needed on how this field would capture information on a test such as immunohistochemistry (IHC), where samples are referred to one laboratory for staining and where the actual interpretation is performed in another laboratory. The ability to enter details may help laboratories provide appropriate information, but additional guidance will promote consistency within the GTR.

Test Orderable By: – Pull-Down List – Optional (pages 25-26): Who can order a test is generally determined by state and federal law. Because of this, we recommend that this field be removed. NIH may have been trying to address whether a patient can order a specific test, which would depend on where the patient is located and the applicable law in that state.

How Does the Laboratory Deal with Variants of Unknown Significance (VUS) Results? (page 27): In general, we feel that too much detail is being requested under this heading. This field is only significant for sequencing and is not significant for other more routine genetic tests. This field should not be included for routine tests and should be eliminated from the GTR. Some of the specific fields under this heading, such as What Software is Used to Interpret Novel Variations? – Text Field – Manual Entry – Optional, seem to be irrelevant to the purposes of the GTR and not useful for health care providers or for patients.

Will the Laboratory Re-Contact the Offering Physician if Variant Interpretation Changes? – Yes/No Checkbox – Optional (page 27): This question addresses detailed issues of laboratory policy that are inappropriate for inclusion in the GTR and raise legal and liability concerns. This field should be removed.

Research Laboratory's Policy on Returning Results – Text Field – Manual Entry – Optional (page 27): Because most research laboratories do not report clinical results, this field is confusing within the context of the GTR. Rather than including this field here, we recommend that the distinction between clinical and research laboratories be made in the general information

provided about the submitting laboratory. If a laboratory identifies itself as a research laboratory, tailored fields should be included in various parts of the GTR. Research laboratories will not have some information, as they do not report clinical results.

Purpose of the Test: Pull-Down Menu – Multi-Select – Optional (page 28): The description of this field should be revised to clarify what is meant by "purpose." We suggest language similar to what laboratories use in their "Directory of Services" such as "Indications for Use." This field could create legal issues related to the types of claims being made, and what types of references laboratories must be able to provide in order to support a listed "purpose" or "use." Because laboratories have some information on use of tests in their directories of services, laboratories would have some level of comfort in providing corresponding information in this field. We note that this field will not be able to capture all possible uses of a test, and ultimately, ordering physicians, rather than laboratories, will have to determine how a test is used.

Disease Identifier(s): Automatically Provided (page 29): This field and those immediately following should automatically populate for common diseases or markers, as it would be burdensome for laboratories to fill in each of these fields. NIH should clarify whether this is what is meant by "automatically provided."

Description of the Target Population: Text + Citations – Optional (page 30): This field may be duplicative of other fields related to "intended use." NIH should clarify where such information should be provided and eliminate unnecessary fields.

TEST METHODOLOGY (page 30): In general, we feel that too much detail is being requested within this category of fields. Information provided here should parallel what laboratories provide in their directories of services.

Method Category: Pull-Down List – Required (page 30): Providing this information should not be required, and such information may not be useful. We recommend removing this field and focusing on the Primary Test Methodology field below.

Primary Test Methodology: Pull-Down List with Ability to Suggest New – Required (pages 30-31): This field should be made optional, with the pull down list expanded.

Platforms: Laboratory-Specific Pull-Down List – Optional (page 31): The usefulness of this field is not readily apparent, even if providing such information is optional.

Instrument(s) Used During Testing: Laboratory-Specific Pull-Down List – Optional (page 32): This field is not useful. The specific instruments used to perform a test may vary day to day or change when equipment is updated or replaced. Ordering physicians and patients do not need this level of detail regarding how a test is performed.

ANALYTES (page 32): Within this category, the field titled What the Test Measures (page 32) is likely appropriate, but much of the additional information requested focuses on

unnecessary detail. Specifically, the fields related to Exon(s) Being Tested (page 34), Mutation(s)/Analyte(s) Tested (page 34), Sequences(s) Being Tested (page 34), Probe(s) Being Tested (page 34), and specific Protein information seem overly detailed and unlikely to provide useful information.

Gene(s) Being Tested: Text Field – Manual Entry or Possibly a Pick List – Required (page 33): For some tests, particularly multi-arrays, this information may be proprietary. To address this concern, this field should be made optional. Additional issues may arise under this field related to the fact that markers, not genes, are sometimes targeted by tests. Further, it is unclear how biomarkers would be handled.

PERFORMANCE CHARACTERISTICS (page 35): In general, we feel that the information requested in this category is not relevant for the purposes of the GTR. NIH should consider what technical information is important to the intended audience and limit the requested data to a more targeted set of fields. Specific fields are discussed below.

Analytical Validity: Test + Citation – Optional (page 35): Laboratories can provide this information, but it is unclear how useful it will be. In most cases, analytical validity is not of a concern with genetic tests, because there is little dispute about the ability of the test to accurately test for the genetic markers in question.

Analytical Sensitivity (page 35): Again, laboratories can provide this information, but its usefulness is questionable. Analytical sensitivity is almost universally high for genetic tests, and differences in data reported in this field may have more to do with laboratory policy for how such figures are calculated than the true sensitivity of tests.

Number of Specimens use to Calculate (page 35): It is unclear why this information would be important to users of the GTR.

Precision (page 36) and Accuracy (page 36): Both of these fields are of questionable importance in the GTR. Further, please note that the descriptions under these fields should be reversed: "Precision" generally refers to the reproducibility of results, or "how close repeated results match each other"; "Accuracy" generally refers to "how close the results match those from independent sources." We note that none of the examples provided with NIH's materials include responses to either of these fields and recommend that both be removed.

Assay Limitations: Text + Citation – Optional (page 36): This information may be better provided elsewhere in the GTR, such as the targeted population or the purpose of the test.

Proficiency Testing Performed on this Test: Yes/No Checkbox – Optional (page 37): We recommend eliminating this field. Laboratories are required to perform Proficiency Testing under CLIA, and such testing is performed for all tests regardless of whether a formal program is available or the laboratory performs an alterative assessment.

Method used for Proficiency Testing: – Check Box – Optional (page 37): If this field is maintained, "Intra-Laboratory" should not be listed separately. Such testing is a type of "Alternative Assessment" and should be incorporated into this option.

Description of Proficiency Testing Method: Text + Citations – Optional (page 37): All laboratories perform Proficiency Testing, and the GTR is an inappropriate place to collect information on Proficiency Testing methods. Individuals seeking test information through the GTR will not understand information on Proficiency Testing provided in this format, and such information could easily be misconstrued.

Internal Test Validation Method Description: Text + Citation – Optional (page 38): Similar to the comment above on Proficiency Testing Method, we feel it is inappropriate to use the GTR to gather this information.

Clinical Validity: Text + Citation – Optional and Clinical Specificity (page 38): These fields are best documented through literature and are not laboratory-specific. For this reason, it would be better to gather this information in a centralized single document than from individual clinical laboratories. These fields are more appropriate for research laboratories than for clinical laboratories. We recommend that these fields and the related fields that follow be removed from the GTR.

Clinical Significance: Pick List + References – Optional (page 39): This field will not be meaningful for patients and providers seeking information through the GTR. For the general public, the reason a test would be ordered is captured elsewhere, as clinical significance is largely equivalent to clinical use.

CLINICAL UTILITY: TEXT + CITATION – OPTIONAL (page 40): We recommend removing this section from the GTR. At ACLA's November meeting with NIH, all parties agreed that the best approach would be to address clinical utility in a centralized manner using materials from experts in the field. This information is not laboratory specific and is inappropriate to include as proposed.

REGULATIONS – TEST (page 41): To the extent that any of the information requested in this section is relevant, it is captured elsewhere in the GTR. If either FDA Category Designation: Pull-Down List – Optional or FDA Reviewed of: Pull-Down – Optional is maintained, "Not Applicable" should be added to the pull down list(s) as an option for selection.

FDA Regulatory Status: Check Box – Optional (page 41): This field is duplicative of the Test Development – Pull-Down List – Optional field listed under TEST INFORMATION (page 22). As discussed in comments above on the earlier field, the proposed list of options is incomplete. Additional options for "RUO," "IUO" and "Not Applicable" should be added. Further, the option, "reviewed" is vague and potentially duplicative of "510(k) cleared," and the option, "Approve" is vague and potentially duplicative of "PMA Approved." If this field is maintained, for any FDA-approved or cleared kit, the GTR should simply include a link to FDA information. Additional details about the FDA application and related documentation may be

appropriate for manufacturers to provide, but this information is not laboratory specific. In addition, many Laboratory Developed Tests are not required to be reviewed by the FDA; therefore, a separate space should be included that so states.

REFERENCES (page 42): It is unclear whether this is being proposed as a category for the GTR. We recommend that this type of information be addressed in a centralized manner.

Dropped Fields (page 43): ACLA supports elimination of the fields listed in this section.

TEST INFORMATION – PHASE II (page 44): We are currently restricting our comments to the fields proposed for "Phase I" of the GTR. We recommend that NIH assess the functionality of the initial GTR before determining what changes or additions may be appropriate in the future.

* * *

Thank you for the opportunity to comment. Please do not hesitate to contact me if you have any questions.

Sincerely,

David Mongillo
V.P. Policy and Medical Affairs
dmongillo@clinical-labs.org
(202) 637-9466