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AMP Presentation to the CMS Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) on February 25, 2009

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I. Introduction

Good Morning. I represent the Association for Molecular Pathology, a medical and professional society comprised of approximately 1,700 physicians, doctoral scientists, and medical technologists. We are here to offer the Committee our expertise and perspective.

II. Desirable characteristics of evidence for most genetic and genomic tests should not differ from those associated with diagnostic testing or other diagnostic medical procedures, generally.

However, DNA and RNA-based tests are heterogeneous in their methodologies and wide-ranging in their clinical applications. Moreover, genetic and genomic tests are integral to the concept of "Personalized Medicine."

An extraordinary volume of new discoveries has combined with evidence-related issues not necessarily specific to genetic testing, to present historically unique challenges in evidence evaluation. Available studies may be limited in size, number, and scope, and study subjects may vary in disease course and presentation. Novel information from genome-wide association studies may present new statistical challenges.

Importantly, both the current and previous administrations have given furtherance of personalized medicine a prominent place among their healthcare policy goals. The evidence standards on which CMS coverage decisions are based will play a major role in the extent to which progress in personalized medicine is made, and the speed with which genuine advancements are introduced into medical practice.

III. CLIA and professional society laboratory accreditation programs help ensure analytic and clinical validity of genetic and genomic tests within individual laboratories.

Analytic validity encompasses analytic sensitivity and specificity, assay reproducibility, linearity (for quantitative tests), and consistency in response to limited changes in preanalytic and analytic variables. Yet the meaning of sensitivity and specificity may vary with the assay under review, and the diagnostic question posed.

Some genetic tests lack a gold standard for comparison of results. In these cases, collaborative studies using a single, large, representative panel of well-characterized samples that are tested and reported blindly under routine laboratory conditions, are desirable. However, such ideal studies are rarely performed.

Fortunately, molecular diagnostic methods tend to excel analytically. Although assays differ in technical features and clinical applications among laboratories and institutions, the CLIA regulations and the laboratory accreditation program of the College of American Pathologists help ensure their analytic and clinical validity.

IV. Clinical and analytic validity should be prerequisites to non-investigational use of genetic and genomic tests.

However, those of us who are proponents of evidence-based medicine must recognize that it has inherent limitations when applied to genetic and genomic assays. For these tests, evidence of analytic and clinical validity may be adequate, but clear demonstrations of clinical utility may be lacking, even for

tests widely believed to have medical value. In the absence of direct proof of clinical utility, an important role for physicians' experience and judgment remains.

Medical assessments are rarely based on a single test alone, genetic or otherwise, but instead consider patient history, physical signs, and the results of other diagnostic modalities. Detection of genetic variants (*Kras* being one example) supplements the pathologic evaluations of tumors. DNA-based testing is combined with clinical and other laboratory data in the diagnosis of inherited disorders. The multiplicity of factors contributing to drug metabolism renders clinical judgment essential for the use of pharmacogenetic testing in medical practice.

V. The absence of high quality, direct outcome-based data often necessitates reliance on surrogate markers.

Although changes in physician-directed patient management may indicate a consensus within the medical community about the value of a particular test, they do not necessarily ensure that clinical utility of the test has truly been demonstrated. In some instances knowledge later acquired will cause rethinking or refinement of practice changes.

Indirect or intermediate outcomes can be helpful in assessing the clinical utility of a test. Yet surrogate markers can be misleading because they may overlook the effects of variables not considered. Again, because direct outcomes-based data is rarely present for genetic or genomic tests, clinical judgment, context, and expert opinion remain necessary to assess utility, and argue against rigidity in CMS' approach to coverage.

VI. Ethical issues ordinarily should not adversely impact the rigor of clinical studies of genetic testing.

However, there may be areas for which ethical issues could potentially affect study quality. Diagnostic testing for heritable diseases has implications for a patient's family members. Studies of cancer patients address diseases that are often fatal, and for which therapies may be highly toxic. Concerns about the implications of genetic information, or the apportionment of potentially useful diagnostic approaches among terminally ill patients could potentially hinder the recruitment of study subjects or bias results in unforeseen ways.

VII. The age of the Medicare population usually should not adversely impact the generation or interpretation of clinical studies of genetic testing.

However, it is possible that age-related attitudinal or demographic characteristics, or a greater overall likelihood of death, could potentially interfere with study recruitment and/or bias results. Moreover, if test validation has not been performed on significant numbers of older patients, or is unreflective of their disease status, generalization of results to Medicare patients may not be appropriate. Lastly, in disorders characterized by age-related expressivity, disease features that could impact assay performance may be different in Medicare patients than in the larger affected population.

VIII. As experts in the clinical use and technical aspects of genetic and genomic testing, the Association for Molecular Pathology stands ready to assist the Committee, CMS, and its contractor medical directors to help address the complex evidence-related issues associated with genetic and genomic testing.