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AMP Comments regarding the Agency for Healthcare Research and Quality (AHRQ) draft Technology Assessment, *Systematic Reviews on Selected Pharmacogenetic Tests for Cancer Treatment*

The Association for Molecular Pathology (AMP) is an international medical professional association representing more than 1,800 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 the Clinical Laboratory Improvement Act (CLIA), the College of American Pathologists (CAP), the American College of Medical Genetics (ACMG), and the United States Food and Drug Administration (FDA). Our members lead and work at the majority of clinical molecular diagnostic laboratories in the United States and laboratories in many other countries. We are frequently involved in the development of novel molecular tests, and in the validation of laboratory developed or commercial assays.

We very much appreciate the authors' statistical expertise of this technology assessment report; however, we note a number of shortcomings that compromise the relevance of the report's conclusions. We believe that many of these shortcomings could have been avoided had there been prior input from clinicians and molecular pathologists intimately familiar with the performance and clinical utilization of these tests.

This lack of clinical input is immediately evident in the definition of genetic test adopted by the study:

"The analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes. Such purposes include predicting risk of disease, identifying carriers, establishing prenatal and clinical diagnosis or prognosis. Prenatal, newborn, and carrier screening, as well as testing in high-risk families, are included. Tests for metabolites are covered only when they are undertaken with high probability that an excess or deficiency of the metabolite indicates the presence of heritable mutations in single genes."

Two of the three tests evaluated in the study do not fulfill this definition, highlighting a superficial understanding of the biology underlying these tests and how they are used clinically. Acknowledging that pharmacogenomic tests can be a special type of genetic tests, it is noteworthy that the authors fail to appreciate that of the three tests evaluated in the report, only the CYP2D6 qualifies as being heritable. Alterations in the KRAS gene and in the BCR-ABL translocation are not heritable, but are tumor specific, intrinsic to the neoplastic process. This distinction is not moot. Polymorphisms that influence drug metabolism can be identified in healthy individuals and can have bearing on dosing or drug selection of numerous therapeutic agents. Tumor specific genetic

changes, in contrast, have significance beyond simple choice of drug, influencing disease recognition, disease prognosis, tumor aggressiveness, and potential response to multiple and combinational chemotherapeutic agents. Therefore, the value of a genetic test in specific malignancy is more than for the selection of one specific chemotherapeutic agent. These genetic changes need to be considered in the clinical context of the specific tumor for each patient. The clinical decision to treat or not treat with a specific agent takes into account all of these factors and is not made on the basis of a single test result.

The naiveté of the concept of "one bioanalyte – one drug" becomes apparent in consideration of the drug dasatinib, one of the drugs used in the setting of Bcr-Abl+ leukemias resistant or intolerant to prior therapy. There is evidence that this drug also has activity against Src family kinases as well as Flt3 and c-Kit. (Corey, et al, Clin Cancer Res 16:1149-58, 2010).

Additionally, pre-analytic issues are critical to the performance of each assay, and must be given consideration. For example, the choice of method used for the detection of a mutation will have a major impact the sensitivity of the assay, with limits of detection ranging from 1 cell (or less) in one million for a PCR approach targeting the mutant allele, to the requirement that greater than 15-20% of cells contain the mutation for most sequencing methods. The selection of pure tumor cells prior to sample processing can further exaggerate apparent variations in analytic sensitivity, so that a study utilizing relatively insensitive conventional sequencing, along with selection for tumor cells, will likely vastly underestimate the true occurrence of the mutation in a case series being studied. These "false negative" results will lead to an inaccurate assessment of the clinical correlation or clinical utility.

In January 2009, AMP published laboratory practice guidelines for detecting and reporting BCR-ABL drug resistance mutations in CML and ALL. Those guidelines effectively discussed the state of knowledge regarding BCR-ABL mutation testing not only in considering analytical factors, but also in the clinical contexts for which such testing has import (Jones, et al, J Molec Diag 11:4 – 11, 2009). We asked Dr. Dan Jones, one of the authors of that report, to comment on the technology assessment's conclusions regarding BCR-ABL mutation testing:

Key Question 1:

The commentary in Key Question 1 is fair. However, the literature on CML and mutations is pretty vast right now and some studies have been omitted. Therefore, some qualifications on the conclusions reached in that Key Question is recommended. The Authors need to emphasize that there are big differences in the incidence of mutations (particularly T315I) and the therapy responses depending on the phase of disease (chronic, accelerated and blast phase) and lumping all together as "CML" is probably not useful for interpretation of test results.

Key Question 2:

There is some gathering data on levels of drug metabolizing genes on responses to TKIs but agree that this question is not really relevant to interpretation of BCR-ABL testing.

Key Question 3:

I would encourage the Authors to include the reference Jabbour E, Jones D, Kantarjian HM, O'Brien S, Tam C, Koller C, Burger JA, Borthakur G, Wierda WG, Cortes J. Long-term outcome of patients with chronic myeloid leukemia treated with second-generation tyrosine kinase inhibitors after imatinib failure is predicted by the in vitro sensitivity of BCR-ABL kinase domain mutations. Blood. 2009 Sep 3;114 (10):2037-43

which does show (retrospectively) that if mutations are matched to the Kd for in vitro inhibition of second (or third) TKIs that there are differences in outcome in chronic phase CML. This would contradict the general statement in the first line of 3.4 Discussion.

Given the already extensive data on in vitro responses to particular TKIs, a prospective study is unlikely to be done in CML to randomize treatment choice based on mutation result. However, the European LeukemiaNet guidelines (Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J et al. Chronic Myeloid Leukemia: An Update of Concepts and Management Recommendations of European LeukemiaNet. J Clin Oncol 2009 November) are an attempt to codify current clinical practice on how detection of T315I impacts choice of therapy.

The homoharringtonine clinical trial (published in abstract form, Khoury HJ, Michallet M, Facon T, Guilhot F, Jones D, Hochaus A, Benichou A-C, Schwartz R, Cortes J. Safety and efficacy study of subcutaneous homoharringtonine (SC HHT) in imatinib-resistant chronic myeloid leukemia (CML) with the T315I BCR-ABL kinase domain mutation – initial report of a Phase II trial. Blood 110(11):318a, 2007.) and to some extent the TKI-MK-457 clinical trial (Blood, 15 January 2007, Vol. 109, No. 2, pp. 500-502) use presence of the T315I mutation as enrollment criteria, based on the selective responses of those particular agents against that mutation.

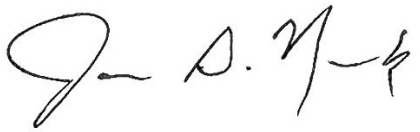
Key question 4:

Different 2nd and 3rd-generation TKIs (and non-KI therapies) have different toxicity profiles so the use of BCR-ABL mutation data to influence choice of a particular TKI will have benefits and harms to patients.

In summary, we believe that if the authors had access to appropriately qualified clinical and technical input, the value of their study would have been markedly enhanced. Certainly, surveying the literature at a single point in time for a rapidly growing field suffers the danger of being irrelevant by the time the results are analyzed. This deficit would be very apparent to anyone with true clinical experience. As it is, the conclusions can only be regarded as having limited marginal value. We offer the Guidelines published by AMP in 2009 as an example of a rational, coherent approach to assessment of test efficacy and utility that recognizes that such an assessment must be a dynamic, clinically relevant process. We strongly urge that future meta analyses of published reports include appropriate scientific and clinical expertise to better design the inquiries and better assess the outcomes for reasonableness. We further urge that any such technical assessments be presented in the appropriate clinical contexts. We believe that introducing these elements will significantly enhance the validity and utility of future studies.

AMP is eager to provide whatever information that may assist the Agency's work in this area. Please feel free to contact me at jnowak51@comcast.net.

Sincerely,



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