



Association for Molecular Pathology

Promoting Clinical Practice, Basic Research, and Education in Molecular Pathology

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Association for Molecular Pathology (AMP) Comments to the SACGHS Draft Report on the *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of HHS*

December 21, 2007

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The Association for Molecular Pathology (AMP) is pleased to have this opportunity to comment on SACGHS's recent draft statement on oversight of genetic testing in the United States. AMP is an international medical professional association representing approximately 1,500 physicians, doctoral scientists, and medical technologists who perform laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Since the beginning of our organization we have dedicated ourselves to the development and implementation of molecular diagnostic testing, which includes genetic testing in all its definitions, in a manner consistent with the highest standards established by CLIA, the College of American Pathologists (CAP), the American College of Medical Genetics (ACMG), and FDA. Our members populate the majority of clinical molecular diagnostic laboratories in the United States. They are frequently involved in the origination of novel molecular tests, whether these are laboratory developed or commercially developed. Our members proudly accept their responsibilities in assessing the analytical validity, clinical validity, clinical utility, and the clinical utilization of these tests for each specific patient.

The majority of our pathologist members also claim membership in CAP, and they are largely responsible for the current proficiency testing (PT) programs available for genetic testing through that organization, as well as establishing the CAP Laboratory Accreditation Program (LAP) guidelines for inspecting and accrediting molecular pathology laboratories. Our members make up the majority of CAP's molecular genetics and molecular pathology inspector corps. Moreover, the majority of our geneticist members are also members of ACMG, which has worked closely with CAP to establish nationwide proficiency testing programs covering all of the highest-volume molecular genetic tests extant.

The considerations expressed by the Committee's draft document are very familiar to us. Indeed, the kinds of oversight gaps identified by the Committee are precisely the issues that AMP members have been working to address since our founding. Some specific comments follow.

Definition of Genetic Test

Page 27: The definition of a 'genetic test' should be consistent throughout the document. SACGHS uses a very broad definition of a "genetic test", going beyond heritable changes to include somatic variations, and going beyond DNA and RNA to include proteins. Under this definition, the tests would more accurately be called molecular tests rather than genetic tests. In addition, the intended use limitation requires further clarification, because the specific intended use required to classify a procedure as a

“genetic test” is not defined; rather, a single example is provided in this page. In fact, nutritional status is frequently related to states of disease and health, which therefore should be included as a genetic test according to the first sentence. While the first sentence of the definition extends to somatic variants, beyond heritable variants, the intended use and context throughout the SACGHS document seems to specify the tests related to heritable conditions and that “genetic test results generally do not change over one’s lifetime” (page 27). The definition is not used consistently throughout the document, which becomes self-contradictory in the usage of “genetic” test. The document needs to define which intended uses are included in the intended oversight of genetic testing. It might be useful to define which types of molecular tests are being included in the regulatory oversight suggested in this document, *i.e.* oncology, simple single-gene inherited diseases, complex genetic diseases, identity testing for medical purposes, HLA typing (which are already heavily regulated but still would qualify under the genetic test definition used), and infectious disease tests (since these too are molecular, are often laboratory-developed, and can be associated with high risk).

Line 65: While a genetic test is defined, a genomic test has not been defined. The Committee should define the difference between genetic and genomic applications.

Are Genetic Tests Different from Other Clinical Laboratory Tests?

Page 27: SACGHS seems to conclude that genetic tests, given the anticipated breadth of use in the future, should not be considered as significantly different from other clinical tests. Many of our members would agree with this perspective, which is consistent with the approach taken by CMS not to establish a genetic specialty under CLIA. This is consistent with arguments against genetic exceptionalism. But if this is so, then why are genetic tests proposed to need greater oversight than non-genetic tests that are similarly molecular, laboratory-developed, complex, and potentially high-risk? We recognize that there is, at the very least, a perception that genetic tests are categorically distinct in application, if not in performance. There would be no need for the Genetic Information Nondiscrimination Act (GINA) if this were not so.

We also recognize that tests **for heritable diseases** are unique in several respects. Genetic tests are increasingly performed not only for diagnostic purposes in symptomatic patients but for predictive purposes or recessive mutation carrier screening in apparently asymptomatic individuals. While some polymorphisms and variants may be related to certain disease states, these confer predictive value of genetic risk but cause no pathology at the time of testing. Consequently, individuals are asymptomatic and there are no other corroborative laboratory test results. In addition, unlike the situation for acquired clinical disorders, the revealed risk for heritable conditions may extend to other family members. While it is clear that the standards for genetic tests can be no lower than for other tests, we recognize the risk for misinterpretation in this setting by practitioners who are unfamiliar with the limitations of genetic risk assessment. With the increasing deluge of new technology and genetic information, it is likely that a significant lag will persist between what is necessary for the responsible use of these tests and the knowledge base of most clinicians. For this reason, Laboratory Directors and Clinical Consultants should have appropriate expertise in all areas of testing that the laboratory provides. At the technical level, the diagnosis of genetic disease by molecular methods does not differ significantly from the same techniques used to diagnose infectious and neoplastic diseases. Therefore, it is not logical to establish stringent technical and personnel standards for molecular genetic testing that do not also apply to molecular oncology and molecular microbiology testing. Molecular genetic testing *is* unique in the pre- and post-analytic phases, in which particular attention must be paid to appropriateness of test ordering and accurate interpretation with awareness of the full clinical implications of genetic test results. This applies especially to predictive genetic tests and others performed on healthy people, as noted above. The laboratory’s responsibility to the patient does not end with the generation of analytical results, but continues with the interpretation and utilization of that information for a specific patient’s care. Our members, as Laboratory Directors, have always recognized this as their responsibility, both professionally and as dictated by CLIA and CAP.

In summary, risk of harm is present in all areas of health care. No data exists currently to demonstrate that potential harm from clinical genetic testing is greater than that which may result from other medical procedures or clinical tests. We would attribute this to the high standards our members have developed and enforced in their laboratories. AMP recognizes that this field is still very young, and that many of the nuances of Clinical genetic testing have not yet been recognized. AMP's mission will continue to include exploration and awareness of these very issues, and we encourage the Committee to adopt a more realistic position related to clinical genetic testing, recognizing the contribution that the laboratory professionals who are members of AMP bring to this issue. AMP is also concerned that certain types of health-related genetic testing marketed directly to consumers fall outside the current regulatory oversight of CLIA and have the potential to impact public health negatively. We encourage the committee to further explore this issue of the potential harm of health-related direct-to-consumer marketed genetic testing on the public health and to state the distinction between clinical genetic testing and health-related direct to consumer marketed genetic testing.

Requirements for Laboratory Personnel

The Committee recognizes that most genetic testing is performed in laboratories suited to perform high-complexity testing, and that there are federal regulations for laboratory personnel in such laboratories. AMP has always promoted those requirements and is actively engaged in ensuring that our members are qualified to fill those positions, including laboratory directors (MD and/or PhD), supervisors, and testing personnel. AMP was instrumental in establishing specialty certification for pathologists in Molecular Genetic Pathology, and we count among our members the vast majority of individuals (approximately 120 since 2001) with that specialty certification. We believe that these individuals can serve not only as laboratory directors, but are uniquely qualified to perform as the clinical consultants mandated by federal regulations. They are distinctly qualified to “discuss the appropriateness of the tests ordered; the interpretation of test results; and the diagnosis, treatment and management of patient care with the laboratory’s clients.”

The recently published OECD Guidelines for Quality Assurance in Molecular Genetic Testing underscored the requirement that the qualifications for laboratory director include formal training in molecular genetics and, where available, certification in the specialty of clinical laboratory molecular genetics, or another relevant discipline. Although CMS may have determined that recognition of a genetics specialty was not a useful approach at this time, we are not oblivious to the need for specifically trained laboratory directors to oversee genetic testing, and we will continue in our mission to provide appropriately trained individuals to fill that need.

CLIA regulations already stipulate the responsibilities of the Laboratory Director and the Clinical Consultant. We recommend that these roles be re-emphasized with regard to genetic testing. Recognizing that different kinds of genetic tests may demand different levels of expertise, we suggest that fulfillment of these responsibilities be addressed through an invigorated inspection program staffed by trained professionals. We would like to encourage SACGHS to recommend that CMS work with the different organizations such as AMP to develop interpretative guidelines for their inspectors regarding the levels of expertise that are required for different kind of genetic testing.

Quality Assurance/CLIA, FDA Regulations

At a time when reports about molecular genetic testing appear in the lay press on a daily basis, numerous bills addressing quality assurance in this area are circulating in Congress, and the FDA has proposed new strategies to increase its own oversight of these tests. This area is now the subject of more intense scrutiny by other agencies than any other sector of the clinical laboratory. Defining molecular genetic testing explicitly would allow for appropriate regulation and oversight of these applications by the agency best suited and legally mandated to performing these functions. The majority of these tests are performed using in-house, laboratory-developed assays in the absence of FDA-licensed kits, and therefore

represent a practice of laboratory medicine that is under the purview of CLIA, as is appropriate, and not FDA. While FDA could play an important consultative role in the oversight of laboratory developed tests, CMS, as the agency with responsibility for enforcing CLIA regulations, should continue to play its long-standing role as the primary authority in the oversight of these clinical genetic testing services. Defining these molecular targets as regulated analytes would promote expansion of proficiency testing programs, better oversight of direct-to-consumer marketing of clinically dubious “genetic” tests, and reassurance of the public and members of Congress.

We support enhanced standards for appropriate training of genetics laboratory directors and other individuals involved in test interpretation. We feel that this could best be judged by training and experience rather than specific board certifications, but support exploring these issues in more detail. Our organization, which represents the broadest constituencies involved in molecular diagnostic testing, is eager to work with the Committee in these deliberations.

It is important to realize that voluntary standards organizations, such as the Clinical and Laboratory Standards Institute (CLSI), create detailed practice guidelines which effectively fill many of “holes” that some individuals believe exist in the FDA and CLIA regulatory framework. This voluntary consensus process brings together government officials, usually from FDA and CMS, with professionals that understand clinical practice and representatives from industry who have deep understanding of the technologies, to effectively address issues for which neither FDA nor CMS has sufficient staff or expertise. The resulting “team approach” in which government, industry and practicing clinicians work together is a viable alternative to regulation for many genetic and genomic tests.

Voluntary Registration

With regards to registration efforts, we would like to point out to the committee that currently all CLIA certified laboratories are required under CLIA to submit to CMS information regarding all tests currently offered and technology used to perform these tests. Furthermore, each laboratory is even required to update CMS when changes in technology occurred. AMP is concerned that creation of a voluntary registry would be a duplicative effort as CMS is already provided this information.

Proficiency Testing

We agree with the SACGHS report that proficiency testing is an effective measure to assess performance of clinical laboratories. We support the recommendation to increase the availability and utilization of proficiency testing for genetic assays and to expand the list of regulated analytes to encompass existing and near-future needs in genetics. Timely and rapid updates are needed to keep pace with the development of new genetic tests. However, other options should be considered until the list of regulated analytes is updated and a process for regular review and additions is implemented.

We support the CAP/ACMG proficiency survey program which is available for all of the relatively common genetic tests. Additional analytes can be included relatively quickly as new genetic tests are introduced into a number of laboratories. However, many genetic tests for rare disorders are offered by only a few laboratories. For rare disorders, CAP is facilitating sample exchanges between laboratories that test for the same disease, and we support this. In fact, AMP has been administering programs along this line for several years.

Alternative assessments should also be considered, with funding for pilot programs to assess feasibility. For example, technology-challenges may be an efficient means to assess proficiency for a large number of disorders, but potential problems must be resolved prior to full implementation. Prior published work on this type of assessment and professional organizations in molecular diagnostics should be consulted to optimize the programs.

The availability of reference material (samples containing mutations of interest) for proficiency testing is also problematic. Resources are needed to obtain, maintain and certify reference material, either through government agencies (*i.e.*, CDC, NIST) and/or private enterprises (non-profit and for-profit).

We encourage strengthening CLIA to enforce proficiency requirements and strengthening CMS oversight of proficiency test providers. Laboratories should be enrolled in the CAP/ACMG or equivalent

proficiency programs, with meaningful actions for poor performance exercised during laboratory inspections.

Clinical Validity

AMP is well-acquainted with this difficult issue. Our members are regularly involved in clinical validation studies, whether through formal research projects or through local collaborations with clinician-investigators. Our members are frequently the early adopters of emerging concepts, methodologies, and tests. We understand what is required to demonstrate clinical validity, especially that the ability to do so will often go well beyond the capabilities of any one laboratory. For that reason we favor reliance on the peer-reviewed literature, consensus statements by professional practice organizations such as CAP, ACMG, and AMP, and collaborative epidemiologic studies by CDC and other agencies.

Effective Communication and Decision Support

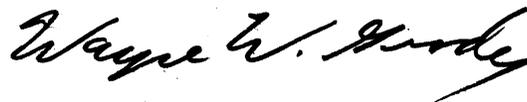
In Chapter 6, the report states, "...[T]he nature and complexity of genetic testing requires a different degree of communication between clinician and the laboratory both at the point of test ordering and when the result is reported."

AMP recognizes the role of the laboratory in the reporting of molecular test results and this topic is a central focus for our organization. The AMP Clinical Practice Committee organizes work groups to address issues related to ordering and reporting practices for a number of molecular tests (Cystic Fibrosis screening, BCR-ABL, Bone Marrow Engraftment), and we have been involved in the development of several reporting guidelines (publications on molecular test reporting, nomenclature). Furthermore, both CAP and the JCAHO have requirements that facilitate effective communication of laboratory results to clinicians and patients

Moreover, as noted above, CLIA requires that laboratories provide clinical consultants precisely to provide clinical guidance with regard to laboratory tests, a role that AMP has fully and enthusiastically embraced. Hence, we are dismayed that the report fails to recognize the contribution of eminently qualified laboratory professionals in its solutions to this gap, and focuses on impersonal mechanisms, active or passive. Entertainment of a "just-in-time" educational approach suggests actions motivated more by desperation than insight. Certainly, these approaches may be useful as we move forward, but the Committee should know that they have a cadre of laboratory professionals at their service who are very willing and capable of filling many of these "gaps".

We reiterate our commitment to participate not only in pursuing the success of this project, but in translating the results of this effort for the betterment of the public's health and well being. Please contact me at wgrody@mednet.ucla.edu if we can provide further information.

Respectfully yours,



Wayne W. Grody, MD, PhD
Chair, AMP Professional Relations Committee