



Advancing Excellence

College of American Pathologists

**Statement to the
National Institutes of Health on
the proposed Genetic Testing Registry**

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**College of American Pathologists
1350 I Street, NW, Suite 590
Washington, DC 20005
(202) 354-7100
(202) 354-7155 – fax
(800) 392-9994
www.cap.org**

CAP Comments on proposed NIH Genetics Test Registry

The College of American Pathologists is a national medical specialty society representing more than 17,000 pathologists who practice anatomic pathology and laboratory medicine in laboratories worldwide. The College's Commission on Laboratory Accreditation is responsible for accrediting more than 6,000 laboratories here and abroad. Our members have extensive expertise providing and directing laboratory services and participate as peer inspectors in the laboratory accreditation program. The College has been a leader in developing quality improvement programs for laboratories, including programs in genetic testing. The College appreciates the opportunity to provide our perspectives on the proposed genetic testing registry.

Potential benefit:

The College recognizes that an expanded, detailed database of test performance could assist laboratory scientists, but it is unclear how this could be served by the broad topics described in the proposal. The College supports transparency for all non-proprietary laboratory test information in order to create better understanding among healthcare providers and patients. A reference to other resources and published studies would enhance the educational value of the genetic testing registry. Centralized information could provide benefit, although practical value would depend on the type, accuracy, and currency of the information included in the genetic testing registry.

Target audience for the registry

While we agree that there is value in providing information about genetic tests to consumers and providers, we are concerned that the implementation of the registry is fraught with unintended consequences. The College is not convinced that the proposed genetic testing registry can serve all the user groups listed, because the needs for each are very different. We are concerned that information important to clinicians for clinical-decision making will not be the same as information useful to consumers, and it will not be feasible to appropriately target all of the different audiences that may use the registry. As NIH proceeds with the registry, the College encourages consideration of issues that have arisen for consumers in ClinicalTrials.gov including concerns that adverse events may or may not be caused by a particular intervention and that individual trials do not

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reflect the totality of information on a particular topics.¹ Similar concerns arise when complexities of laboratory assay performance and test methods are presented in a simplified fashion. We urge the NIH to fund comparative effectiveness studies to fairly evaluate assay performance by applying tests to the same patients in the context of a well designed clinical trial.

- We are also concerned that the registry will provide information on tests which provide similar diagnostic information but may use different methodologies. If data submission occurred via a web-interactive product, it could allow for qualifying comments by laboratories where appropriate. The database would need to be designed in a way that accommodates both reasonable standardization and qualifications.
- There are risks associated with public access to information that could be subject to misinterpretation. Interpretations could potentially lead to inaccurate conclusions by individuals who do not understand the advantages and limitations of individual variables. Comments on benefits, harm and outcome may be widely different among laboratories, potentially leading to confusing and inconsistent entries.
- In addition, NIH may appear to be tacitly endorsing a particular test just by including it in the registry. If NIH appoints someone to curate the registry, they may become a *de facto* regulator. The College is concerned that this registry would become a vehicle for advertisements of newly developed translational testing rather than a comprehensive, balanced, and verified resource.
- The College is very concerned about redundancy and effect of the registry on other widely used public resources. GeneTests[®] is a publicly funded resource that is already being used widely to locate clinical laboratories, research testing, and current descriptions of a large number of inherited genetic conditions. For acquired genetic diseases, a test registry (the Test Directory) is also available, through of the Association of Molecular Pathology. Other

¹ As presented by Deborah A. Zarin, M.D., at the November 12, 2009 FDA Risk Communication meeting.

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redundancies include the requirement of entry of regulatory clearances, which can be obtained from FDA, and performance on proficiency testing, which is already monitored and actionable by accrediting bodies such as the CAP.

Genetic test reports issued by individual laboratories address detailed information about what the test detects and the specific methods employed.

The College doubts whether the registry would provide additional benefit to researchers. The resources needed to create the registry might be better invested enhancing existing resources, e.g.; GeneTests[®]

The College's experience from its proficiency testing and laboratory accreditation programs is that the overwhelming majority of genetic tests performed in the U.S. are safe and effective; the performance on multiple CAP molecular genetics surveys has been excellent over a wide range of methodologies used for genetic tests. Of note, the performance of laboratory-developed tests on proficiency surveys is equivalent to assays that are FDA- cleared or approved. We already have better measures of the quality of laboratory tests through laboratory inspections than for most other aspect of medical practice. This is due in part to the robust nature of the analytes along with rigorous attention to CLIA quality standards and practices as well as medical oversight of every clinical laboratory by a physician. The College's Laboratory Accreditation Program stresses both analytic and clinical validation prior to introducing any new test into routine practice, recognizing that tests will continue to be periodically improved after introduction with each improvement revalidated by the laboratory before use on patient samples. The College's program brings an element of professional oversight that will be lacking in public registry.

Scope of the genetic testing registry:

The College recommends more specificity in the description of the goals for the proposed genetic testing registry, as well as clarification of its envisioned scope. The stated goal is to create a "centralized public resource that will provide information about the availability, scientific basis, and usefulness of genetic tests." Currently, all genetic tests appear to be grouped together without distinction among those that are very well

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established diagnostic tests (such as, for example, Huntington's disease or organic acid analysis) and those that are being used for research or that are emerging translational genetic tests (including genome-wide-association studies, single nucleotide polymorphism arrays, and tests offered direct-to-consumers in a variety of clinical and other contexts).

Given that NIH has a tradition of focused research discovery rather than on clinical diagnostic practice, regulation, and standards, the College is unclear whether the genetic testing registry will include non-clinical laboratories (i.e., research laboratories) since one of the stated goals is to expedite the translation of testing from research to the diagnostic setting.

Data Elements for submission

The potential data elements listed in the NIH Notice may not all be feasible to supply or easily understood by all of the intended users. Specifically:

- Information on penetrance and modifiers, other than what has been described in the scientific literature, is frequently not available for many disorders at all.
- Cost to consumers will depend on many factors; not all of the information on cost will be available to individual laboratories providing information on a particular test.
- Laboratories will be highly unlikely to enter or even know whether they are the sole provider of a test or how many other laboratories are offering the testing.
- In the section of Performance characteristics, some aspects do not apply to some or all genetic tests. Other listed parameters are dependent on variables that differ among laboratories. For example: positive and negative predictive values are directly associated with prevalence and patient population tested, which can be markedly different from laboratory to laboratory, depending on the population served.

Moreover, a consensus has not been reached on many of the data elements which would cause additional confusion for the intended users. In particular, clinical utility will differ

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for different individuals and this type of information may not be easily adapted to a registry format. The College is currently sponsoring a project to define elements and standards that laboratories can use in clinical validation for accreditation purposes. The project is expected to be completed in 2011; therefore it would be premature for us to comment on clinical validity elements at this time.

In addition, though voluntary, the breadth of information suggested in the Federal Register Notice for inclusion in the registry will be difficult for many laboratories to provide. Not all laboratories will have the resources required to prepare a submission if all of the proposed elements listed or required; this could have a profound effect on small laboratories and financially strapped academic institutions and increase the importance of marketing over quality as assessed by laboratory inspections. The registry could become a vessel for advertisements of newly developed translational testing rather than a comprehensive, balanced, and verified resource.

The genetic test registry would be a significant added expenditure for laboratories without obvious benefit. The effort of entry would come at the expense of already limited laboratory budgets and this is not a reimbursable activity. Therefore, it would be a non-negligible added indirect cost.

Recommendations on Implementation

The College asks that NIH seek public input on each step of the implementation of the proposed genetic test registry and that the registry must remain voluntary. We would also encourage the NIH to revisit many of the questions posed in this Request for Information, as there was insufficient time allowed to fully develop a comprehensive response.

However, the College offers the following recommendations:

- Any new mechanisms for collection of information should be tested before implementation to assure that the most useful information is included and that submissions are not overly burdensome to laboratories.
- We recommend that the genetic test registry not include information on non-human genomes, such as used in molecular genetic testing for infectious agents.

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- It would be useful for the registry to indicate somewhere (perhaps an introductory section) that variants listed in locus-specific databases as disease-associated mutations sometimes later are reclassified as non-disease polymorphisms based on follow-up information from additional patients. Information should be culled from other publicly available resources as much as possible, including other government agency databases (CMS, FDA, CDC, etc.)
- CLIA already requires submission of test lists by laboratories as a condition of inspection; thus, additional information submitted should remain within the context of CLIA and CMS. This information could then be made publicly available, informing clinicians and patients of the availability of laboratory services and their quality as assessed by CLIA inspection, while not impeding the medical practice of pathologists.
- The interface should be made very user-friendly and facile. The IT question of how blank fields should be distinguished could be solved by not allowing the participant to progress through the form when a field is left blank. One of the selectable entry options could be “no data available” in order to differentiate between absence of evidence/data or other reasons. A variety of options could be offered so that all fields will be filled in a user-friendly way.

Summary

We appreciate this opportunity to provide the College’s perspectives on the proposed genetic testing registry. Pathologists and other laboratory professionals are key sources of knowledge and experience on the delivery of high quality, cost-effective laboratory services, and the CAP is willing and eager to contribute to ongoing discussions with NIH on our common interests. Please don’t hesitate to contact Fay Shamanski, CAP Assistant Director, Public Health and Scientific Affairs at fshaman@cap.org if you have any questions on these comments.