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AdvaMed
Advanced Medical Technology Association

April 8, 2011

Genetic Testing Registry Draft Document Release
National Institutes of Health National Library of Medicine
National Center for Biotechnology Information

Distributed via email to gtr@ncbi.nlm.nih.gov

Re: Request for Comments; NIH Genetic Testing Registry Draft Document Release; Design and Development Elements

Dear Sir or Madam:

On behalf of AdvaMedDx, a Division of the Advanced Medical Technology Association (AdvaMed), we provide these comments in response to request for comments regarding the "Genetic Testing Registry (GTR) Draft Document Release" on design and developmental elements.

AdvaMedDx member companies produce advanced, *in vitro* diagnostic tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and reduce overall health case costs. Functioning as an association within AdvaMed, AdvaMedDx is the only multi-faceted, policy organization that deals exclusively with issues facing *in vitro* diagnostic companies both domestically in the United States and abroad.

We appreciate the opportunity to provide comments on the draft design and development elements and hope that you will consider our recommendations in development of the prototype database. Our comments are intended to support the quality and accuracy of the data as well as overall usefulness of this information to the public, whether one is a healthcare professional, researcher, or a patient. We thank the National Institutes of Health (NIH) for the detail that has gone into the preparation of these draft materials. Please find AdvaMedDx's general and specific comments regarding these documents.

GENERAL COMMENTS

AdvaMedDx appreciates NIH's efforts to solicit industry feedback regarding GTR design considerations and field definitions. We believe a database can be a useful tool to provide transparent information to the public on the increasing number of genetic tests available. As shared in our earlier comments regarding development of the database, we believe that NIH

should implement safeguards to verify the accuracy and reliability of information in the database. As the database will be made available and relied upon by healthcare professionals and other members of the public in potential health care decisions and outcomes, the database should serve as a trusted scientific resource.

In the case that safeguards are not planned for incorporation into the GTR and accuracy of the data is the sole responsibility of the submitter, then we continue to urge that the initial phase of the GTR be focused on the following information; test name; manufacturer/ institution name and contact information; premarket review regulatory status (i.e., whether FDA cleared or approved) and option to link to test data that has already been appropriately reviewed (e.g., FDA decision summaries or ClinicalTrials.gov clinical trial results). While entry flexibility and the use of multiple optional fields can encourage participation, the potential breadth of unvalidated, misleading, or even potentially false data, including test use and validity information, has potential to harm the public health. While intended use claims and other key elements proposed are reviewed by FDA as part of its premarket review process and are subject to promotional and labeling regulations, not all tests in the database will have been subject to this scrutiny. This is discussed later in our specific comments.

If NIH does not plan to implement a process to verify the accuracy of data entered into the database, at a minimum and to support transparency, a prominent disclaimer should be placed on all pages of the website, including individual test entries, stating that the information contained cannot be verified and no endorsement is made of the test nor the accuracy of the information submitted. Further, the disclaimer should also note that in some cases, test developers may not have reviewed or are aware of the data presented therein. This is an important disclosure as the draft documents propose that laboratories may report on all tests offered in their labs including manufacturers' test kits. If manufacturer test information is being provided apart from the manufacturer, this is critical in order that the manufacturer not be held liable for information that is inaccurate or inconsistent with the labeling reported by a third party.

We also note that clarity in definitions will be important as terms such as "indications for use" have specific meaning under device regulation. Thus, we offer more detailed recommendations in our comments for fields that best reflect the information being asked, do not conflict with the Federal Food Drug and Cosmetic Drug (FD&C) Act or regulation, and rely on terminology widely used by developers. We note that NIH has engaged FDA for feedback and made efforts to reduce duplicative reporting through linkage to test data such as FDA registration and listing and potentially decision summaries. We support such consultation in all phases of GTR implementation to support coordination and efficiency in reporting among NIH and FDA as well as manufacturer participation.

With these general comments in mind, AdvaMedDx's specific comments follow in table form for further consideration and clarification by NIH. Specific edits are offered in most cases along with questions or comments.

We hope that you find our feedback helpful. We are willing to answer any questions and/or meet with you to further discuss our comments. Please feel free to contact me at 202-434-7267 or kcalleja@advamed.org.

Sincerely,

Khatereh Calleja

Khatereh Calleja, JD
Vice President
Technology and Regulatory Affairs

Cc: James Ostell, Ph.D., Information Engineering Branch, National Center for Biotechnology Information, NIH
Cathy Fomous, Ph.D., Office of Biotechnology Activities, NIH

ADVAMEDDX SPECIFIC COMMENTS

AdvaMedDx Comments on NIH *Genetic Testing Registry Draft Document Release; Design and Development Elements*

Comment number – Edit No.

Document/Section/Page – Document and section/ page cite if applicable

Proposed Change – Proposed change to the draft documents

Comment/Rationale – Reason for proposed change

Comment Number	Document/ Section/ Page	Proposed Change	Comment/Rationale
1	Design Considerations and Proposed Field Definitions General	Clarify applicable data fields for IVD manufacturers.	Overview document describes the GTR as a repository for genetic tests entered by the test developer. Yet the draft field definitions refer to required laboratory information (e.g., name of laboratory) that would not apply to tests developed by test kit manufacturers.
2	Design Considerations and Proposed Field Definitions General	Address off-label use.	Test entries by IVD manufacturers and laboratories in the same database must address the topic of off-label use. The inclusion of journals, statements, etc. about FDA cleared/approved tests that are not consistent with the FDA cleared/approved indication may result in off-label promotion (a violation of the FD&C Act) and cannot be supported by IVD manufacturers. Clearer database design with this topic in mind and discussion and input from FDA is needed on this topic in order for appropriate information for consumers and avoidance of potential, unintended violations. This should be in addition to the disclaimer as noted in

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			our earlier general comments. Intended use claims and other proposed key elements are reviewed by FDA as part of its premarket review process and are subject to promotional and labeling regulations. However, other tests will not have been subject to this scrutiny including claims-based review. Thus, it is misleading to group these tests together in the database when open-ended responses are permitted for entry of validity data without required source data, including peer-reviewed publications, for claims made.
3	Design Considerations General	As part of the GTR design, it should include appropriate notification that a) clinical tests can only be provided by CLIA-certified labs and b) not all tests entered into this database have been cleared or approved by FDA. Such information could be included in the disclaimer outlined in our general comments or set forth in separate introductory information where one first accesses the database.	Transparency about key qualities of the database is necessary to maintain integrity.
4	Design Considerations Overview	Replace "intended purpose(s)" with another term. While we suggest "intended use", other possible terms might be "reason(s) for performing the test" or "purpose of the test."	This appears to be an amalgam of different nomenclatures. For transparency and clarity, align with current well recognized nomenclature.

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	p.1	Replace "assayed" with "validated" in describing the tests.	It is unclear what is meant by someone who develops and assays a test.
5	Proposed Field Definitions Personnel Information p.17-18	Clearly denote that contacts identified in the database, including those for specific tests, are not required to share their employee id #. If an id# is required for bulk loads, then offer an option to create a unique id # through the GTR.	A personnel id # is personal, private information. Similarly, other related information including "person private phone number" and "person private email address" should not be required, even if not made available to the public. Work email and phone number should be adequate.
6	Proposed Field Definitions GTR Accession Id p.21	Provide clarity regarding expectations and process for updating of a record in GTR and what constitutes an update for purposes of the database.	A reference is made to "updating" of a test by a laboratory and issuance of an updated version reference in the accession #. Although it appears that an update may be any change other than related to laboratory or personnel information, clarification would be helpful regarding what constitutes an update and expectations for upkeep of information in the database.
7	Proposed Field Definitions Test Development p.22	The test development options should be revised to: FDA cleared/approved LDT (FDA cleared/approved) LDT (not FDA cleared/approved) Research use only (not for diagnostic use) Modified FDA (FDA cleared/approved entry, but with lab modifications/field	The test development categories are confusing and should better reflect test status. The fields also should be revised so they are technically correct. Specifically, FDA-reviewed is unclear. This could mean tests cleared/approved by FDA or items reviewed by FDA but which have not received clearance or approval. Further, there have been LDTs cleared/approved by FDA. The menu should

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		changes) Combination (could include reflex & panels doing multiple tests)	distinguish those that have clearance/approval. Also, use of the term "manufactured" with research use only is misleading. The category should be clearly stated as research use only. For Modified FDA, replace FDA-reviewed with FDA cleared/approved for the reasons described above.
8	Proposed Field Definitions Availability p.24-25, additional references throughout	Clarify what entries have been reviewed by any external reviewer. Furthermore, any statements about external review in the GTR should clarify what has been reviewed beyond the "test performed externally" field.	In review of the proposed field definitions and availability, it is unclear what is reviewed by an external reviewer. Such information is essential to support transparency as to the accuracy and verification of data entered.
9	Proposed Field Definitions Indications for Use p.28	Replace "indications for use" header with another term. If not "intended use", then other possible terms might be "reason for performing the test" or "purpose of the test."	"Indications for use" is a legal term used in the FDA submission review process to determine whether or not to clear or approve product and product labeling. Furthermore, the proper term is "intended use." It is incorrect to include "indications for use" as a header and an inappropriate use of the term as many tests anticipated for use into the GTR are not FDA-cleared or approved. This field is particularly concerning in the case of tests that have not been cleared or approved by FDA as this type of

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			information may not have been assessed for accuracy.
10	Proposed Field Definitions Test Methodology p.31	In the platform laboratory-specific pull-down list, provide secondary or expanded menu to address the requirement for FDA cleared/approved IVDs to use cleared/approved platforms.	FDA requires that any IVD test be used only on platforms that have been cleared or approved for IVD use.
11	Proposed Field Definitions Quality Control and Quality Assurance p.37-38	Clarify applicable data fields for IVD manufacturers (i.e., FDA Quality System Regulation) rather than "Proficiency Testing Performed on This Test."	Similar to our earlier comment, this section does not contain applicable data fields for test kit manufacturers. Reference is needed to quality systems under current regulation.
12	Proposed Field Definitions Clinical Utility p.40	The database should clarify that studies or data that are not published and subject to peer review should not be included in the database. To the extent that such studies are of concern or considered questionable, a mechanism should be permitted for a manufacturer to denote such concern so that members of the public who view the information understand the issues that have	As discussed in our November 2010 comments, we support the posting of peer-reviewed studies that contain information about clinical utility. It should be noted that assessing tests presents unique challenges. Unlike the situation that exists for evaluating therapeutic treatments—where treatments tend to lead directly to results—the impact of a diagnostic test on patient outcomes is

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		been raised (any may wish to consider) in relation to such studies. We are open to the concept of providing field choices (e.g., professional organization guideline, peer-reviewed published study) but value of information to the patient must be recognized and open data fields should also be provided. While the field is optional, any field choices provided should be supplemented with such open data fields to allow submitter to reference appropriate studies specific to tests and the context in which tests are provided.	not direct. There are typically several steps between the performance of a given test and a clinical outcome. Tests inform physician and patient decision-making and the ability of the test to influence outcomes is typically subject to factors that are beyond (or independent of) the technical attributes of the test itself. Most evaluative studies of diagnostic tests focus on intermediate outcomes, such as diagnostic accuracy or impact on diagnostic thinking, not patient outcomes. This fact underscores the need for evaluations that are sensitive, and include consideration of, the specific context in which a particular test is provided.
13	Proposed Field Definitions FDA Category Designation p.41	The test category designations should be revised to: IVD – In Vitro Device RUO –Research Use Only IUO – Investigational Use Only	The FDA categories are confusing and should better reflect test status. The fields also should be revised so they are technically correct. Specifically, IUO is a legal term which does not include "information." LDT is not an FDA category designation, but is considered a description of a developer of the device; inclusion as an FDA category designation misrepresents the FDA's regulatory system.
14	Proposed Field Definitions	The regulatory status options should be revised to: 510(k) Cleared	The regulatory status categories also require revision. FDA regulatory status does not include reviewed. PMA and HDE approved are correct approval statuses. A 510(k) exempt category should

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	FDA Regulatory Status p.41	PMA Approved HDE Approved 510(k) Exempt Designated Pending Not Submitted	be added to reflect tests which FDA has explicitly exempted from submission of 510(k).