



By e-mail to GTR@od.nih.gov

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

July 12, 2010

**Re: Response to request for Information on the NIH Plan to Develop the Genetic Testing Registry**

General Comments: On behalf of the Directors of GeneDx, a provider of genetic testing for rare and ultra-rare hereditary disease, we thank you for the opportunity to respond to NIH's request for information.

It is unclear from the RFI what the motivation is to develop a GTR. There is, of course, already a registry of available genetic tests, also voluntary, that is curated by experts in clinical genetics (under direction of Dr. Bonnie Pagon at Univ of Washington since 1992, and funded by various grant and contract mechanisms through the NIH) and the website is currently hosted by NCBI. One of the primary strengths of GeneTests is its manual curation by board-certified clinical geneticists and genetic counselors, who evaluate submissions with respect to their appropriateness to the mission: “[to provide] current, authoritative information on genetic testing and its use in diagnosis, management, and genetic counseling, GeneTests promotes the appropriate use of genetic services in patient care and personal decision making.” Only laboratories with a current CLIA-certification are listed as “clinical” laboratories, differentiating them from laboratories that are performing research. They have wisely chosen not to include the DTC (recreational) gene testing services. It is thus very easy for a clinician who is evaluating the utility and availability of testing for a patient to get the necessary information, and chose a reputable lab that is offering a test with clinical utility. The questions that we have been asked to consider don't seem to be addressing 1) the manual curation by subject-matter experts, 2) the relationship between GeneTests and the GTR (or the replacement of GeneTests by the GTR?), 3) the differentiation between clinical diagnostic testing and other services. These are important issues to be discussing and considering.

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

Only those tests with high sensitivity, specificity, and clinical utility that can/should be ordered by health care professionals in the diagnosis, management, and genetic counseling of patients as it pertains to their medical care should be included in the GTR. DTC tests, especially those based on associations established through retrospective (rather than prospective) population-based studies should not be listed in the GTR, as their inclusion may lead the non-cognoscente to incorrectly interpret results to have specific implications for an individual, when that is not correct. *Caveat emptor* is not appropriate when dealing with the health of individuals.



- 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) policy makers, and (8) electronic health records?**

Researchers would likely use the GTR to identify other research laboratories studying the same genes, and to identify clinical laboratories that are available to provide clinical confirmation of research results in a CLIA-certified setting so that they can be shared with patients and referring physicians. Patients (who should not be lumped with consumers) might use the GTR to learn more about the genetic test being ordered by their physician. Health care providers would use the GTR to learn what genetic tests are available, from what labs, and what the sample requirements, TAT, sensitivity, etc (which should be available on the laboratory's website or in the information they provide directly to the health care provider) for a test they may be considering for a patient. Payers might use the GTR to determine the cost of a test (if the laboratory provides it), the sensitivity and clinical utility, and if there is more than one lab offering the test. Genetic testing entities could use the GTR to determine what other lab is offering the test and their parameters for testing. Policy makers might use the GTR to help facilitate the translation of tests from the research to the clinical arena. Electronic health records – possible utility will be the inclusion of pharmacogenetic test results in direct patient care.

- 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) policy makers, and (8) electronic health records?**

The necessary data elements are those that are currently available in GeneTests (gene name, method, contact information) or on the websites of the laboratories whose links are provided by GeneTests in a specific disease listing.

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

- a. Availability and accessibility of genetic tests?*
- b. Scientific basis and validity of genetic tests?*
- c. Utility of genetic tests?*

Generally, the benefits are the transparency provided so that ordering physicians/health professionals know the limits of the testing they are seeking for their patients. Risks are incurred when those using the GTR do not understand the information that is presented. Ordering the wrong test is the biggest risk. As long as DTC testing is not included in the GTR, risks will be minimized. If the GTR includes scientific basis, validity, and utility of a test, the accuracy of that information must be assured, and this will require hands-on curation by medical genetics professionals.



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?

While this may be a question for bioinformaticians and not stakeholders, it is likely best to just state “data not available”. It is unclear how the GTR is supposed to identify research opportunities, or why that would even be a purpose of such a registry.

6. To adequately and accurately describe 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?

- a. *Contact information (e.g., location, name of the laboratory director, and contact information for the laboratory performing the test)* YES, contact information should be provided
- b. *Laboratory certifications (e.g., Federal or State certification of the laboratory that performs the test)* YES, status of CLIA-certification should be provided
- c. *Name of the test (e.g., common test name YES, commercial name YES, marketing materials about the test NO, should be available on lab’s website and/or genetic testing entity Lab Name? YES, standard identifier (e.g. CPT codes On Lab’s website, LOINC-not generally used in genetics and not likely to be useful or understood).*
- d. *Regulatory clearances (e.g., for tests reviewed by the Food and Drug Administration, the 510(k) or premarket approval (PMA) number).* If one exists
- e. *Intended use of the test (e.g., diagnosis, screening, drug response).* YES
- f. *Recommended patient population* YES, if this means “for diagnosis, for carrier testing, for prenatal diagnosis, etc.
- 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?)* YES
- h. *Test methodology* YES (sequencing, FISH, SNP detection, oligoarray, SNParray, etc)
- i. *Analyte(s)—What is being measured in the test (e.g., genetic sequence)* YES, to differentiate sequencing from evaluation only of specific variants and from copy number evaluation
- j. *Specimen requirements (e.g., blood, saliva, tissue samples, amniotic fluid)* YES, although referral to lab’s website for details about volume, shipping, etc. would be necessary.



- k. Availability (e.g., is the submitter the sole provider of the test or are there multiple providers?)**  
All laboratories that have submitted to the GTR that they provide a specific test (and who are found upon review by medical genetic professionals to provide a clinically useful test in a certified laboratory or a research setting) should be listed. All of these should come up on a search of the site by gene/test. However, specifically stating that a submitter is the sole provider, or that there are “other providers” is not within the scope of the GTR, as keeping such information current is nearly impossible.
- l. Accessibility (e.g., accessible through a health provider, public health mandate, and/or direct-to-consumer)** DTC should not be listed on the GTR, so only tests available through a health care provider should be listed. A separate listing of newborn screening tests by state could also be considered.
- m. Performance characteristics**
- i. Analytical sensitivity** YES, or link to provider’s info/website. As this kind of information can change frequently as labs change methodology or testing protocol, the provider’s website is most likely to be the most current source of all performance characteristics.
  - ii. Analytical specificity** YES, or link to provider’s info/website
  - iii. Accuracy** not sure what this means in this context
  - iv. Precision** not sure what this means in this context
  - v. Reportable range of test results** YES, for quantitative tests, if biochemical testing is to be included for metabolic disorders
  - vi. Reference range** Makes no sense for sequence-based tests, but might be for metabolic, although should be reported with each test result (like any quantitative assay)
  - vii. Method used for proficiency testing (e.g., formal PT program, alternative assessment) and score** NO, as any lab providing “clinical testing” is, by definition, CLIA-certified and thus participates in proficiency testing. For rare disorders testing, the scores are not test specific, as no proficiency testing samples are available for the majority of the specific genes. If this is left blank for such tests, and payers use this information to determine whether a test is covered, patients with rare disorders can lose coverage for their testing. *This is dangerous.*
- n. Clinical validity** Most of these parameters are not available for many clinical diagnostic genetic tests, particularly the ultra-rare disorders. Citations to the literature should be provided to provide, as much as possible, information needed by a clinician who is considering ordering a test. However, for DTC tests for common traits, clinical utility SHOULD be provided. One would hope, however, that DTC test are not included in the GTR.
- i. Clinical sensitivity**



- ii. *Clinical specificity*
  - iii. *Positive and negative predictive value*
  - iv. *Prevalence*
  - v. *Penetrance*
  - vi. *Modifiers*
- o. *Utility (e.g., clinical and/or personal utility) or outcomes* YES, although not likely useful for the rare/ultra-rare disorders
  - p. *Benefits* This would be “purpose of testing” as above and (f).
  - q. *Harms* Should be included on the consent document provided by the testing laboratory
  - r. *Added value, compared with current management without genetic testing* YES, for a small subset of available tests (Warfarin response, BRCA1/2), otherwise, NO, this is what the physician/counselor should be discussing with the patient
  - s. *Cost (e.g., price of the test, health insurance coverage)* refer to lab’s website for cost information, if it is available. In many situations, due to contractual relationships with insurers, prices will not be provided. Additionally, it is not within the scope of a scientific resource to provide pricing information.

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

For rare disorders it will not be possible to provide most performance characteristics measurements as the data is simply not available. Commercial entities may not be able to provide price, as negotiated discounts with different institutions or insurance carriers will not be public knowledge. Should the GTR require (as we have heard) submission of primer sequences, or other specific protocol information, these would be considered proprietary and not available for submission.

## 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?

Detailed information will be very time-consuming and expensive to collect and submit. Even as simple a system as GeneTests is a time-consuming endeavor for labs that have an extensive test menu. Much of the information related to methods, etc. is proprietary and will not be available. If it eventually becomes a requirement to submit information that an entity considers proprietary, thus giving competitors information to allow development of the same test without the expense and time incurred by the submitting lab, this will have a severe dampening effect on the development of new genetic tests.



- 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)?**

References that support the clinical utility of the test should be required, and published recommendations from professional organizations and government entities can be referenced.

- 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)?**

NCBI will need to take responsibility for the transfer of all information currently in GeneTests, without re-submission of that data by the testing laboratories. A link to CMS to verify the current status of CLIA certification would be important. Again, a system of manual curation of the data to determine what should/should not be in the GTR is extremely important and appears not to be an element that has been considered by the developers.

- 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?**

Proprietary information must be completely protected; Assurance that inclusion in the GTR is reserved only for legitimate clinical diagnostic genetic testing that has been reviewed and approved for inclusion by appropriate clinically-trained subject matter experts; Ease of submission; Ease of updating information and adding new information; lack of excessive time between submission to the GTR and its appearance in the GTR; preservation of the laboratory links that are currently in GeneTests.

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

Regular meetings of an advisory board composed of appropriate individuals and entities.

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

To inform medical professionals of the availability of genetic tests that are relevant to the medical care of their patients.



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

Specific inclusion of providers of genetic tests for rare disorders, and of patient/support organizations, and practicing clinical geneticists and genetic counselors in the advisory board of the GTR is essential, both at its inception and beyond.

Sincerely,

Sherri J. Bale, Ph.D, FACMG  
President and Clinical Director  
GeneDx