Association for Molecular Pathology
Promoting Clinical Practice, Basic Research, and Education in Molecular Pathology
9650 Rockville Pike, Bethesda, Maryland 20814
Tel: 301-634-7939 ▪ Fax: 301-634-7990 ▪ Email: amp@asip.org ▪ *www.amp.org*

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Federal Coordinating Council for Comparative Effectiveness Research
Department of Health and Human Services
200 Independence Ave. SW
Washington, DC 20201

Dear Coordinating Council Members:

The Association for Molecular Pathology is pleased to have the opportunity to provide comments to the Federal Coordinating Council for Comparative Effectiveness Research (the Coordinating Council) on the subject of comparative effectiveness research (CER) and share our recommendations on priority areas on which to focus CER activities.

AMP is an international medical professional association representing approximately 1,600 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.

CER is garnering substantial attention in Congress and among other policy makers who see it as a method to examine the comparative effectiveness of treatments, including how they relate to coverage and reimbursement decisions. Diagnostic tests will most definitely be included in this paradigm, especially when the effectiveness of treatments will vary among different population subgroups. Unfortunately, the value of diagnostics in improving clinical outcomes has not been appreciated adequately in the past; therefore, considering the role of genomics under CER will be critical.

In order for CER to be a success, it will be essential to train experts in diagnostics (including molecular diagnostics) in current health services research methods as well as to train health services researchers in the technical areas they will assess. This cross training will be essential to ensure that the research methods are technology appropriate. For example, in molecular diagnostics, there are situations where a prospective, randomized clinical trial will not be feasible

and/or a research outcome could be achieved through an alternative study design such as a retrospective analysis of available data. Further, outcomes studies conventionally assess technologies as interventions, often using the diagnostic test as a benchmark or endpoint, without consideration of the characteristics of the diagnostic. There is much less experience in assessing the role of the diagnostic test itself in appropriate and cost effective management of individual patients. Therefore, AMP encourages the Coordinating Council to invest in the cross-training of researchers and diagnostics experts as well as to build the infrastructure within the agencies to understand and review data from different types of technologies.

While not specifically requested for the listening session, AMP would like to provide the Coordinating Council with the following list of high priority areas of CER identified by the Association's membership:

Infrastructure. Infrastructure should be developed to design a model and process for CER regarding laboratory tests. This should include the following:

- The creation of a panel of experts consisting of physicians and scientists, including laboratorians with molecular diagnostics expertise, economists, and reimbursement specialists.

- AMP encourages the creation of an electronic clearinghouse for information on CER projects similar to www.clinicaltrials.gov. Reliable tracking and coordination of CER activities will be crucial to avoid duplication and redundancy and to ensure appropriate use of CER funds. Moreover, access to the tracking data should be available to all entities conducting CER, both from the private and public sector.

- AMP encourages the development and adoption of standards for the collection and storage of data from genetic testing laboratories in order to establish an archive, and to ensure interoperability among databases. Moreover, these databases should include information on the reason for the test, the type of test, test results and availability of genetic counseling and testing centers.

- It should be required that data from technologies and tests being assessed be generated from CLIA-, CAP-, ISO-, or FDA- certified institutions. Consulting with or recruiting professionals from the molecular pathology community will aid the assessment committees in evaluating the quality of proposals and the data generated.

Clinical Outcomes in Pharmacogenetic Molecular Pathology. As information becomes available that relates clinical outcomes to genetic variations, the regulatory, medical and lay communities expect that it will be immediately incorporated into routine clinical care. FDA labeling that relates pharmacogenomic response to maintenance dose, for example, has created demand for both testing and reimbursement in the absence of large clinical trials that demonstrate the effectiveness of such laboratory testing by comparison with either "usual care" or alternative approaches. An example of this is the use of daily home prothrombin time testing under medical supervision during the first few weeks of anticoagulation versus *CYP2C9/VKORC1* mutation testing. Funding for large, carefully designed comparative effectiveness trials for molecular tests should be coupled with funding for observational comparative effectiveness studies that complement randomized controlled trials by including patients who may be tested, but do not meet the inclusion criteria for prospective trials.

Evaluating the Effectiveness of Genomic Tests and Clinical Molecular Diagnostics Laboratories. For the public to reap the benefits of effective molecular tests, it is critical that all laboratories meet high performance standards and participate in proficiency testing programs utilizing appropriate reference and control materials.

- *Development of reference materials.* AMP recommends funding for a program to develop reference materials, exploiting traditional and innovative methodologies, to aid the continued advancement of quality measures in the field of laboratory medicine.

- *Novel ways to evaluate laboratory proficiency*. AMP supports the development of proficiency testing methods as alternatives to distributing surrogate test specimens. As is evident in cytogenetics, it is impossible to send out surrogate specimens for every known translocation and rearrangement. Categorical methodologic proficiency testing should be evaluated as one such alternative.

- *Methods to evaluate novel and emerging types of genomic testing.* AMP believes efforts should be taken to develop appropriate quality assurance for new technologies such as whole genome sequencing, using carefully designed methods to determine the relative effectiveness of various quality assurance methods in improving laboratory testing and ultimately clinical outcomes.

Interpretation and Reporting of Molecular Pathology Test Results. The data collected by AMP's Clinical Practice Committee in recent years indicates there is room for improvement regarding the transmission of genetic test information. The influence of this information on ultimate clinical outcomes cannot be overstated and could be an important area for CER. Studies to evaluate the use of information by clinicians are critical to understanding clinical utility and effectiveness.

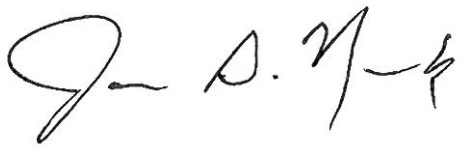
Valuation and Reimbursement. Government and healthcare payers should use CER to identify which laboratory services add benefit to patient care and work to implement valuation and reimbursement strategies to help improve clinical outcomes. Reimbursement of diagnostics, including molecular based tests, is extremely poor. Despite the possibility of saving the healthcare system thousands of dollars per patient and improving the quality of care, diagnostics have been historically under valued. AMP hopes that any CER activities will include research to explore the value, beyond simply cost, of diagnostic tests to patients, providers, payers and the larger health care system. . It has been noted that the "value" of diagnostics in general is not well studied. Assessing the role of laboratory information in medical decision making could improve appropriate utilization of laboratory tests and clinical outcomes, with potential savings to healthcare. Although reimbursement is one important function of the current coding system (CPT), these codes are also intended to reflect clinical evaluation and management practices. AMP believes the health care system is in need of an entirely new coding vocabulary to describe the types of "evaluation" and "management" practices that are emerging with regard to molecular and genomic testing.

Comparative Methodology Research. Many different technical approaches are available for generating the same genetic test result. Relating testing approaches to health outcomes is a neglected area of comparative effectiveness research. AMP supports the evaluation of a multiplicity of platforms in the development and evaluation of companion diagnostics. This approach is not only good science in that it promotes refinement and improvement in

methodologies, but is critical to the evolution of medicine. There is no question that therapeutic effectiveness is influenced by test methodology. A prime example of this is the selection of patients with breast cancer for treatment with Herceptin. Determination of eligibility for treatment can be through fluorescence *in situ* hybridization (FISH) testing or through imunohistochemical methods. Discrepancies between the two methodologies have resulted in patients being inappropriately treated, either exposing them to potential drug side effects without therapeutic benefit, or simply in not treating them with a potentially beneficial drug. These data can be obtained using retrospective studies, but they do need to be pursued.

Thank you for your attention and consideration of our comments. AMP hopes to continue to be a valuable resource to you as the Coordinating Council works to implement and advance CER. Please contact us if you need any clarification or further information.

Sincerely,



Jan A. Nowak, MD, PhD
President