Response to request for Information on the NIH Plan to Develop the Genetic Testing Registry (GTR)

Comments:

The goals and scopes for developing a new GTR have not been clearly defined yet. It needs to be determined what is the need for a GTR and how will it be used, who are the intended users and who will participate. Another critical question is how will the GTR differentiate between different types of genetic tests, such as diagnostic testing, risk assessments, pharmacogenetic tests, tests offered directly to the consumers for 'recreational' purposes, etc. What standards should be applied to laboratories, test developers etc. in order to become listed and should these standards be similar to all types of tests listed above. The spectrum of 'genetic tests' available to the public and health care providers is already extremely broad and diverse. For diagnostic genetic tests already exists a prime source of information, the GeneTests registry. This voluntary laboratory registry is carefully curated by ABMG-certified geneticists and genetic counselors, and widely used by US and international health care providers to see if a specific diagnostic genetic test is available, if it is clinical useful, and which CLIA-certified laboratories can provide this service. The main advantages of GeneTests are its ease of use, the participation of a very large number of labs and test providers, and the curated information provided. Will the planned new GTR replace GeneTests or compete with it? Or will the new GTR function similar to GeneTests but with focus on all other types of genetic tests, for which currently no registry exists? Who will oversee the content and scope of the registry? Will the experts in the field of genetics become the leading curators? Many of these are burning questions have not been addressed in the RFI albeit they are crucial for this discussion. It is very difficult to answer many of the detailed questions in the RFI as the key points have not been discussed and established first.

This can be illustrated on question 1, "1. Are there any types of genetic tests that should not be included in the GTR?" **The answer depends on the scope of the GTR. There is a tremendous difference between tests for Mendelian disorders that can be used for diagnosis, prognosis, and patient management, and those that assess the risk for developing multifactorial disorders based on one or a few genetic markers or constellations. The public (and sometimes even scientific) knowledge about these complex traits and the utility of risk assessment tests is very superficial at best, and therefore it is imperative to distinguish those from diagnostic tests.**

This leads to question 4, "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?" **The biggest risk is for the GTR to be misleading, and for individuals and their health care providers to select inappropriate genetic tests. The different types of genetic tests should not be listed side-by-side in one registry as if they were comparable (for example, direct-to-consumer testing [DTC] vs diagnostic testing). The GTR should provide easy to use access and at-a-glance information that helps individuals and their health care providers to identify what test to order and what lab to choose. It is important to be transparent about the limitations of each test. Participating labs should provide information about their methods, test validity and utility of their tests on their websites.**

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?

This is a confusing question, and why should a GTR be used for research purposes?

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**
    b. Laboratory certifications (e.g., Federal or State certification of the laboratory that performs the test) **YES**
    c. Name of the test (e.g., common test name **YES**, commercial name **YES**, marketing materials about the test **NO, should be available on website of each laboratory** and/or genetic testing entity **Lab Name? Yes**, standard identifier (e.g. CPT codes **On website of each laboratory**, LOINC **NO (is this used at all?)**
    d. Regulatory clearances (e.g., for tests reviewed by the Food and Drug Administration, the 510(k) or premarket approval (PMA) number). **If applicable**
    e. Intended use of the test (e.g., diagnosis, screening, drug response).

    YES, important and should be approved by a group of genetic experts!

    f. Recommended patient population

    What does this mean? Ethnic groups? Would be better to classify if test can be used for diagnosis, for carrier testing, for prenatal diagnosis, for determining drug response, 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, broad category, like Sanger sequencing, FISH, SNP detection, oligo array, SNP array, etc.**
    i. Analyte(s)—What is being measured in the test (e.g., genetic sequence) **YES**
    j. Specimen requirements (e.g., blood, saliva, tissue samples, amniotic fluid) Possibly YES, I would refer **to the website of the test laboratory**
    k. Availability (e.g., is the submitter the sole provider of the test or are there multiple providers?) **NO**
    l. Accessibility (e.g., accessible through a health provider, public health mandate, and/or direct-to-consumer)

    Depends on the scope of the GTR, whether DTC is included or not. DTC should not be confused with diagnostic tests and an abundantly clear distinction should be provided, best by separating diagnostic tests from DTC and other risk assessment tests.

    m. Performance characteristics
        i. Analytical sensitivity **YES, or link to provider's info/website**
        ii. Analytical specificity **YES, or link to provider's info/website**
        iii. Accuracy **??**
        iv. Precision **??**
        v. Reportable range of test results **YES, for quantitative tests**
        vi. Reference range **If applicable (ie., metabolic tests)**

vii. Method used for proficiency testing (e.g., formal PT program, alternative assessment) and score **NO, as this Is part of CLIA, state and CAP certification process, and proficiency testing is only available for very few for rare genetic orders.**

n. Clinical validity

i. Clinical sensitivity
ii. Clinical specificity
iii. Positive and negative predictive value
iv. Prevalence
v. Penetrance
vi. Modifiers

For majority of clinical diagnostic genetic tests this information is not available, since disorders are rare. For DTC and risk assessment tests for common and complex traits, this information should be required.

o. Utility (e.g., clinical and/or personal utility) or outcomes - **YES, like carrier testing, prenatal diagnosis, determining drug response, etc.**

p. Benefits **– see above**

q. Harms **Refer to patient consent documents**

r. Added value, compared with current management without genetic testing **– Isn't this what the physician, GC, health care provider should determine for each specific case?**

s. Cost (e.g., price of the test, health insurance coverage) **Unlikely that many labs will provide this information voluntarily**

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

Proprietary information, such as oligo sequences, specific methods developed by a lab/test provider; Price and discount information; Clinical sensitivity, specificity, positive and negative predictive value for rare disorder testing. For genotype based risk assessment studies, many labs consider the information, which specific SNP is used for testing proprietary although this maybe critical for test performance.

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?

Refer back to the lab's websites for details, will clutter GTR with too many details and prohibits user friendliness, and much of the methods will be proprietary. Each lab/test [provider should have information about the molecular basis of their genetic tests publicly available.

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)? **YES**, r**eferences that**

support the clinical utility of the test should be required, and published recommendations from professional organizations and government entities would be helpful.

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)?

What will happen to GeneTests and the data that were collected there?

As for other data, there should be a possibility to submit data for multiple tests in bulk using exel files or other lists. Data need to be curated by experts, easy online access for updates and edits

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?

Ease of updating information and adding new information; Protection of proprietary information; Providing links from GTR to website of test labs/providers; Listing of only legitimate tests with clinical utility; Immediate availability of submitted information (no delays over months until info is posted)

12. What are the most effective methods to ensure continued stakeholder input into the maintenance of the GTR? **Establish an appropriate advisory board that meets regularly**

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

To retrieve information about the availability and limitations of specific genetic tests, to inform other 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? **See my commentary at the beginning**