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August 2, 2010

NIH GTR RFI Comments
National Institutes of Health, Office of Science Policy
6705 Rockledge Drive
Room 750
Bethesda, MD 20852

RE: Notice No. NOT-OD-10-101, Request for Information (RFI) on the NIH Plan to Develop the Genetic Testing Registry

Submitted via email to GTR@od.nih.gov

To NIH Office of Science Policy,

The Biotechnology Industry Organization (BIO) appreciates the opportunity to submit comments on the National Institutes of Health (NIH) plan to develop a Genetic Test Registry (GTR). BIO applauds the NIH for working to develop a registry that will serve as a centralized public resource to provide information about genetic tests to stakeholders including, patients, healthcare providers, healthcare payers, consumers, and genetic test providers.

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology technologies, thereby expanding the boundaries of science to benefit society by providing better healthcare, enhanced agriculture, and a cleaner and safer environment. Specifically related to genetic tests, BIO represents companies that develop and manufacture novel diagnostic tests, test systems, multivariate index assays, and targeted therapeutics that rely upon genetic testing information for optimum safety and efficacy. For this reason, BIO companies should play a key role in the implementation of the NIH Genetic Test Registry.

As part of NIH's public consultation process for its efforts to develop the GTR, BIO is providing the following comments. These comments include general feedback regarding the need for a GTR, and how the GTR should be created, designed, and maintained; as well as specific comments regarding the questions addressing GTR data elements as posed in the NIH Request for Information (RFI) notice posted in the federal register on May 28, 2010.

General Comments:

BIO supports the view that a system of genetic test registration is necessary to provide stakeholders with information about the spectrum of tests being offered. Making test performance characteristics and reference information (analytical validity and clinical validity) publicly available should increase confidence in these types of tests among healthcare providers and patients, and could help improve the proper utilization of genetic tests. In addition, a genetic test registry could assist regulatory agencies (and Congress, where necessary) in evaluating these tests and developing appropriate pathways for oversight.

While we support the creation of a voluntary genetic test registry, BIO supports ongoing efforts to make registration mandatory for certain moderate- to high-risk categories of tests. We are pleased to see that the registry will be housed at the National Library of Medicine, and implemented by the National Center for Biotechnology Information (NCBI) with input from the stakeholder community and oversight by NIH and scientific groups. As NIH determines how the registry should be designed, we urge that the format for uniform submission be clear, and the information included in test entries easily understood. Current genetic test databases, most notably, the Genetests database (operated by NCBI), are not comprehensive, and information within is typically of a technical nature that makes it difficult to be used or understood by non-technical users. Also, the structure of the registry and the format of submissions should be pilot-tested to ensure that they are not overly burdensome and generate useful, accessible information for the intended purposes. Well-defined objectives, such as purpose and intended audience, are a necessary first step prior to determining the appropriate data fields of the GTR. Wherever possible, the GTR data fields should permit linkages to existing data sources, such as ClinicalTrials.gov, FDA clearance/approval databases, and product instructions, to reduce the need to enter the same information in multiple sources and promote consistency in information provided by multiple sources.

Due to the potential impact of the GTR on development of appropriate pathways for regulation of genetic tests, we believe that federal agencies including the Food and Drug Administration (FDA) and Centers for Medicare and Medicaid Services (CMS) should be consulted throughout the process of development of the registry.

Specific Comments that Address Questions in the RFI:

1. A comprehensive genetic test registry that includes all available genetic tests would most effectively address the intended purposes of providing a centralized public resource with information about genetic testing to patients, consumers, healthcare providers, healthcare payers, and other

stakeholders. This includes all commercially available tests, Laboratory Developed Tests (LDTs), and In Vitro Diagnostic Multivariate Index Assays (IVDMIA). Tests should be listed by the biomarker(s) (such as gene sequence(s)) that is analyzed with the ability to easily re-organize or search the list by test names, therapeutic areas, disease indications, or treatment regimens, with cross reference.

A key question is, “At what stage of development should new tests be added?” The registry needs to have clearly defined each development stage and its criteria. Since the GTR is a voluntary database, BIO believes that test developers should be encouraged to submit a test entry for investigational genetic tests for which clinical investigation is ongoing and nearing completion (for example FDA reviewed IUO-level diagnostics). This could be facilitated by including information from ClinicalTrials.gov or linking the two databases. In some cases this might further the objective of ClinicalTrials.gov by helping physicians or patients identify opportunities to be involved in clinical data accumulation for tests being developed (for example, entry into pivotal trials for patients who may want to get tested with a primary test). Depending on factors such as accessibility of tests to patients, stage of clinical development, and validation of association with biomarker; the richness of test entry information may vary. The parameters of information for all stages of development of tests should be defined so that entries are consistent. Commercially available tests, LDTs, and IVDMIA test entries should include similar data elements.

If the GTR is to include Direct-to-Consumer (DTC) tests, it will be important for the database to clearly indicate which tests are offered DTC, and which are ordered through a medical professional. It is important to note in most cases that DTC tests are not FDA approved, and although DTC tests are often performed in CLIA-approved laboratories, questions of validity of test results exist. It is also important to note that DTC tests are usually not covered by insurance providers.

2. It will be necessary to put in place processes to verify the accuracy of the voluntarily entered information before allowing its use in the registry.
3. The data elements that are critical to different stakeholders may vary, and should be matched to well-defined database objectives. For example, elements currently present in GeneTests/GeneReviews have made this a useful resource for health care providers, but it may not be as useful for patients or payers. The GTR needs to include data elements that represent the needs of the medical community as well as for patients and consumers, test manufacturers, and healthcare payers, and it would be helpful for individuals from these communities to be involved with GTR development and oversight. BIO recommends the creation of an advisory board made up of key stakeholders outside of the NIH including clinical genetics professionals and other users of this resource to determine critical data elements and to determine the format for submission.
4. A benefit provided by such a system is that the user can easily identify products/tests that are available and whether they are FDA cleared/approved. A risk associated with such a system is a

patient may be incorrectly treated and or counseled if data and/or statements entered are incorrect, for example as it relates to the clinical utility of the product/test.

5. Once appropriate safeguards are in place to verify the accuracy of the data collected, completion of data fields necessary to ensure safe use of tests should be mandatory. If the data/information is unavailable, the data field should clearly indicate information not available.
6. To adequately and accurately describe a genetic test, certain data elements should be included in test entries. Some of the data elements that would be included for available tests may not yet be available for investigational tests, and when this is the case, it should be noted. Presuming that safeguards are in place to assure that the entries provide verified and accurate information, the following data elements should be considered.
 - Information on who submitted the information to the GTR and last update should be included, however there needs to be some context around what is known or unknown at the time of submission. Rules regarding information update need to be defined. For example, within certain period of time, the information should be updated in the registry when a developmental test moves to the next level, or fails the next level of verification.
 - The name of the test, all laboratory certifications, and regulatory clearances should be included. If investigational tests are included within the GTR, an indication that the test is investigational should be included here, and the investigational stage of development should be indicated. In the case of FDA-reviewed diagnostics, indicating whether tests are Investigational Use Only (or Research Use Only (RUO) if applicable) would be helpful.
 - “Intended use of the test” can be interpreted in many different ways, and therefore must be clearly defined. This data element is obviously important, but runs the risk of allowing false claims. “Intended Use” must be clearly defined and must be subject to verification of accuracy.
 - Applicable patient population needs to be included. Particular uses not related to subpopulations of patients should also be included. However, these data elements should not be referred to as “limitations of the test”, as that may be interpreted with a negative connotation.
 - Test methodology should be included as a drop down menu to prevent different names for the same methodology. We also recommend adding a field for “test complexity” with a drop down menu, for example - single gene, 2-5 genes, >5 genes, etc.
 - Biomarker analyzed (for example, genetic sequence) is an important data element.
 - Specimen requirements including type of specimen, collection method, and handling requirements should be included.
 - Test provider(s), and accessibility (through health care provider, public health program, or DTC) should be included. It is important for the GTR to clearly note tests that are offered DTC, and not ordered by a medical professional. Validity and accessibility (coverage) limitations of these types of tests should also be noted so as to avoid confusion to patients and consumers.

- Analytical validity and clinical validity should be included, however, these data elements must be clearly defined, and supplying information regarding these elements must not pose too great a burden to test submitters. Again, to avoid risks to patients, such as incorrect treatment or counseling, a system for vetting and verifying data accuracy is needed. The specific data and other information that is required regarding analytical performance characteristics and clinical validity should be determined in consultation with various stakeholders, including test manufacturers, in order to ensure that the GTR reflects a contextual discussion. For example, the importance of having a highly sensitive or specific test is tightly linked to the context in which it is being used (diagnosis of life threatening disease vs. information about special populations or for a very rare safety event) and the relative risk of having an incorrect result. Contributors may view “publishing” this information without context discussion as a downside to entry submission.
 - “Utility”, or health outcomes measures, is the most controversial potential data element to be considered for inclusion. The interpretation of utility may vary depending on various contexts and when alternative test options may exist. However, we see the value of including utility elements such as benefits, harms, and value to patients, the healthcare system, and further research. If clinical utility is included it needs to be clearly defined and the definition should be agreed upon by all stakeholders. Consensus in defining test utility may be difficult to achieve, but it may be necessary because of the potential impact that inclusion of this information might have on the regulatory landscape of genetic tests.
 - “Costs” of tests may be difficult to identify, due to variations in cost in different contexts and over time, and should not be included without consistency and clarity (which may not be able to be achieved).
 - Coverages for the test by CMS and/or private insurers and health plans should be included wherever possible. NIH should work with CMS and private payers to ensure appropriate rules and updates for this data field.
7. Some data and types of information may be a challenge to include with submissions depending on the format and guidelines for relative data elements. For example, how will clinical utility be captured and defined? Submissions for clinical utility may be subjective unless clear and consistent definitions are in place and information quality assurance safeguards are applied. For many potential data elements, a key question is how to ensure that information in the registry will be kept up to date and accurate and who has the responsibility to do so? There is a lot of information that could easily get out of date, ranging from the practical and personal (such as test provider(s)) to the scientific and technical (latest knowledge about clinical validity and utility). In order to assure that all data elements are accurate and up-to-date, NIH needs to develop mechanisms for submitters to update entries, and a system to check and maintain accuracy of information.
10. Some important processes to consider so that submission is not overly burdensome to the data provider include: a. A uniform test entry submission data format with clear instructions for how to handle potential data elements for which information may not yet be available; b. The ability to link

to existing data contained in FDA clearance/approval databases and clinicaltrials.gov; c. A process to submit test description summaries written at a level that non-technical users can understand with the capability of linking to other databases and approved information sources. Summaries should have defined parameters so that potentially alternative testing option entries are quantitatively and qualitatively similar; d. A process for additional education about the registry and the benefits of genetic testing to the public. This may serve to help ensure that healthcare providers and potential patients look at the information; and, e. A process for Q&A (either telephone contact, or online help desk) should be made available.

Conclusion:

If the NIH GTR succeeds in its goal to provide transparent access to information about accessible genetic tests, and if most test providers participate in the GTR, then the registry represents an opportunity to enable informed decision making by healthcare providers and patients and policy-makers. It can provide a centralized information source in which genetic test providers can list information about their products, and for which payers can access test information when evaluating coverage decisions. The GTR may also allow for side-by-side comparisons where competing test options exist (and possibly extended to different targeted treatment regimens for the same disease indication) so that patients can evaluate competing tests on the basis of features that are most relevant to their own personalized needs. Considering the potential importance of this information to the healthcare system, and the potential impact on future diagnostic regulatory oversight decisions, we believe that NIH, as well as all appropriate government agencies, should regularly review processes and submission formats, and that the test manufacturer industry should be regularly consulted regarding continued development and maintenance of the registry. Information included in the GTR must be reliable and up-to-date, and we strongly encourage NIH to develop information accuracy and updating mechanisms.

BIO greatly appreciates the opportunity to provide these comments to NIH regarding the plans to develop the GTR, and we look forward to further opportunities to provide feedback. We are united in our goal to provide patients and healthcare providers with accurate up-to-date information about genetic tests so as to best serve the needs of the healthcare system.

Respectfully submitted,

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