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Dear Dr. Fomous;

Hayes Inc. is pleased to provide follow-up comments on the development of a proposed genetic test registry (GTR). 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 90 genetic and genomic tests from a wide range of therapy areas.

The notice of the upcoming public meeting regarding the GTR, poses several specific questions. This letter will address the questions in the order they were presented in the meeting notice with the questions in black and Hayes' responses in blue:

1. Based on an analysis of RFI comments and other operational issues, NIH is considering a phased approach to developing the GTR in which some types of tests would be eligible for early entry in the GTR and other types of tests would be added later. If NIH adopts this approach, what criteria should be used to determine which genetic tests should be included in the first phase of the GTR, and what types of tests would meet these criteria?

   There are two possible scenarios for a phased approach:

a. Begin with tests that are likely to have the most evidence associated with their use and therefore the entries would be as complete as possible. In Hayes' opinion, this would likely be single gene tests (i.e. tests in which finding a sequence variant in a single gene would indicate a positive result; although multiple genes may be associated with the disorder, a pathogenic variant in any one of those genes causes disease). Examples of these would be Lynch syndrome, cystic fibrosis or fragile X syndrome. To further stratify single gene disorders, one might consider starting with the most commonly used tests rather than rarer disorders.

b. Begin with those tests that have the highest likelihood of impacting patient outcomes. Examples of these would be pharmacogenomic tests that influence treatment decisions (e.g. *KRAS* testing in metastatic colorectal cancer, OncotypeDx Breast Cancer or *CYP2C19* testing in patients considering clopidogrel treatment) or multi-gene expression assays used to stage or provide prognostic information in patients with cancer (e.g. OncotypeDx Colon Cancer, DecisionDx-GBM, DecisionDx-UM). The main advantage of starting with these tests is that this type of information is not generally available to healthcare providers or patients at this time, whereas at least some information on single gene disorders is currently available through GeneTests. The main limitation of this approach is that the information currently available on complex tests is limited and, as such, these entries are unlikely to be as complete.

Hayes would recommend beginning with single gene disorders as this would likely be more straightforward for setting up and assessing the format of the entries.

2. Several RFI responders, who are potential data submitters, noted that it makes more sense for clinicians and genetics professionals to be the source of clinical utility evidence rather than test developers and/or test providers. Given that data submitters are unlikely to have clinical utility information, how is this data element best addressed in the GTR?

Evidence of impact on patient outcomes is critical to demonstrating the value of a test. Too many genetic tests are "nice to know," but have no impact on patient care or outcomes. This is not acceptable from the point of view of healthcare costs. One option to overcome the issue of who provides the evidence of clinical utility is to have two separate fields regarding clinical utility: one to be completed by the test provider and one that can be completed by clinicians and genetics professionals. The first step in this process, however, would be to establish a clear definition of what constitutes "clinical utility" for a given class of tests. For example, are clear improvements in patient outcomes (including patient-important outcomes such as quality of life as well as the more traditional improvements in morbidity or mortality) necessary? Is physician-adoption of a particular test, even in the absence of clear

patient benefits, sufficient to indicate clinical utility? Finally, if patient benefits can be inferred, even in the absence of demonstrable improvements in outcomes (e.g. carrier testing in a disorder that has surveillance options to improve outcomes in those at risk such as Lynch syndrome or Long QT syndrome), should less (or no) evidence of outcomes be needed? Answering these questions and developing guidelines is critical before information on clinical utility can be included in the GTR.

3. Among responders to the RFI question about including a data element for test cost, half were in favor of including cost information and half were opposed. What are the benefits, risks, and challenges of including cost information in the GTR?

   Hayes believes that inclusion of cost information in the GTR is important. There are, of course, benefits, risks and challenges associated with including cost information:

   a. Benefits – Including cost information allows direct comparisons among similar tests, which can help patients and providers with planning. Currently, obtaining cost information can be problematic because many test providers are reluctant to provide pricing, perhaps because different prices exist for different consumers (i.e. insurance companies can often negotiate better pricing than direct-pay patients).

   b. Risks – Including cost information may deter the use of some tests strictly due to cost, even if the test has demonstrated clinical utility and/or is better than other, similar tests. To overcome this, providers need to ensure that GTR entries are as complete as possible to allow accurate comparisons among tests.

   c. Challenges – The biggest challenge to including cost information is ensuring that this information is kept current. In addition, it is critical that any cost information provided include all aspects of testing, including sample collection and transport costs, costs of the test itself, and costs of interpretation.

   On balance, Hayes believes that the benefits of including cost information outweigh the risks and challenges and therefore this information should be required.

4. What safeguards can be put in place to prevent GTR users from misunderstanding, misinterpreting, or misusing the information in the Registry?

   This is likely be one of the most challenging aspects of the GTR. Genetics can be one of the most widely misunderstood areas in medicine and given the explosion of genetic and genomic tests on the market, this is only likely to increase. Hayes makes the following suggestions to help to overcome these challenges:

   a. Ensure information is accurate and up-to-date. This can be achieved by either requiring review and updating of information by the provider on a regular basis (e.g. every 6 to 12 months) or by requiring updates any time there is a significant

change in the test. The challenge associated with the latter approach is defining what constitutes a “significant” change. As such, the former approach may be more feasible.

b. Utilize expert, independent reviewers to validate information contained in the registry. Ideally, the GTR should have at least one genetic counselor (and likely more than one given the volume of data to be included in the GTR) responsible for validating the information contained within the registry. As necessary, other experts could be consulted for very specialized tests.

c. Provide easy-to-understand definitions for all commons terms used in the GTR and provide links to educational resources on genetic or genomics tests, including evidence-based assessments.

5. What mechanisms can be used to provide materials that explain the GTR’s data elements to audiences with varying technical expertise?

   Again, this is likely to be a very challenging aspect of the GTR. Providing frequently asked question (FAQs) pages that are unique for the professional and lay audiences may be a good start. In addition, definitions, separate downloadable fact sheets and links to educational resources would be important. The provision of an individual with genetic expertise who can answer specific questions either in “live” (i.e. telephone) or a chat (live chat or email) format would be ideal although we recognize this may not be feasible. An alternative may be to provide quick links to genetic counselors from companies providing different tests.

Thank you for the opportunity to respond to these follow-up questions regarding the GTR. 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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