



Association for Molecular Pathology

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

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The Association for Molecular Pathology (AMP) appreciates the opportunity to comment on the recent AHRQ Draft Report, “Update on Genetic Tests Currently Available for Clinical Use in Common Cancers.” In reviewing this update in light of your 2006 and 2011 reports, AMP has identified methodologic flaws in the data gathering process that have led to gaps in the report’s findings. These concerns would likely have been obviated by including pathologists with subspecialty expertise in molecular pathology, i.e., the medical practitioners who are largely responsible for performing and interpreting molecular tests in solid and hematopoietic tumors, as well as geneticists with subspecialty interests in hereditary cancer syndromes, in drafting and reviewing the report. Molecular pathologists and cancer geneticists primarily work at academic medical centers and cancer centers; AMP recommends that they and their laboratory test menus should be included as informational resources in this TA. AMP will be happy to provide a list of such experts to AHRQ. In addition, a few examples of cancer center and academic medical center molecular pathology laboratories include those of MD Anderson, the test menu of which is readily available on the internet, Memorial Sloan Kettering, and the University of Pittsburgh Division of Molecular Genomic Pathology. However, it should be understood that molecular pathology procedures for cancer are likely performed by well over a hundred academic medical centers.

While providing a summary of the commercial laboratories, the report fails to capture and describe the numerous tests validated and performed in academic and hospital based labs throughout the US. It is unclear why the report’s authors chose to only focus on larger commercial labs and not the molecular pathology labs providing a significant portion of these clinical tests. Further, AHRQ’s contracted Evidence-based Practice Center (EPC) has produced a scattered, unorganized list of tests comprised of antigen, protein, biochemical, flow cytometry, in situ hybridization, and immunohistochemistry tests, along with some amplification-based molecular tests that use PCR, sequencing, or chip based variant detection. Their list also includes somatic disease, inherited predisposition to cancer - encompassing both Mendelian diseases and dubious tests for low odds ratio cancer predisposing single nucleotide polymorphisms obtained from GWAS studies, drug metabolizing enzymes or other general pharmacokinetic or pharmacodynamics characteristics, and tests for genetic variants that predict of response or lack of response to specifically targeted therapies. Hence, the list is disorganized, incomplete and at times, incorrect in its characterization and inclusion of specific tests for cancer.

In the stated inclusion criteria, the EPC incorporates tests that have “applications in the common solid tumors (breast, lung, colorectal, pancreas, etc.) as well as tests that are used in hematologic cancers (leukemia, lymphoma) and are already available in clinical practice.” As discussed in the previous paragraph, the EPC has chosen to include an extremely broad range of test types, many of which would not typically be considered as molecular pathology or even “genetic” tests. As a result, in some cases there are but a few examples from test categories that themselves potentially represent significant numbers of tests.

In order to achieve manageability, completeness, and coherence we recommend only including tests that interrogate or measure levels of DNA or RNA, unless the test represents a direct alternative to a DNA or RNA-based test. Further, if the horizon scan is to include tests used in both somatic and inherited diseases, as well as drug metabolizing alleles, the assays should be separated in tabular form in this manner. If organ specificity is also used, tests should still be broken down into these categories under the specific organ. There are many inherited conditions that predispose to cancer, most of which do not appear to have been included in the horizon scans to date. Inherited cancer syndromes often

result in a multiplicity of cancer types. Therefore, while organ specificity can be useful for the categorization of some inherited cancers, it is also very limiting approach to classifying tests for these entities.

Because somatic tests usually have very different implications and uses than tests for inherited cancer syndromes, these should also be separately identified. In addition, it should be noted that increasingly somatic tests are being applied in more than one cancer or organ type. AHRQ should also be aware that methodologic breakdown into amplification-based molecular diagnostics, in situ hybridization, and other categories, e.g. flow cytometry, if these are to be included. There are significant numbers of these types of assays, and the failure to understand the methodologic and clinical differences in and implications of these types of tests probably contributes to the scattered and very incomplete nature of the report. Finally, expression array testing, which represents a novel class of assays that are largely proprietary commercially provided tests, should be distinguished from more conventional tests that are performed by multiple laboratories because of the differences in their delivery models, their novelty, and their more limited use and/or the more limited evidence regarding their clinical performance.

The EPC's search methods should be expanded to include an advisor who is an expert in the relevant testing to greatly enhance the search design, interpretation, and the application of results. The search terms the EPC used appeared to be far too limiting. For example, somatic genetic tests are frequently referred to as molecular pathology or molecular oncology tests by practitioners in the field, and there many other search terms that could be used to capture tumor testing. The websites selected for review were extremely focused commercial laboratories, many of which have limited and/or unusual test menus. The failure to include cancer centers and academic medical centers not only contributed to the absence of many tests within the same categories as those that have been included, but conveyed to the investigators and therefore to AHRQ and your readers a false understanding of the actual delivery of these services.

To improve the utility and accuracy of this report, AMP encourages the authors to include tests offered by laboratories in cancer centers and academic centers and further organize the tests based on type, technology, tumor site, and whether or not the test is for a somatic or inherited mutation.

Lastly, the American Medical Association (AMA) CPT Editorial Panel has published new Molecular Pathology CPT codes that went into effect on January 1, 2013. These codes include placement of over 650 molecular pathology tests, including many for somatic tumor testing and syndromes that predispose to cancer as a primary feature. These CPT codes are an invaluable listing of amplification-based molecular tests, and can serve as an important resource within the EPC's gray literature.