

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Request for Information (RFI) on the National Institutes of Health Plan to Develop the Genetic Testing Registry

Response to comments submitted by:

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Request for Comments	Illumina Response
1 Are there types of genetic tests that should not be included in the GTR?	The genetic testing registry should include only those tests that involve analysis of human chromosomes, DNA, RNA, genes and whole genomes. Tests utilizing gene products such as proteins, enzymes, and other metabolites should not be included in the genetic test registry.
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?	The GTR has the potential to be a valuable resource to a broad number of stakeholders, from clinical research to healthcare management. (1). For researchers, the GTR would provide a means of facilitating studies and connecting with other laboratories also focusing on the same disease/diagnostic. It may also facilitate outreach for establishing clinical trial participants, in support of FDA submission of new genetic tests. (2). Patients/consumers could utilize this single, consolidated and controlled site as an educational resource for understanding genetic tests, including their utility and limitations. It could help to facilitate discussions with their physicians and genetic counselors, particularly if the patient/consumer is considering undergoing a test. (3). Health care providers could utilize the site as an educational tool for understanding new diagnostic tests, and be provided with listings and information on the laboratories that perform the various tests; this will aid providers in choosing the most appropriate test for their patient's needs. (4). Clinical Laboratory Professionals would be able to use the site to list their test service, define and differentiate specific markers in their panels, and establish proficiency programs with other laboratories performing the same genetic test – which can be challenging for new genetic tests that are complex. Labs will also have the opportunity to highlight the coverage, accuracy and other characteristics of test performance, which in the space of LDTs will develop transparency and industry standards. (5). Payers would be able to utilize the site to better understand genetic tests, and investigate the clinical utility for addressing specific disease/diagnosis. Payors will also be better able to establish appropriate uses of tests. (6). Genetic testing entities/data submitters could potentially use the site to help provide information on new genetic tests and/or research on genetic tests to clinical laboratories, health care providers, patients and policy makers. It would help facilitate uniformity across the industry for addressing genetic testing, and standardize how information is presented for genetic tests. (7). For policymakers, the registry could provide a single, consolidated and controlled site as a resource for understanding genetic tests, including their utility and limitations. It could help to guide development of policy and facilitate discussions around reimbursement and advocacy. (8). The registry should allow for download of de-identified electronic health records, to enable robust accumulation of data on test performance, clinical utility, specify, and if appropriate, outcomes.

<p>3 What data elements are critical to include for use by</p> <ol style="list-style-type: none"> (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? 	<p>We believe that the data elements listed in section 6 appropriately captures the critical information that would be of use to each of these groups.</p>
<p>4 What are the potential benefits and risks associated with facilitating public access to information about the:</p> <ol style="list-style-type: none"> a). Availability and accessibility of genetic tests? b). Scientific basis and validity of genetic tests? c). Utility of genetic tests? 	<p>(a). <u>Availability and accessibility of genetic tests:</u> <u>Benefits</u> – provides education and facts on genetic tests. Provides the public with clinical use, and limitations of genetic tests, and clearly identifies the regulatory status of the tests performed by the various labs. <u>Risks</u> – could result in increased questions by patients to their physicians and/or genetic, particularly by those who do not have a basic understanding of genetics. This may present challenges to physicians who have limited knowledge of genetics, and add pressure to the limited availability of genetic counselors in the U.S.</p> <p>(b). <u>Scientific basis and validity of genetic tests:</u> <u>Benefits</u> – establishes means to begin establishing and clarifying the scientific basis and validity of genetic tests. By standardizing the means and content of data submission, it may be possible to remove some of the confusion/ambiguities that currently exist, with information posted on different sites, with different content. <u>Risks</u> – if data is submitted to the GTR for a test that is used in research and undergoing clinical trials to establish utility, it may face greater scrutiny when data submitters change the standing from low validity to high validity as a result of new data sets. Test developers may opt to withhold submitting data until more clinical validity and utility is demonstrated – which would limit the informational resource that the site could have been able to provide for researchers.</p> <p>(c). same as above</p>
<p>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?</p>	<p>In order to ensure transparency, including new research opportunities, we believe that fields should not be allowed to be left blank. We believe that the system should accommodate drop-down menus, that require data submitters to select the reason for lack of input to a particular field. This should be simple, and could indicate “Lack of Data/Evidence” or “Not established” (particularly for policy related fields).</p>
<p>6 To describe adequately and accurately a genetic test, which of the following data elements should be included</p>	<p>We believe that a great portion of the data elements as proposed by NIH should be included in the GTR.</p> <ol style="list-style-type: none"> (a). agreed (b). agreed (c). agreed – with lab certification number/registration

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)

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

(c). Name of the test (e.g., CPT codes, LOINC))

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

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

(f). Recommended patient population

(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?)

(h). Test methodology

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

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

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

(l). Accessibility (e.g., accessible

(d). agreed – with requirement to indicate “Research Use Only” or “Laboratory Developed Test” if not reviewed by the FDA

(e). agreed

(f). agreed

(g). agreed

(h). agreed

(i). agreed – but we need to implement a standardized means of identifying the analytes within a given test (ie., gene name; SNP locus; genetic sequence information) for greater clarity of content. For example, a variant identified only by an amino acid change could result from multiple differences at the genomic DNA level, making it difficult to know what molecular genetic change is being monitored in the genetic test.

(j). agreed

(k). we do not agree that the submitter of the data needs to indicate whether they are sole provider of the test, or if there are multiple providers. This puts unnecessary responsibility of the data submitter to survey the entire market on a regular basis and determine whether other providers are offering the identical test

(l). agreed

(m). agreed

(n). agreed

(o). agreed

(p). we do not agree that the cost should be included as a required field in the GTR. There are too many factors that can greatly skew the cost, which could contribute to significant inaccuracies. For example, test manufacturers (kits), could potentially submit the list price of the test kit itself. This would not include the labor and overhead burden that the test labs (service providers) would include as a part of their cost. Additionally, we believe that it is inappropriate for test submitters to be responsible for submitting whether the test is covered by health insurance. Presently, reimbursement is not well standardized and sometimes only approved on a case by case basis by the insurance provider.

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- through a health care provider, public health mandate, and /or direct to consumer)
- (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
 - (n). Clinical validity
 - 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
 - i. Benefits
 - ii. Harms
 - iii. Added value, compared with current management without genetic testing
 - (p). Cost (e.g., price of the test, health insurance coverage)

7	What types of information might be difficult for test providers to submit and why?	Information that may be difficult for test providers to submit is described in the above section (k and p).
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	<p><u>Advantages</u> – provides a single, consolidated public resource for information on the validity and usefulness of genetic tests. This will help to facilitate research and enable health care providers, patients, insurers and policymakers to make informed decisions</p> <p><u>Disadvantages</u> – before broad adoption by the public as a resource, it may require additional training programs to be implemented, to educate physicians, patients and others who may not be well versed in molecular biology, or the assay methods used in these genetic tests</p>

detects and the specific methods employed?

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| <p>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. Preventative Services Task Force, or Evaluation of Genomic Applications in Practice and Prevention Working Group)?</p> | <p>If applicable to the test data being submitted, we agree that references to other published resources and guidelines, especially professional guidelines (issued by such groups as ACMG, ACOG, CAP, etc.), as well as expert panels should be included. Additionally, we would like to ensure that the site includes reviews similar to those currently available on GeneTests.org (Gene Reviews). Gene Reviews are written by clinical experts in the field, and are quite useful for those using and developing tests, and/or for helping physicians decide which tests are needed.</p> |
| <p>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)?</p> | <p>A standard template format for data submission (ie., .csv file) should be utilized for submitting data to the GTR. This will ensure uniformity across all data submitters, and enable easy uploading of information. Additionally, if the test has been reviewed by the FDA, there should be the ability to link this to the test information.</p> |
| <p>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?</p> | <p>We believe that most researchers, test developers and manufacturers see great benefit to the genetic test registry. Not only would this help to support demonstrating clinical utility for genetic tests, but would help connect laboratories with health care providers and patients looking for specific tests. We see one potential challenge that may likely affect the decision to submit data to the GTR – specifically by laboratories that have developed LDT's. With the recent increase in FDA focus on LDT's, laboratories may opt not to submit data at the risk of inviting greater scrutiny to their organization.</p> |

12	What are the most effective methods to ensure continued stakeholder input into the maintenance of the GTR?	Establish a public schedule for routine review and updates to the GTR by the various stakeholders. An annual review meeting, perhaps linked to a major conference such as AMP or ASHG, could help to ensure participation and continued growth of the registry.
13	For what purpose(s) would you use the Registry to support your professional efforts?	We would use the registry to support education and awareness to laboratories, health care providers, patients and insurers. The site will help us to better network with research institutions working on similar diseases as Illumina, and support proficiency testing for our clinical applications.
14	Are there other issues that NIH should consider in the development of the GTR?	As described in section 11, the air of uncertainty over LDT's may hinder broad participation by some clinical laboratories
