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

To Whom It May Concern:

Hayes, Inc. is pleased to respond to the RFI on the NIH plan to develop the genetic test registry (GTR) (NOT-OD-10-101). Hayes, Inc. is an independent healthcare technology and consulting company with more than 20 years' experience in evidence-based evaluation of new, emerging, or controversial health technologies. Currently, there are more than 800 evidence-based reports available on our subscriber website. Our worldwide clients, who include hospitals, healthcare systems, government agencies, employers, and managed care organizations, use the research in our reports to help inform policies around the use and reimbursement of technology. Several years ago, Hayes recognized the lack of available information regarding genetic and genomic tests and the need for specialized expertise to evaluate these tests. To meet this need, we created a program devoted entirely to the evidence-based evaluation of genetic and genomic tests. Since its inception in January 2008, Hayes' Genetic Test Evaluation (GTE) program has evaluated the evidence behind more than 70 genetic and genomic tests from a wide range of therapy areas.

The RFI specifies a series of key questions to which responses are requested. This letter will address the questions in the order they were presented in the RFI with the questions in black and Hayes' responses in **blue**:

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

All human genetic and genomic tests should be included in the GTR. These include tests for inherited, somatic, and acquired genetic changes, as well as gene expression assays designed to provide information about a given disease state. Tests of nonhuman DNA or other nonhuman genetic material, such as bacterial or viral DNA, should not be included in the GTR.

2. What are the potential uses of the GTR for
 - a. Researchers – **to find providers and obtain information about a given test; to determine the need for a given test (i.e., establish those disorders or conditions for which no genetic or genomic test currently exists and further research is needed)**

- b. Patients/consumers – to determine if a test for a particular condition is available; to obtain information about the risks and benefits of a test
- c. Health care providers – to find a provider of a given test; to obtain information about the risks and benefits of a test; to assist in the appropriate selection, use, and interpretation of a genetic test
- d. Clinical laboratory professionals – to find referral laboratories of a test; to investigate potential testing methodologies for a given disease; to determine the need for a given genetic/genomic test
- e. Payers – to help establish coverage policies for genetic/genomic tests and, as appropriate, pharmacotherapy
- f. Genetic testing entities/data submitters – to increase transparency of testing provided; to determine the need for a given genetic/genomic test
- g. Policy makers – to determine coverage policies for genetic/genomic tests; to establish minimum criteria for testing/laboratories; to ensure transparency in genetic/genomic testing
- h. Electronic health records – to record information about the use of genetic tests

It is important to note, however, that it will be very difficult for the GTR to be all things to all people and, therefore, prioritization of the goals of the GTR should be considered. In our opinion, the target audience for the GTR should primarily be Healthcare Providers, Patients/consumers, Policy makers, and Payers.

- 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?

Hayes believes that the following data elements are critical for all potential users of the GTR:

- a. Laboratory name/contact info
- b. Accreditation/licensing status
- c. Test name (especially proprietary names)
- d. Test components (i.e., genes tested)
- e. Test methods
- f. Test codes (as they currently exist)
- g. Intended patient population and patient selection criteria

- h. **Performance characteristics – analytical sensitivity; analytical specificity; positive predictive value; negative predictive value; failure rate; clinical sensitivity; clinical specificity**
 - i. **Limitations of test**
 - j. **Evidence of clinical utility**
 - k. **Social/ethical/legal considerations**
4. What are the potential benefits and risks associated with facilitating public access to information about the:

- a. Availability and accessibility of genetic tests?

Benefits – information readily accessible about the availability and application of genetic/genomic tests

Risks – potential over-utilization if sufficient information is not provided regarding clinical utility and limitations; misunderstanding and/or anxiety and/or poor decisions associated with the inappropriate use of genetic tests

- b. Scientific basis and validity of genetic tests?

Benefits – education regarding performance of tests

Risks – lack of understanding of the meaning of validity versus utility

- c. Utility of genetic tests?

Benefits – education regarding improvement of patient outcomes with test application; improvement in expectations regarding the value and lack of value specific to various genetic tests

Risks – utility is not clearly defined for genetic/genomic testing; therefore, it is difficult to establish standards for determining what constitutes utility; it is not clear that evidence of clinical utility is considered important by many stakeholders thus further complicating this requirement

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?

Make all data fields required and provide a “not applicable” option that requires an additional explanation. This is critical to ensure collection of complete information and enhance transparency.

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, commercial name, marketing materials about the test and/or genetic testing entity, standard identifier (e.g. CPT codes, LOINCii)) – **Yes**
- d. Regulatory clearances (e.g., for tests reviewed by the Food and Drug Administration, the 510(k) or premarket approval (PMA) number) – **Yes**
- e. Intended use of the test (e.g., diagnosis, screening, drug response) – **Yes**
- f. Recommended patient population – **Yes, including patient selection criteria**
- 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**
- 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) – **Not so critical as long as links to laboratory websites are provided**
- k. Availability (e.g., is the submitter the sole provider of the test or are there multiple providers?) – **Not as critical, although this may factor into cost and judgments of test reliability**
- l. Accessibility (e.g., accessible through a health provider, public health mandate, and/or direct-to-consumer) – **Yes**
- m. Performance characteristics
 - i. Analytical sensitivity – **Yes**
 - ii. Analytical specificity – **Yes**
 - iii. Accuracy – **Yes**
 - iv. Precision – **Yes**
 - v. Reportable range of test results – **Where available**
 - vi. Reference range – **Where available**

- vii. Method used for proficiency testing (e.g., formal PT program, alternative assessment) and score – **Yes**
- n. Clinical validity – **Yes**
 - i. Clinical sensitivity – **Yes**
 - ii. Clinical specificity – **Yes**
 - iii. Positive and negative predictive value – **Yes**
 - iv. Prevalence – **No**
 - v. Penetrance – **Where available**
 - vi. Modifiers – **Only if significant**
- o. Utility (e.g., clinical and/or personal utility) or outcomes
 - i. Benefits – **Yes**
 - ii. Harms – **Yes**
 - iii. Added value, compared with current management without genetic testing – **Yes**
 - iv. Cost (e.g., price of the test, health insurance coverage) – **Yes**

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

Most difficult will be clinical utility because this is variably or ill defined for genetic/genomic testing, and applicable high-quality research is often lacking. Providers may also be reluctant to provide proprietary information regarding methodology because this will then be available to competitors.

7. 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?

**Advantages – better able to assess and compare tests
Disadvantages – methodology changes rapidly and frequently in molecular testing, thereby requiring frequent updates by providers**

8. 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 – any evidence-based evaluations of genetic tests

9. 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)?

GTR must be designed to allow quick and easy submissions and updating of data. Standardized text, drop down menus, and links to other databases (FDA, CMS, PubMed, OMIM) would all be very useful.

10. 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?

Protection of proprietary information will be a major consideration for labs/manufacturers. The only way to ensure participation is to require it.

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

Make participation in GTR mandatory for accreditation/licensing of labs.

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

Hayes provides evidence-based evaluation of genetic tests; therefore, if the GTR contains all the required information to evaluate the performance and utility of a test, including supporting references, it would be a valuable resource to support the work we do.

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

- i. **The information submitted must be vetted for accuracy by qualified personnel. This will be especially important for clinical validity and clinical utility, in which:**
 - (a) **there is likelihood for confusion because of differences in term definitions, and**
 - (b) **manufacturers often overstate the data that support the genetic test.**
- ii. **Additional data elements under clinical utility might be useful. It would be very helpful to separate potential from demonstrated clinical utility:**
 - a. **Legitimacy – conformity to the social preferences expressed in ethical principles, values, norms, mores, laws, and regulations**
 - b. **Potential improvement in outcomes – potential of test and associated services to deliver health benefit or improvement in patient-centered outcomes**
 - c. **Demonstrated improvement in outcomes – actual delivery of health benefit in routine clinical setting or improvement in patient-centered outcomes**

- d. **Appropriateness – expected health benefit exceeds expected negative consequences by a sufficiently wide margin that the test is worth doing**
 - e. **Acceptability – conformity to the wishes, desires, and expectations of patients and their families**
 - f. **Economic considerations – efficiency (ability to lower the costs of care without diminishing benefits) and optimization (balancing improvements in health against costs of improvements)**
- iii. **Labs must provide all the information requested regarding each test they offer.**
 - iv. **Labs/manufacturers should be required to provide data to support their statements. For example, they should not be able to simply claim a given sensitivity and specificity without backing this up with data, preferably with published sources. Similarly, studies/information supporting any claims of clinical utility should be required.**
 - v. **Other widely used, existing resources (e.g., GeneTests, GeneReviews, OMIM) must be maintained, or their information must be included in the GTR.**

Thank you for the opportunity to respond to this RFI. Hayes considers this to be a very important initiative in ensuring the effective and responsible use of genetic and genomic information in personal healthcare. We look forward to more details of the GTR as it progresses.

Sincerely,



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