EGAPP 'Discourages' CYP450 Testing To Choose SSRIs for Depression

January 09, 2008
By Turna Ray

There is insufficient evidence that testing patients for cytochrome P450 gene mutations with Roche's AmpliChip or other platforms can help physicians treat depression with selective serotonin reuptake inhibitors, the Evaluation of Genomic Applications in Practice and Prevention Working Group has found.

"In the absence of supporting evidence, and with consideration of other contextual issues, EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed," the working group said in a statement issued last week. "In the absence of data that testing influences treatment or outcomes, there is a risk that the CYP450 test could increase costs without helping patients."

More significantly, EGAPP noted that with the lack of evidence supporting CYP450 testing, "there is also a possibility of harmful effects, such as less-effective treatment or inappropriate use of genetic information."

While several genotyping tests for CYP450 are available as home brew assays, EGAPP singled out Roche's AmpliChip in its report. While EGAPP's findings acknowledge recent studies showing that certain CYP450 mutations can impact the efficacy of some SSRIs, the group noted that specific applications of Roche's test require additional validation.

EGAPP's findings could further hurt a test that has had a difficult time getting traction in the marketplace since its approval nearly four years ago [see *PGx Reporter 10-31-2007*]. However, EGAPP emphasized that their findings "don't mean that CYP450 testing is not potentially useful." According to the working group, there is "currently 'insufficient evidence' either for or against the use of CYP450 testing in patients beginning SSRI treatment for depression."

EGAPP's recommendations are part of a pilot project developed in 2004 by the National Office of Public Health Genomics at the Centers for Disease Control and Prevention. The project aims to evaluate genetic tests and other genomic applications currently in transition from research to clinical use.

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*.

SSRIs comprise a wide array of antidepressants, including the blockbusters Prozac (fluoxetine) and Zoloft (sertraline). Coincidentally, around the time EGAPP was formed,

Most Viewed | Most Emailed | Blogs

1. **GenomeWeb Daily News**
Celera Revenues Drop 21 Percent in Q2
2. **GenomeWeb Daily News**
DNA Electronics Licenses IP to Ion Torrent
3. **GenomeWeb Daily News**
Bio-Rad's Q2 Revenues Jump 9 Percent on Strong Dx Sales
4. **Pharmacogenomics Reporter**
Agendia Moving to Larger Lab to Keep Pace with Growing MammaPrint Testing Volume
5. **GenomeWeb Daily News**
Minnesota Genomics Partnership Soliciting Requests for Research Proposals

In this issue of Pharmacogenomics Reporter

- Genomic Health, Pfizer to Co-Develop Renal Cancer Dx Based on Oncotype DX Platform
- **EGAPP 'Discourages' CYP450 Testing To Choose SSRIs for Depression**
- OHSU Team Develops Assay to Help Pick Tyrosine Kinase Inhibitors Against AML
- ClinXus, Critical Path Institute, GATC Biotech, LifeCode AG, Center for Molecular Medicine, Children's Oncology Group, University of Pittsburgh, WaferGen, Third Wave Technologies, Inverness Medical Iberica, Osmetech, Prodesse, Luminex

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 CYP450 test could increase costs 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 SSRI or dose.

The lack of clinical data suggesting that 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."

Young Investigator Profile

Rotem Sorek
Principal Investigator
Department of Molecular Science
Weizmann Institute of Science

Mining Microbial Genomes

The Rotek lab is focusing their efforts on the discovery and characterization of novel biological systems in microbial genomes. They are currently utilizing a combination of computational genomics techniques, metagenomics, Solexa high-throughput sequencing technologies and experimental approaches to uncover new biological functions in prokaryotes.

Blog
Papers of Note
People on the Move
Upcoming Events

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.

Related Stories

Agendia Moving to Larger Lab to Keep Pace with Growing MammaPrint Testing Volume
August 4, 2010 / Pharmacogenomics Reporter

Almac Diagnostics' New Biopharma Biomarker Program Will Include Arrays, qPCR
August 3, 2010 / BioArray News

DiagnoCure Laboratory Gets New York Permit
August 3, 2010 / GenomeWeb Daily News

BD Group B Streptococcus Assay Gets 'Moderate Complexity' Status
August 3, 2010 / GenomeWeb Daily News

Enzo Clincal Labs Joins Empire BlueCross BlueShield Network
August 3, 2010 / GenomeWeb Daily News

TechGuides Listings

- Clinical Focus Technical Guide
- Tech Guide Archives

Polls

Open access advocates and journal publishers appeared before US lawmakers last week to discuss access to research results. What do you think the policy should be?

- If taxpayers paid for it, they should be able to see the results right away.
- Having results be publicly available within a year would be good.
- As long as scientists can chose to publish so the public can see it I'm OK with that.
- Publishers need to recoup their costs, so subscriptions are necessary.
- Doesn't matter to me.

Science

Researchers from Harvard University and the University of Toronto have assessed single molecule proteome and transcriptome profiles in individual *Escherichia coli* cells and found that mRNA levels for specific genes did not correlate with protein levels for products of the

Business

Complete Genomics has filed documents for a proposed initial public offering to raise about $86.3 million. The sequencing services firm said that it would use proceeds to finance further development and commercialization of its technology, sales and marketing activities, and to

Funding

NIAID intends to provide $14 million in 2011 to support genomics research aimed at identifying and characterizing gene variants and expression patterns that may correlate with and be used to predict transplantation outcomes, define immune responses related to graft rejection, and

Genome Technology Magazine

This month's Case Study focuses on SNIP-seq, a novel way to identify SNPs from population sequence data. Scripps Research Institute's Vikas Bansal, who developed the method, says it is highly accurate and reduces the rate of false positives.

same genes in the single *E. coli* cells.	expand its facilities and operations.	predict responses for tailored therapies.	

Vote
View Results

Open access advocates and journal publishers appeared before US lawmakers last week to discuss access to research results. What do you think the policy should be?

- If taxpayers paid for it, they should be able to see the results right away.
- Having results be publicly available within a year would be good.
- As long as scientists can chose to publish so the public can see it I'm OK with that.
- Publishers need to recoup their costs, so subscriptions are necessary.
- Doesn't matter to me.

Vote
View Results

Drupal