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July 13, 2010

NIH GTR RFI Comments  
National Institutes of Health  
Office of Science Policy, Rm 750  
6705 Rockledge Drive  
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To whom it may concern:

This letter is to provide feedback on the planned Genetic Testing Registry. I am the laboratory director for the CLIA-certified Laboratory for Molecular Medicine at the Partners Healthcare Center for Personalized Genetic Medicine. My laboratory currently maintains our own website for listing test information ([pcpgm.partners.org/lmm](http://pcpgm.partners.org/lmm)) and we also use the GeneTests website for listing all of our tests. In general, I am supportive of the GTR initiative. One of the benefits of such an approach is that it enables the provision of test level information as opposed to only gene level information as is currently maintained through GeneTests. Overall, I think the proposed system sounds like a very good one. However, I have a few specific areas on which I would like to provide feedback.

Regarding the types of genetic tests that should not be included in the GTR, the answer to this depends on how the system will be used. If there is a chance that the system will be viewed as a way to substantiate any level of validity of a genetic test, then there should be some control over its content and certain tests deemed to be harmful or address areas that have no data to support their use, should not be allowed to be entered. On the other hand if there is a mechanism to differentiate and identify tests that are not clinically valid, then it is better to put everything in but enable the inclusion of fields that will highlight the lack of validity for such tests. Later in this letter I comment on such fields.

My most important concern about the development of the GTR is how much oversight there will be to ensure that labs appropriately provide the requested data and that they actually understand what data should be provided for certain fields. In my experience there is often a wide range of interpretation for what data should be used to provide statistics like analytical sensitivity and specificity as well as clinical sensitivity and specificity, etc. So it would be critical that knowledgeable staff be available to assist the labs who are submitting the data and to provide at least a basic review of the data being submitted. I know that the GeneTests group spends a lot of time helping labs submit their data, checking the appropriateness of the provided information, and then ensuring that the data is reviewed annually. Ensuring an appropriate level of resources to accomplish this activity is critical if this resource will provide the needed function that it aims to provide. Furthermore it is important that the entries be reviewed annually. GeneTests has a good system to do this and they will not allow us to submit new tests if we are delayed in our annual reviews. This is a good mechanism to get labs to comply.

I would also suggest that there be a minimum set of fields, agreed upon by the larger community that must be filled out for a lab to submit a genetic test. For certain fields such as performance characteristics, it is important that raw values be supplied for calculated percentages. For example, reporting an analytical sensitivity of 100% is less useful if the data represents 5/5 mutations detected vs 400/400.

With respect to the list of fields suggested (a-p), I would advocate for all fields being required to be provided by the lab except for “k” (availability). For this field, I think it is more appropriate for the GTR to have a system to classify tests so that one could easily search within the system to see who else provides the test. It should not be the responsibility of the lab to figure out who also offers a test. On the other hand, if a lab believes they have exclusive IP to be able to offer a particular test or method, it may be appropriate to enable a mechanism to note that opinion or note when licensing has been obtained.

For all fields, it is important that labs reference all sources of data. This will be particularly important for fields reporting clinical validity where data is often from external sources.

Regarding the provision of reference ranges and reportable ranges of results, it would be useful if the GTR develop required standards for defining the content of a test. In an ideal world, there would actually be a function or ability to compare content of tests, or at least provide data in a manner such that others could compare content easily. For example, genotyping tests should map the genotype locations to a standard reference map, and full gene sequencing tests should provide structured coordinates of the sequences being analyzed.

For data reporting the utility of testing, I think there needs to be a mechanism to annotate the information by level of validity (e.g. opinion of lab offering test, results of independent studies, guidelines of professional organizations, etc). Ideally, there should also be a system for an approved entity, like EGAPP, to be able to provide unsolicited annotations for tests. If the GTR approves the group as a provider of genetic test evaluations, then their annotations about utility and validity could be entered by their organization, to be displayed alongside the lab’s annotations.

Finally, labs should be asked to provide information related to their process and metrics for interpreting the clinical significance of variants identified in their tests. In addition, the lab should report the percentage of cases for which variants of unknown significance are identified and their process for following up on such VUSs.

Regarding the question of what factors will influence a lab’s decision to use the GTR, I think it comes down to the quality of the system and the extent to which it provides a valuable resource. In my experience, most clinical labs offering gene-based tests use the GeneTests site recognizing that many physicians look for tests there because they value it as a resource. So if you build a high quality and useful resource, it will be populated.

Thank you for your efforts to consider building this infrastructure. If you would like further feedback, I would be happy to participate.

Sincerely,



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