Association for Molecular Pathology
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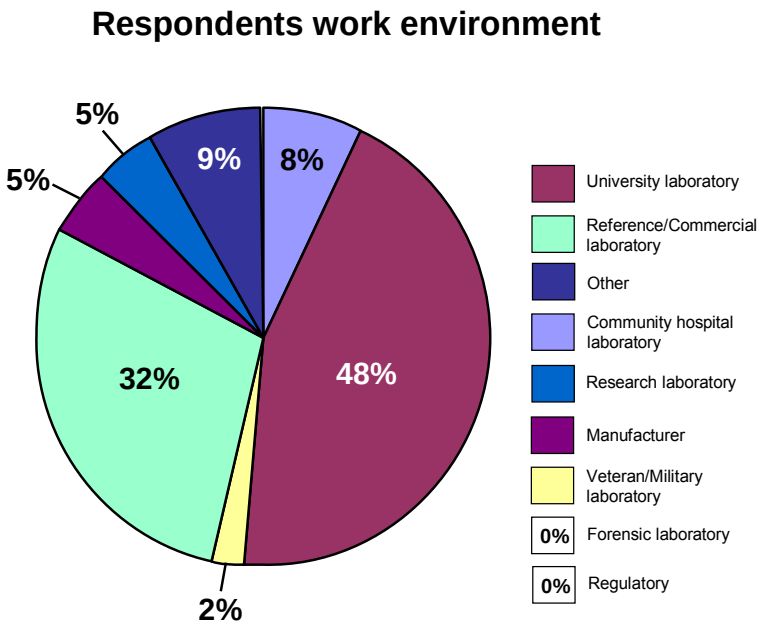
Dear Dr. Fomous

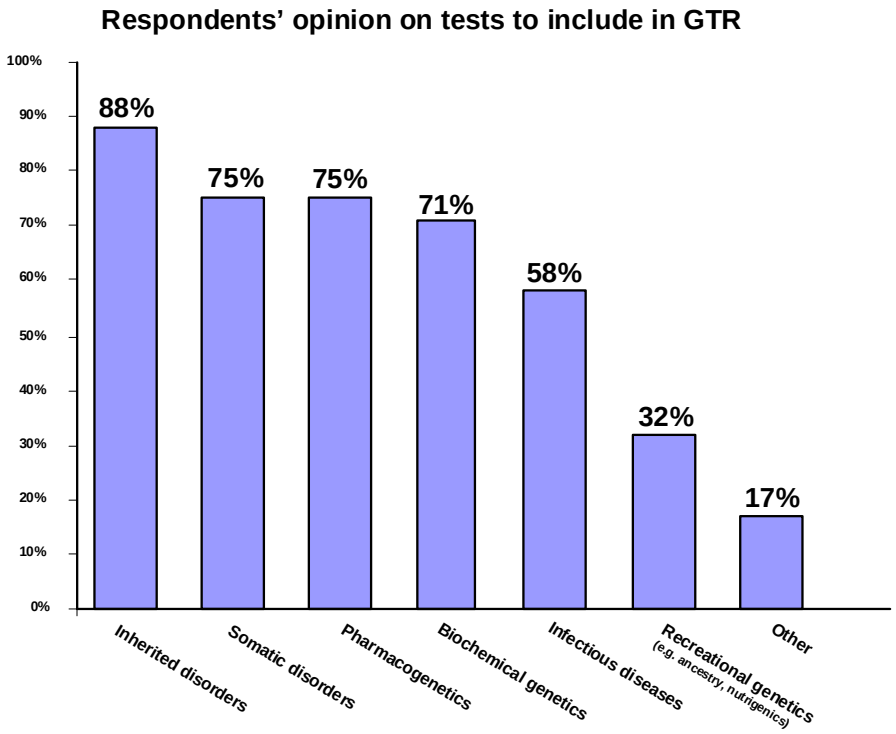
The Association for Molecular Pathology (AMP) is an international professional association representing approximately 1,800 physicians, doctoral scientists, and medical technologists who perform genetic and genomic diagnostic laboratory testing. Our members populate the majority of laboratories that perform clinical DNA and RNA -based testing in the United States. Their efforts are central to the development and clinical introduction of genetic and genomic assays that are applied daily for diagnosis, prognosis and patient management in all medical specialty areas, including cancer, infectious diseases, heritable disorders, and histocompatibility testing.

As primary providers of genetic and genomic tests, AMP members bring a practical perspective, real world experience, and accurate, current information on the development, validation, and utility of genetic and genomic tests. With this in mind, we have performed an impromptu survey of our members regarding the proposed Genetic Testing Registry (GTR).

The results of the AMP survey are as follows:
Sixty-three members replied to the survey. Nearly 90% of respondents work in a clinical laboratory setting. Approximately half of the respondents work in a university laboratory environment (48%; 31/63), with one-third working in a reference/commercial laboratory environment (32%; 21/63), and remainder in other aspects of the laboratory. The work environments of the respondents are shown in the following chart. The majority of the responders were familiar with the Genetic Test Registry proposal (83%; 53/63). Almost three-quarters were interested in participating in the Genetic Test Registry (72%; 47/63).



Nearly three-quarters of the respondents identified themselves as “laboratory directors”. This is significant since these are the individuals who have responsibility under the Clinical Laboratory Improvement Amendments (CLIA) program for many of the same elements proposed for inclusion in the GTR (i.e. specimen type, specimen requirements, intended use, reference range, limit of detection, interfering substances, analytical validity, reproducibility, etc). For those laboratories accredited by the College of American Pathologists (CAP), the Director is also accountable for the medical significance, interpretation and correlation of laboratory data for diagnosis and patient management, as well as assurance of quality for all laboratory testing. The majority of respondents to this survey are those who are presently most engaged and knowledgeable in the activities proposed for the registry, and who would be most directly involved in acquiring, composing, and submitting the directory elements.



AMP members understand that the definition of genetic or genomic tests encompasses more than inherited genetic disorders.

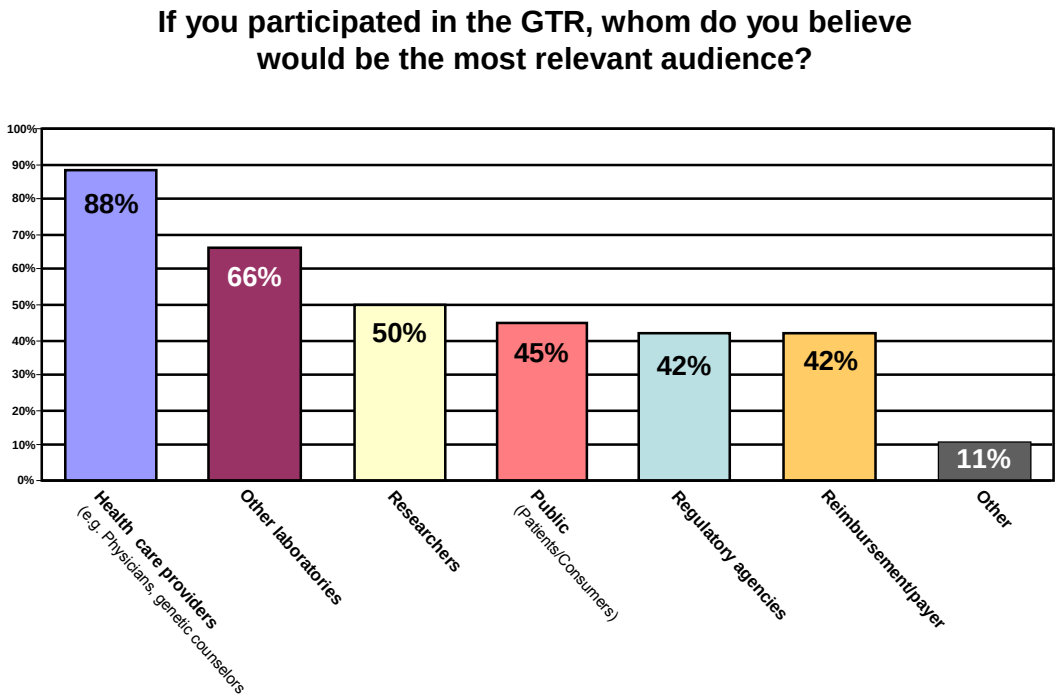
When asked what clinically related test categories should be included in a registry, most respondents indicated that it should include tests for inherited disorders, somatic disorders, and pharmacogenetics. Greater than 50% of respondents would include biochemical genetic tests as well as tests for infectious agents. A minority of respondents would include recreational genetic tests (e.g., ancestry, nutrigenetics). Other tests mentioned for inclusion in a registry were cytogenetics tests, HLA related tests, and all clinical tests.

We interpret this spectrum of responses as a reflection of the importance of genetic and genomic testing in virtually all traditional aspects of laboratory medicine. The extensive reach of molecular diagnostic testing does raise important questions regarding the spectrum of tests intended to be addressed by the GTR. Many traditional laboratory tests are being supplanted, or more commonly supplemented by genetic testing, and to simply extract the genetic component of these tests from their clinical context for inclusion in a directory may be difficult and potentially counterproductive.

The RFI states that for the purposes of the GTR, a genetic test is "a test that involves an analysis of human chromosomes, DNA, RNA, genes and/or gene products (e.g., enzymes, other types of proteins and selected metabolites) which is predominantly used to detect heritable or somatic mutations, genotypes or chromosomal variations in structure or number, related to disease, health and/or personalized medicine."

This definition of a genetic test is indeed problematic. Perhaps a more global definition to include both heritable and somatic mutations would be "genomic(s)." Yet, this also poses difficulty

because gene products (e.g. proteins and the subset enzymes) are components of the "proteome" and not the "genome." Under this definition, testing for a protein (or specifically an enzyme) would not necessarily constitute genetic or genomic testing. As an example, the protein product of the c-ERBB2 gene (HER-2/neu) has been routinely tested as work-up for breast carcinoma in pathology laboratories, using the classic antigen-antibody immuno-histochemical method and is not considered a "genetic" test. Yet using FISH to detect the amplification of this gene would be considered a genetic or genomic assay.



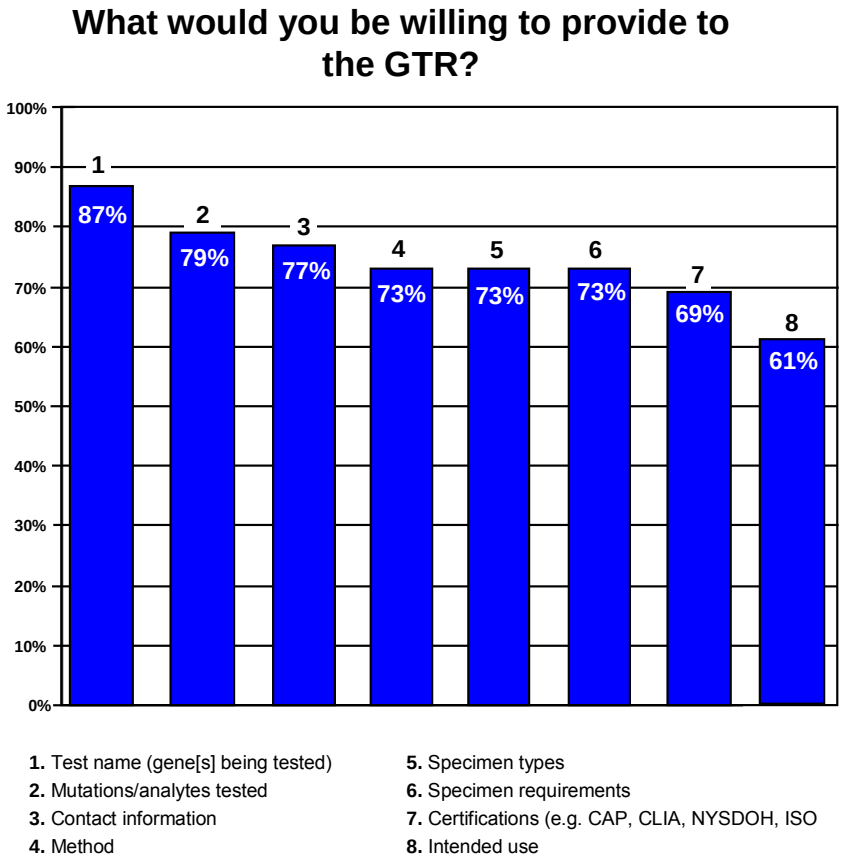
A registry could be a resource for healthcare providers. A majority of respondents indicated that the genetic test registry would be most relevant for healthcare providers (88% (56/63)) and to other laboratories. The latter is likely related to the laboratory's responsibility under CLIA to only refer specimens to CLIA-certified reference laboratories, and under CAP to assure the appropriateness of test selection for the clinical context. This is consistent with responses that the laboratory directory within GeneTests and the AMP test directory were already providing this service. Notably, only half of the respondents thought that the current concept of the GTR would be relevant for genetic research. The GTR must differentiate between the goals of research laboratories and clinical laboratories, the latter of which are regulated according to the Clinical Laboratory Improvement Amendments and other applicable laws and standards and provide patient results. The multiple potential users of a genetic test registry should be critically examined, and we question whether this can be achieved by a single product. The quality measures required of clinical laboratories are much more extensive and rigorous – as enforced by mandatory inspections – than existing measures, if any, in research laboratories. Indeed, the elements included in a registry designed for clinician and laboratory use will be very different than a registry intended for genetic research or for public education. This dichotomy is evident in the NIH's own disease information websites in which the data available is different for the general public and the medical community

and differentiated upfront in the menu selection. There is also further divergence in the approach and interest a researcher would have compared to a diagnostic or treatment oriented information seeker. Information from clinical laboratories is directed to clinicians.

Efforts to distinguish these intended audiences through further focus of the requested data elements is essential if an effective and relevant information resource is to be created.

Content for a genetic test registry.

When queried about a variety of test registry elements, most respondents were agreeable to submitting such test information as is currently included in AMP's Test Directories, e.g. Test name, Analytes tested, Contact information, Method, Specimen type/requirements, and Certification information.



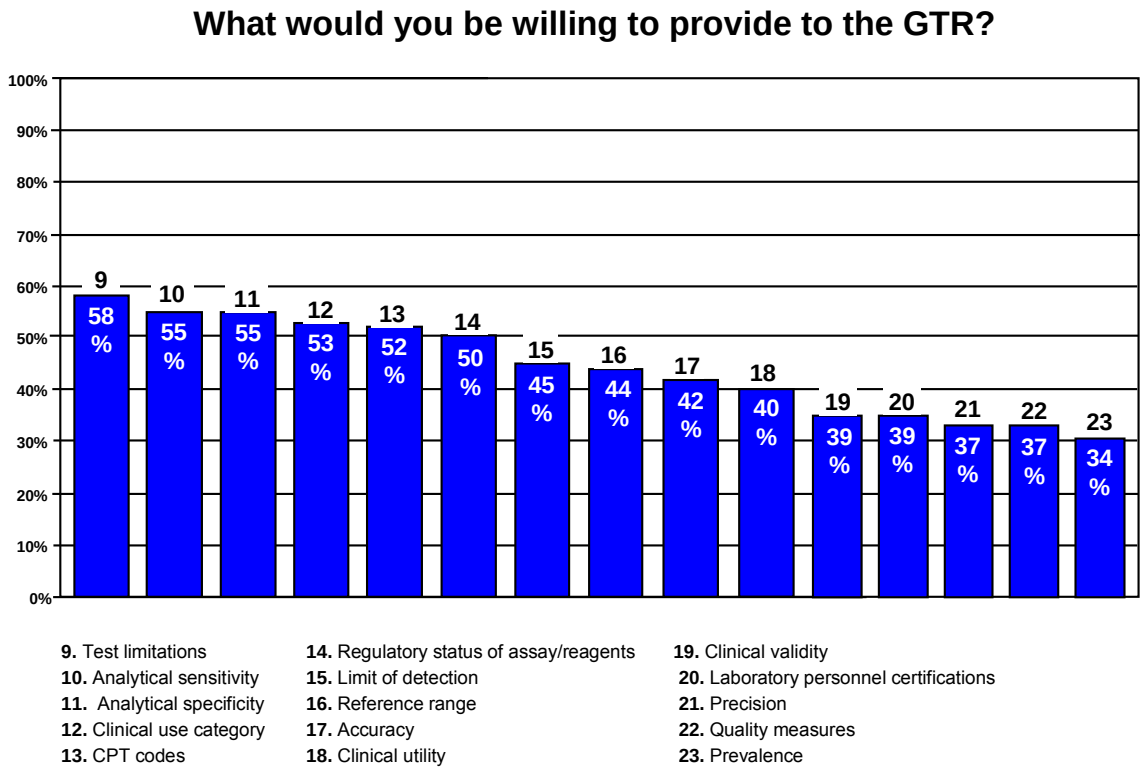
AMP members (less than 60%) were willing to provide analytical and clinical validation information to the GTR.

Responses varied for other data elements provided. Fifty to sixty percent of the respondents were willing to include analytical sensitivity and specificity. Fewer (40% or less) were willing to provide clinical utility and validity. These two measures are complex and evolve continually as data is generated that shed more light on disease pathogenesis. The information is neither static nor

complete. These measures are beyond the sole responsibility of clinical laboratories but involve clinical trials and patient response data. Perhaps, the NIH itself may be suited to compile and provide this information similar to the NCCN guidelines that are issued for cancer treatment purposes.

The generally low interest in submitting performance characteristics for these tests may relate to the knowledge and assurance that come with CLIA certification and CAP accreditation that all laboratory tests in those laboratories are appropriately validated, and that the specific information is readily available from the laboratory director. The perceived use of the directory primarily by clinicians and other laboratories suggests that communication among knowledgeable professionals can be adequately and efficiently accomplished directly with relatively few information elements.

Conceivably, other potential users or audiences of the directory may rank the importance of data elements differently. This underscores the need to distinguish clearly the purpose of the directory, with design linked to intended function.

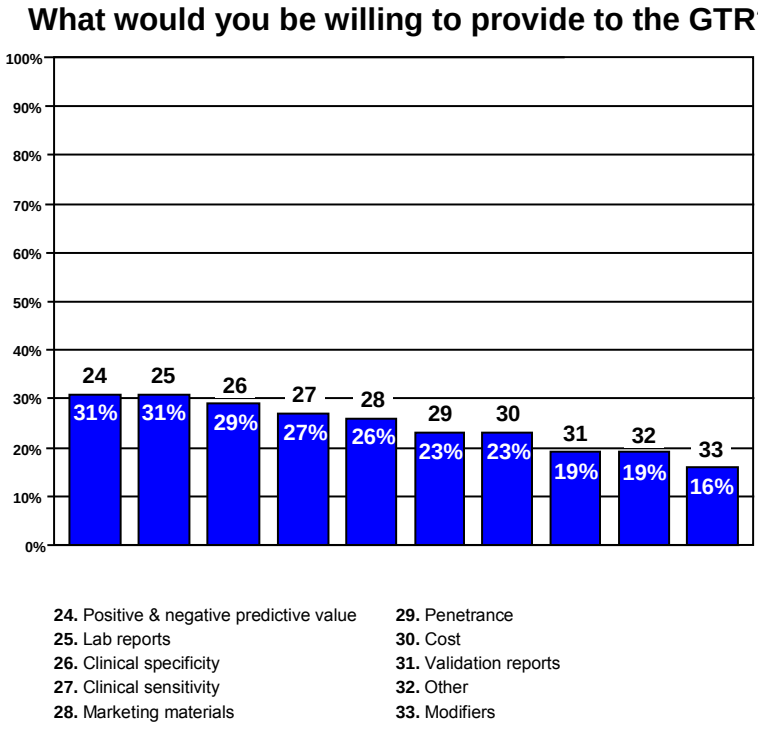


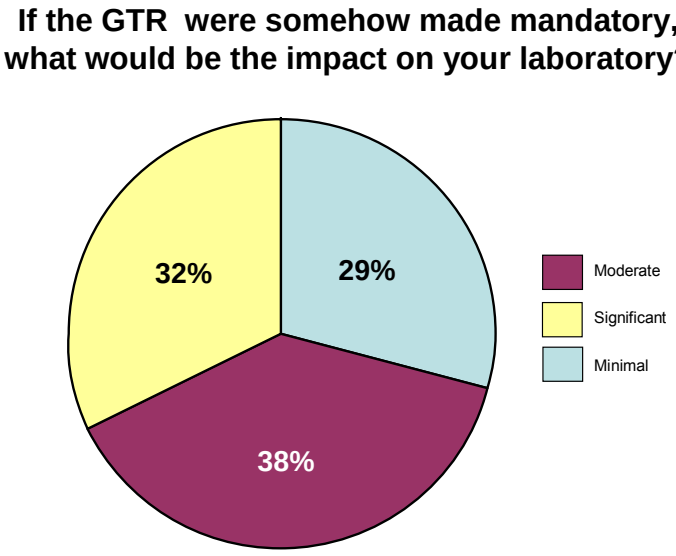
Of note, less than a third of AMP respondents were willing to provide parameters about clinical validity such as clinical sensitivity, clinical specificity, negative predictive value and positive predictive value. CLIA certified clinical laboratories are not required to demonstrate clinical validity. Moreover, clinical laboratories base their clinical validity on supportive medical literature references rather than internal data. This information would be the same for comparable tests

between laboratories and mainly determined by published studies. Preferably clinical validity parameters for various diseases could be provided in a test registry with hyperlinks to references of the supporting studies.

Respondents were less willing (<25%) to provide confidential information such as price and validation reports. The NIH must consider the legal restrictions and implications of some laboratory operations on the submission of data, as well as securing proprietary information or data. Would patent holders be required to submit their patent numbers in lieu of actual data? One concern of any test registry is the risk of litigation based upon perceived or real infringement of patents. Other legal concerns about how the NIH will minimize participants' exposure to litigation due to a user's misunderstanding or misuse of GTR information in decisions ranging from health care to payment decisions. Lack of assurance that such exposure is minimized or, best yet, eliminated may dissuade would-be participants from contributing this information to the GTR.

The percentage of respondents who were willing to provide each of the data elements are listed below





Two-thirds of survey respondents indicated that the GTR would have moderate to significant impact to their laboratory.

Several providers outside the United States were not interested in participating in the registry. Others noted that they currently participate in the AMP Test Registry and/or GeneTests and viewed the Genetic Test Registry as redundant. Twelve percent (8/63) indicated that their laboratories would curtail test offerings if required to participate in the Genetic Test Registry. If the GTR subsequently becomes mandatory many more questions would need to addressed and definitive solutions will be needed for legal purposes.

AMP members expressed opinions about the registry.

The survey allowed for open comments, of which the most widely expressed are discussed here.

Some of the main themes in favor of participation in the GTR included: to provide a resource for clinicians and the public about what tests are offered, to increase transparency of testing, to provide a resource for health care professionals, to streamline testing, to improve data sharing, and to standardize tests.

A main concern was that the extent of detail and content of information requested would be burdensome for limited laboratory resources in order to submit and maintain up-to-date information.

Similarly, respondents were concerned about how information would be used by competitors, payers and regulators. We hope that the NIH will work to ensure that the GTR is designed as a scientific resource rather than as a platform for advertisement or as a mechanism for companies that wish to gain proprietary information about their competitors. The GTR will be most useful if it remains a scientific resource.

A second major concern was curation of the database, without which the resource would quickly become obsolete. We urge NIH to address the issue of the accuracy, standardization, and verification of the data. Would there be independent verification (perhaps through data audits) or would that responsibility rest with the data supplier? Many of the survey respondents expressed concerns about being excluded from directory development processes.

A third major concern was preservation of proprietary information within the NIHGTR. We believe that the NIH should respect the user's right not to disclose proprietary information as essential to the GTR's credibility.

Another concern expressed is that the practice of medicine is performed in a hospital/physician office setting with collaborative management plans that evolve from discussions involving the diagnostic laboratory and the treating physicians. NIH 'endorsement' or 'non-endorsement' of a specific assay (clinical validity) may or may not be applicable for every patient's situation. However, the patient or relatives may feel compelled by the data available from the NIH's GTR website to insist upon a specific course of medical care. Ultimately, the patient determines the treatment, as physicians cannot force a patient to consent to a treatment option. How will the NIH deal with this potential adverse effect?

In view of the role that many AMP members have as laboratory directors, we believe that the comments generated by this survey are particularly relevant to this discussion. Our members may be directly affected by any registry proposal and will have prominent responsibility not only for its content but for how it will be utilized.

Survey respondents support current registries such as AMP's Test Directory and GeneTests.

A common response among survey participants was that the purpose of a new Genetic Test Registry was unclear as there are similar existing resources (AMP's Test Directory, GeneTests, etc) that provide much of this information to healthcare providers and laboratories. In general, there is deep concern over changes to or loss of GeneTests as it currently exists. This is an important resource to the diagnostic and research community. Many voiced concern over NIH involvement with clinical activities, and jeopardizing important aspects of GeneTests (e.g. quality, independence). The hyperlinks in GeneTests to peer-reviewed or published information (e.g., GeneReviews, OMIM) are extremely important.

Our members have long recognized the need among laboratory professionals to effectively communicate about molecular diagnostic testing. The *AMP Test Directory* was developed to address that need and to encourage cooperation among laboratories who are frequently on the forefront in developing and implementing novel, and often, rare genetic tests. We require that the Laboratory Director of each laboratory be listed in the Directory as the primary contact person. The collaboration engendered by this Directory encompasses not only test selection, but frequently embraces test validation and proficiency among its member laboratories. AMP has always

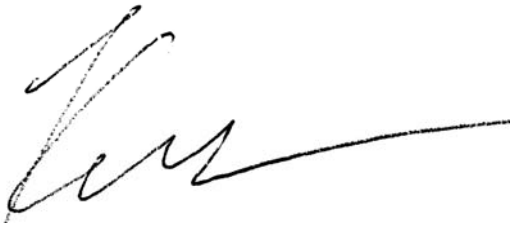
advocated for rigorous adherence to CLIA law and CAP accreditation requirements, and we view our performance of these tests as intrinsic to our medical practice, and subject to the highest ethical standards.

AMP members have also recognized the clinical value of GeneTests/GeneReviews and recommend that this very important resource not be compromised by any new registry proposal. We advise the specific purposes of the registry be more defined and delineated with independent evaluation of these different purposes, acknowledging that some goals might be better addressed through existing registries or mechanisms.

AMP requests that in consideration of the ongoing deliberations by the U.S. Food and Drug Administration (FDA) regarding exercise of its authority over Laboratory Developed Tests (LDTs), NIH proceed with caution in designing a test registry. Furthermore, as we noted in our survey, laboratory tests do not necessarily fall into discrete categories. Overly broad inclusion requirements may create unintended consequences and vague categories.

Thank you for the opportunity to submit this information in response to the Request for Information and for the consideration of our comments. AMP respectfully offers our assistance in designing a practical, useful genetic test directory that will be beneficial to all stakeholders.

Sincerely,



Karen P. Mann, MD, PhD
President