

The recommendations come one year after similar findings were released in a report

written by the Agency for Healthcare Research and Quality and funded by the CDC [see *PGx Reporter 01-10-2007*]. EGAPP recommendations, which are based on the

AHRQ report, appear in the December issue of Genetics in Medicine.

currently in transition from research to clinical use.

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the US Food and Drug Administration approved Roche's AmpliChip, an in vitro diagnostic that interrogates CYP450 mutations to help physicians better identify patients who might benefit from a large group of drugs, including some SSRIs, that are metabolized by that gene family.

The report includes recommendations for future studies that might "help to fill gaps in knowledge regarding the use of CYP450 testing for antidepressant treatment."

Without such data, "there is a risk that the CYP450 test could increase costs without helping patients," EGAPP concluded.

In response, a Roche spokesperson told Pharmacogenomics Reporter that the working group's findings do not take into consideration how physicians are currently using CYP450 testing in their practices.

Roche, "disappointed" with the methodology of the study, said EGAPP's recommendations failed to "provide any new information for physicians, patients or payors, nor does it advance the knowledge of pharmacogenomics."

Chipping Away at AmpliChip

According to EGAPP's findings, "technical studies showed that the CYP450 testing was highly accurate in detecting common CYP450 gene variations, although less data was available for uncommon variations."

For instance, when the working group analyzed AmpliChip's ability to predict key clinical outcomes in patients with depression using SSRIs, "the available data showed no consistent association between the results of CYP450 gene testing and the clinical response" to the drugs.

"In the absence of data that testing influences treatment or outcomes, there is a risk that the SSRI or dose. $\it CYP450\ test\ could\ increase\ costs$ The lack of clinical data suggesting that without helping patients."

Additionally, EGAPP found no evidence that CYP450 testing predicted the risk of side effects, or that results from such tests helped doctors tailor a particular

CYP450 testing improves SSRI treatment is one reason why large insurers such as Aetna have refused to

reimburse for the test [see PGx Reporter 04-25-2007]. In its 2006 policy bulletin, Aetna noted that prospective, randomized, controlled clinical trials may be required before it starts considering the AmpliChip for coverage.

Although in the past Roche officials have criticized insurers for what they consider to be overly stringent evidence requirements, the Swiss diagnostic giant has begun conducting studies to establish the test's clinical validity and utility.

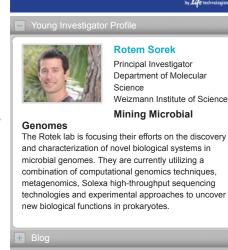
The Roche spokesperson said that the company has sponsored a study that evaluated CYP2D6 testing in patients being treated for serious psychiatric disorders, such as schizophrenia or bi-polar disorder in an in-patient setting.

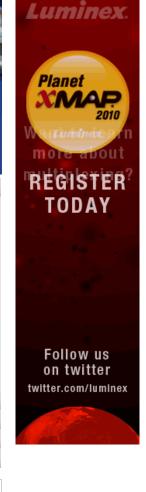
Additionally, Roche is currently studying the use of CYP2D6 testing using the AmpliChip to determine which patients should receive the breast cancer drug tamoxifen as either a chemo-preventive or adjuvant treatment.

Roche Responds

In response to EGAPP's recommendations, a Roche spokesperson said that "no company or entity, that we are aware of, has recommended that CYP450 testing be conducted on all patients new to SSRI therapy. We are disappointed that the study didn't consider how CYP450 testing is currently being used by physicians actively treating patients, nor which selective serotonin reuptake inhibitors have a narrow therapeutic window, making them more appropriate for CYP450 testing."









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According to the Roche spokesperson, physicians are performing CYP450 testing in depressed patients who have been previously treated with SSRIs but who have not responded well, and as a result were switched to another drug, had dose adjustments, or added new treatments to their regimen.

After the AHRQ released its report last year, Roche pointed out that most of the SSRIs analyzed in its study had a "wide therapeutic index," and that the AmpliChip is useful for drugs with a "narrow therapeutic index."

According to the Roche spokesperson, many drugs and drug substrates, such as amitriptyline, venlafaxine, atomoxetine, risperidone, and SSRIs with a narrow therapeutic window meet the requirement for potential clinical validity, but other SSRIs, like the ones reviewed by EGAPP, do not.

In its *Genetics in Medicine* paper, EGAPP acknowledges that it "excluded studies that used probe drugs other than SSRIs to determine metabolizer status, whereas such studies were the basis of Roche Molecular Systems FDA submission."

In the AmpliChip product monograph, Roche indicates that "CYP2D6 and CYP2C19 genotyping is useful for individualizing drug therapy for a wide variety of commonly prescribed drugs including SSRIs." The EGAPP conducted an independent review of 18 articles cited in the monograph that addressed the relationship between genotype and metabolic status.

"In general, poor metabolizers (PMs) with two inactive alleles had clearly reduced metabolic function, but intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultra-rapid metabolizers (UMs) overlapped considerably in metabolic function," EGAPP said in the report. "None of these studies included data on the metabolism of SSRIs."

According to EGAPP this first set of recommendations were challenging for the working group and pointed out some of the problems the healthcare industry faces in ensuring the safety, efficacy and utility of genomic innovations, including the quality of research designs, dealing with proprietary data, the lack of evidence on benefits and harms, the dearth of comparisons with current practice, and information about cost and cost-effectiveness.

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