



January 27, 2010

Joint Comments from the Association for Molecular Pathology and the College of American Pathologists to the Medicare Evidence Development & Coverage Advisory Committee, Centers for Medicare & Medicaid Services

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.

The College of American Pathologists, the leading organization of board-certified pathologists, serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine. The College of American Pathologists is a medical society serving more than 17,000 physician members and the laboratory community throughout the world. It is the world's largest association composed exclusively of pathologists and is widely considered the leader in laboratory quality assurance. The CAP is an advocate for high-quality and cost-effective medical care. The more than 17,000 pathologist members of the College of American Pathologists represent board-certified pathologists and pathologists in training worldwide. More than 6,000 laboratories are accredited by the CAP, and approximately 23,000 laboratories are enrolled in the College's proficiency testing programs.

Pharmacogenomics is often touted as a new field but this not entirely true. Physicians have been tailoring treatments for individual patients for decades, sometimes by monitoring physiologic responses to specific drugs, sometimes predictively, considering a patient's size and metabolic capacity as determined by specific laboratory tests. The treatment of malignancies, in particular, has always been based on the specific biology of the neoplasm as it presents in the individual patient. This is what pathologists do: we study the tumors of individual patients, we measure them, weigh them, examine their histology, their biochemistry and their genetics so we can classify them, stage them and provide

specific information for the patient regarding the tumor’s behavior, prognosis, and optimal treatment choices. In some circumstances, we can address specific therapeutic targets for certain tumors. Evaluating estrogen and progesterone receptors in breast cancers has been standard pathology practice for nearly 30 years. Our understanding of tumorigenesis has become increasingly molecular as we’ve discovered the genetic and biochemical underpinnings of cancer. It is critical to understand that what some might consider isolated “biomarkers” are intrinsic elements associated with specific neoplasms, which can convey prognostic information that goes beyond the response to a specific pharmacologic agent. HER2 is a good example.

This MEDCAC panel is to consider the utility of five pharmacogenomic analytes in determining therapeutic response to specific pharmacologic agents. These analytes represent a spectrum of pharmacogenomic tests, demonstrating varying degrees of clinical use history and clinical utility. In addition, they demonstrate possible differences in clinical impact. The drugs in question are, after all, different agents used to treat different diseases in different clinical situations. It would be naïve to expect that our clinical experiences, as documented in the peer reviewed published literature, should be uniform for these five analytes, or that a single set of parameters can define the criteria for acceptable clinical outcomes.

The body of published data that one needs to make these assessments will continue to grow as we go forward. We would like to supplement that information today with our experiences as laboratory directors on the performance and usage of these tests.

The College of American Pathologists offers proficiency testing for each of the five analytes under discussion. While CAP is not the exclusive provider of proficiency testing, the majority of CLIA certified laboratories which provide such testing are likely to participate in the program and the enrollment

Table 1.

CAP Proficiency Test Survey Enrollment 2009

Survey	Analyte	Enrollment
PGX	CYP2D6	28
PGX	UGT1A1	42
CYH HER2 ISH2	HER2	1,266
MO/MO2	BCR/ABL	86
KRAS*	KRAS*	133*

* Introduced mid 2009. Enrollment to date for 2010

numbers are a good index of test availability and usage. By that gauge, more than 1,200 laboratories test for HER2 in accord with its widespread clinical usage. KRAS testing follows at 133 labs. This is a new

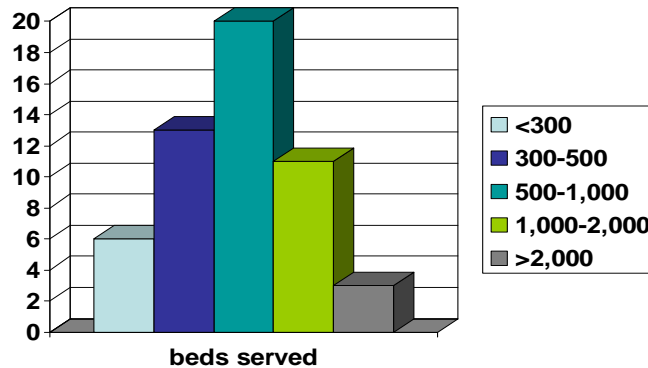
PT survey having been introduced in mid 2009. Since its introduction, enrollment has already doubled, reflecting the increasing clinical demand for the testing.

Testing for BCR-ABL is technically more complex so the number of laboratories offering this test is lower. Together the KRAS and BCR-ABL numbers provide a benchmark for CYP2D6 and UGT1A1. The clinical indications for those tests are more restricted than for KRAS or BCR-ABL and the number of labs offering those tests should be correspondingly fewer.

In preparation for this meeting, the Association for Molecular Pathology performed an impromptu survey of its members. Many AMP members serve as directors of molecular diagnostics laboratories and would likely be knowledgeable and involved in providing testing for these analytes for their institutions, either in their own laboratories or through selected reference laboratories. The numbers we've collected are a sampling that reflects test utilization and as such can be seen a surrogate of clinical demand and utilization. Of the 75 responding laboratories, 28 identified themselves as reference laboratories, while 47 identified themselves as non-reference laboratories. The institutions served by these 47 laboratories varied in size (Figure 1).

Figure 1.

AMP Survey on Pharmacogenomic Testing Size of institution served by non-reference laboratories



The decision to perform a complex molecular test in-house is driven to some degree by demand, but for these complex molecular assays, it also reflects judgment and deliberation on the part of laboratory medical directors that the test has clinical utility for their patient population. This should not be overlooked. For HER2, BCR-ABL, and KRAS the majority of labs responding to the survey perform the testing in their own laboratories (Figure 2.)

Figure 2.

AMP Survey on Pharmacogenomic Testing

Do you perform the test in house?

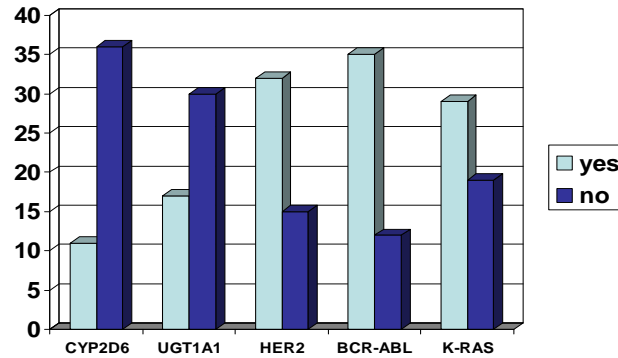
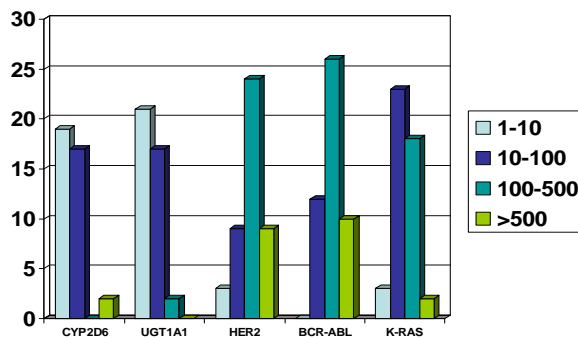


Figure 3 summarizes the number of test requests received for each of the five analytes in 47 non-reference laboratories. The number of test requests received for HER2, BCR-ABL and KRAS is unquestionably high. The volume of KRAS testing, a relatively new analyte, is indicative of the importance of novel pharmacogenomic analytes for molecular medicine and a good example of how quickly molecular discoveries can move from the bench to the clinic. We should anticipate increasing numbers of such discoveries and analytes and should establish mechanisms to evaluate their effectiveness in a timely manner. CYP2D6 and UGT1A1 are less frequently ordered, probably reflecting their more limited clinical indications.

Figure 3.

AMP Survey on Pharmacogenomic Testing

2009 Annual Test Requests (47 non-reference laboratories)

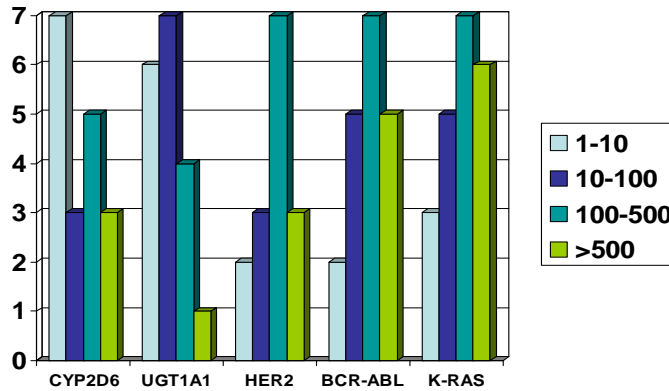


The frequency of test ordering is also reflected in the volume of tests being performed in reference laboratories (Figure 4.). For HER2, BCR-ABL, and KRAS the test volumes are high. Volumes of CYP2D6 and UGT1A1 are somewhat lower but still considerable.

Figure 4.

AMP Survey on Pharmacogenomic Testing

2009 Annual Test Volumes (18 reference laboratories)

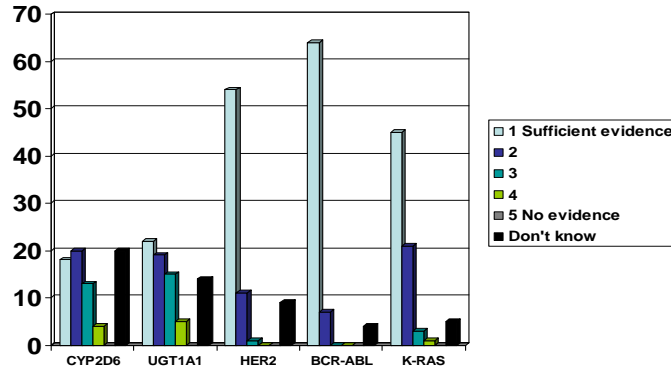


AMP and CAP have within their memberships some of the most knowledgeable physicians and scientists engaged in pharmacogenomic testing. We asked our laboratory directors whether there was sufficient evidence to determine if pharmacogenomic testing could influence health outcomes for each of the five analytes (Figure 5.) For HER2, BCR-ABL, and KRAS there was a very high degree of confidence among the 70 respondents that there exists sufficient evidence to determine whether pharmacogenomic testing affects health outcomes. The responses to the question with regard to CYP2D6 and UGT1A1 were more restrained, with more individuals refraining from judgment. Notably, however, the confidence levels were clearly skewed toward there being sufficient evidence to determine the effect on health outcomes for both CYP2D6 and UGT1A1, as well.

Figure 5.

AMP Survey on Pharmacogenomic Testing

Confidence that there is sufficient evidence...

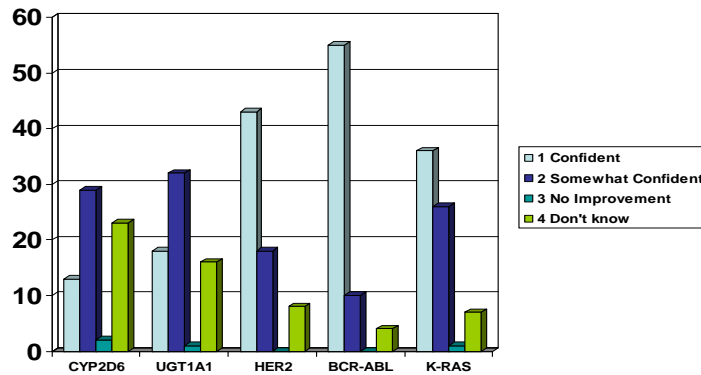


Asked whether pharmacogenomic testing improved health outcomes (Figure 6.), the confidence level among molecular diagnostics laboratory directors was overwhelmingly strong that testing for HER2, BCR-ABL, and KRAS improved health outcomes. The responses for CYP2D6 and UDT1A1 were relatively moderated but unequivocally skewed toward high confidence levels.

Figure 6.

AMP Survey on Pharmacogenomic Testing

Confidence that PGX testing improves health outcomes...



Emphasizing that the five tests under consideration each need to be evaluated individually, we find that the clinical usage, as evidenced by test request and test performance in clinical laboratories, is variable for the five analytes. Some have been in use for a period of time (HER2, BCR-ABL) and are a part of well established patient treatment algorithms. Confidence that these tests alter health outcomes is very high among laboratory directors, and, as judged by usage, among clinicians as well. For KRAS testing, although a relatively recent addition to pharmacogenomic testing menu, there is also a high level of confidence of improved health outcomes and correspondingly high clinician usage.

CYP2D6 and UGT1A1 analyses are both biologically plausible but usage is more limited, a reflection of the limited clinical indications for their use, and possibly their impact on clinical action. This should not be misinterpreted as lack of clinical validity or utility. In addition, clinician education plays a significant role in usage of novel tests, and implementation into routine clinical practice may not be realized in the same time frame for all analytes.

We thank you for the opportunity to share these observations with you, and hope that you find them of value in these very important deliberations.