Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors

*Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group**

This statement summarizes the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group recommendations regarding CYP450 genetic testing in adult patients beginning treatment with selective serotonin reuptake inhibitors (SSRIs), and the supporting scientific evidence. EGAPP is a project developed by the National Office of Public Health Genomics at the Centers for Disease Control and Prevention to support a rigorous, evidence-based process for evaluating genetic tests and other genomic applications that are in transition from research to clinical and public health practice in the United States. A key goal of the EGAPP Working Group is to develop conclusions and recommendations regarding clinical genomic applications and to establish clear linkage to the supporting scientific evidence. The Working Group members are nonfederal experts in genetics, laboratory medicine, and clinical epidemiology convened to establish methods and processes; set priorities for review topics; participate in technical expert panels for commissioned evidence reviews; publish recommendations; and provide guidance and feedback on other project activities.

Summary of Recommendation

The EGAPP Working Group found insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for non-psychotic depression. 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.

Rationale: The EGAPP Working Group found no evidence linking testing for CYP450 to clinical outcomes in adults treated with SSRIs. While some studies of a single SSRI dose in healthy patients report an association between genotypic CYP450 drug metabolizer status and circulating SSRI levels, this association was not supported by studies of patients receiving ongoing SSRI treatment. Further, CYP450 genotypes are not consistently associated with the patient outcomes of interest, including clinical response to SSRI treatment or adverse events as a result of treatment. No evidence was available showing that the results of CYP450 testing influenced SSRI choice or dose and improved patient outcomes, or was useful in medical, personal, or public health decision-making. In the absence of evidence supporting clinical utility, it is not known if potential benefits from CYP450 testing will outweigh potential harms. Potential harms may include increased cost without impact on clinical decision making or improvement in patient outcomes, less effective treatment with SSRI drugs, or inappropriate use of genotype information in the management of other drugs metabolized by CYP450 enzymes. ***Genet Med* 2007:9(12):819–825.**

Key Words: *P450, CYP450, pharmacogenomic, SSRI, depression*

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Disclosure: Margaret Piper is employed by the Blue Cross Blue Shield Association Technology Evaluation Center and has previously authored a technology assessment on cytochrome P450 pharmacogenomic testing (see reference 2). Steven Teutsch is an employee, option and stock holder in Merck & Co., Inc. All other authors have no conflicts of interest relevant to this manuscript.

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BACKGROUND AND CLINICAL CONTEXT FOR THE RECOMMENDATION

Nonpsychotic depression is common and may cause significant impairment; severity and clinical course can vary widely. With a lifetime prevalence estimated as high as 16%, major depressive disorder is the leading cause of disability in the United States.[1] SSRIs are the first-line choice for drug therapy in the United States. Unfortunately, the benefits of treatment take 2–4 weeks to begin, and only 50–60% of patients experience improved outcome.[1] Current use of SSRIs is highly empirical, with clinicians and patients often going through several trials of drug choice and dose. In addition, use of SSRIs is discontinued in about 12–15% of patients treated, because of intolerable, though rarely serious, adverse effects (e.g., nausea, diarrhea, headaches).

The Cytochrome P450 (CYP450) family of enzymes is a major subset of all drug-metabolizing enzymes. CYP2D6 and CYP2C19 are primary CYP450 enzymes involved in the metabolism of SSRIs. Other CYP450 and non-CYP450 enzymes also play a role in the metabolism of some SSRIs, and the dominant metabolic pathway varies for different SSRIs. DNA polymorphisms in CYP450 genes that determine variability in enzyme metabolic activity can lead to variability in response to some SSRIs. Thus, understanding a patient's metabolizer status might be helpful in choosing an initial SSRI that is most likely to be effective. Metabolizer status can be determined with a single bolus of a probe drug known to be metabolized by a particular enzyme. More recently DNA polymorphisms in CYP450 genes have been linked to metabolizer status, as shown in Table 1. Gene polymorphisms can result in enzymes that have no activity, or a spectrum of reduced activity, compared with the "normal" (most common and most active, called "wild-type"). *CYP2D6* and *CYP2C19* each have a few common and many more rare polymorphisms associated with changes in metabolizer status. Prevalence of different polymorphisms varies by race/ethnicity.

In theory, CYP450 genotype could guide SSRI choice or dose to those most compatible with the patient's metabolizer status. Thus, utilizing the test before treatment to individualize SSRI choice and dose could shorten time to clinical response, reduce days lost from work, school and other pursuits, avoid adverse effects, and improve other quality of life outcomes that patients and others (e.g., family members, employers) would notice and value. Whether this potential can be realized in practice is unclear, because other factors also affect SSRI metabolism, including diet and concomitant medications.

In an attempt to answer this question, EGAPP commissioned an evidence-based review to address an overarching question regarding the following specific clinical scenario:

Does testing for CYP450 polymorphisms in adults beginning SSRI treatment for nonpsychotic depression lead to improvement in outcomes, or are testing results useful in medical, personal, or public health decision-making?

REVIEW OF SCIENTIFIC EVIDENCE

Technology

Several laboratories offer genetic testing for various CYP450 polymorphisms using different test formats.[2] Laboratories may develop and validate their own, in-house tests for CYP450 genotyping, known as laboratory-developed or "home brew" tests. Laboratories offering such tests are only required to meet Clinical Laboratory Improvement Amendment standards for high complexity laboratories. The US Food and Drug Administration (FDA) does not currently regulate laboratory-developed tests, but does review manufactured test kits as medical devices. Most genetic tests in current use are laboratory-developed tests.

A significant recent development was the approval by the FDA of the Roche AmpliChip® CYP450 Test.[3,4] The AmpliChip delivers the results of testing for *CYP2D6* and *CYP2C19* polymorphisms in the form of a genotype and predicted metabolizer status ("predicted phenotype"; Table 1). The FDA extensively reviewed the technical performance of the assay; review of clinical validity was limited, and clinical utility was not evaluated.

The evidence report commissioned by EGAPP (see Methods, below) 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. The AmpliChip product monograph indicates that *CYP2D6* and *CYP2C19* genotyping is useful for individualizing drug

Table 1
Example effects of *CYP2D6* polymorphisms on SSRI drug metabolism

Phenotype (metabolizer status)	Examples of corresponding *CYP2D6* genotypes[a]	Expected SSRI drug effects
UM: Ultra-rapid Metabolizer	More than 2 copies of active (wild-type) enzyme gene alleles	Usual doses may lead to sub-therapeutic drug concentration and possible non-response
EM: Extensive Metabolizer	2 copies of active (wild-type) enzyme gene alleles	Usual doses lead to expected drug concentrations and response
IM: Intermediate Metabolizer	1 inactive and 1 reduced activity enzyme gene allele or 2 reduced activity alleles	Drug effects between those of EMs and PMs
PM: Poor Metabolizer	2 copies of inactive enzyme gene alleles	Usual doses may lead to higher than expected drug concentrations; adverse reactions possible

[a]These examples do not represent all possible genotypes; more genotype-phenotype examples are available in the AmpliChip® package insert: www.amplichip.us/documents/CYP450_P.I._US-IVD_Sept_15_2006.pdf.

therapy for a wide variety of commonly prescribed drugs including SSRIs. Therefore, EGAPP conducted a brief independent review of 18 articles cited in the monograph that addressed the relationship between genotype and metabolic status.[5–22] 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. None of these studies included data on the metabolism of SSRIs.

Methods

EGAPP commissioned an evidence review through the Agency for Healthcare Research and Quality (AHRQ); the Duke University Evidence-Based Practice Center (EPC) conducted the review. The review was focused on evidence for the routine use of CYP450 genetic testing for patients with nonpsychotic depression entering therapy with SSRI drugs. In this specific clinical scenario, CYP450 genotype is hypothesized to help physicians personalize SSRI selection and dose. The review does not address the use of CYP450 testing in other possible clinical scenarios (e.g., patients with repeated poor response to antidepressant therapy).

Established AHRQ EPC methods were followed in conducting this review. Because data may not be available to directly answer the overarching question, the EGAPP panel constructed an analytic framework and key questions that address different components of evaluation (e.g., analytic and clinical validity, intermediate outcomes of interest) and that may provide relevant indirect evidence of efficacy. A technical expert panel that included three EGAPP Working Group members provided expert guidance during the course of the review. The final report "Testing for Cytochrome P450 Polymorphisms in Adults with Non-Psychotic Depression Treated with Selective Serotonin Reuptake Inhibitors (SSRIs)" is available from AHRQ (http://www.ahrq.gov/downloads/pub/evidence/pdf/cyp450/cyp450.pdf), and an evidence review is published in this issue (page 826).

In addition, EGAPP Working Group members and technical consultants reviewed key primary publications in detail, and examined other sources of information to address specific gaps in the evidence (see Review of Scientific Evidence: Technology section). The final EGAPP recommendation statement was formulated using a priori criteria based on certainty of evidence and contextual factors.

The evidence reviews are designed around specific clinical scenarios that are converted into explicit literature review strategies. Standard systematic review methods are used to judge the quality of the evidence at the level of individual articles, and the strength of the total evidence around a particular question (high, moderate, or low certainty). The process also includes assessment of relevant contextual factors that are not directly indicative of clinical utility, but that may modulate recommendations, particularly if evidence of clinical utility is missing or uncertain. Contextual issues may include magnitude of effect, severity of disorder, availability of diagnostic or therapeutic alternatives, feasibility and practicality of implementation, family considerations, and cost-effectiveness. Taking evidence and contextual factors into account, the Working Group reaches one of three general conclusions: (1) EGAPP recommends use of the test; (2) EGAPP recommends against use of the test; or (3) EGAPP finds the evidence insufficient to recommend for or against use of the test. If the available evidence is judged insufficient and important contextual factors are discovered, EGAPP may further annotate the conclusion as encouraging or discouraging, pending further evidence. Finally, EGAPP comments on key gaps in the evidence that might be addressed in future research.

Analytic validity

Analytic validity refers to the test's ability to accurately and reliably measure the genotype of interest, and includes measures of analytic sensitivity and specificity, assay robustness, and quality control. For *CYP2D6* and *CYP2C19* polymorphisms, nine published articles and two FDA summaries reported on performance of genotyping methods[3,4,23–31]; only three provided a comparison to the gold standard of DNA sequencing.[3,4,25]

- Analytic sensitivity (how effectively the test identifies specific polymorphisms that are present in a sample) was high for all common polymorphisms, ranging from 94% to 100%. However, less common polymorphisms were tested infrequently.
- Analytic specificity (how effectively the test correctly classifies samples that do not have specific polymorphisms) estimates for all genes tested were 100%.
- Studies of gene deletion or duplication testing were generally small, resulting in wide confidence intervals, and limited by the lack of an accepted gold standard for such tests.
- Only three studies of *CYP2D6* and one study of *CYP2C19* reported results for assay precision (random analytic variability) and assay robustness (e.g., reliability across operators, laboratories, and reagent batches); performance estimates were generally high.

Conclusions. Estimates of analytic sensitivity and specificity were high for common CYP450 polymorphisms; estimates for rarer polymorphisms and for gene deletion/duplications were less reliable.

Clinical validity

The clinical validity of a genetic test defines how well the test results correlate with the intermediate or final outcomes of interest. In this clinical scenario, intermediate outcomes include circulating levels of drug and drug metabolites; final outcomes include clinical response, time lost from work, school or other pursuits, quality of life, and adverse drug reactions.

SSRIs utilized in the studies included citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. Studies in which only a subgroup of patients was treated with SSRIs were also included. Because of scarcity of data, studies of SSRI-treated patients with diagnoses other than nonpsychotic depression were included.

Association of genotype with circulating drug levels. Sixteen studies met inclusion criteria, of which five looked at metabolism of a single bolus of SSRI in healthy adults[32–35] or after a limited number of doses,[36] and 11 investigated the effects of CYP450 genotypes on the blood levels of specific SSRIs in patients at steady state doses.[37–47]

- As expected based on the genotype, three single bolus studies of SSRI (sertraline, fluoxetine, or citalopram) metabolism in healthy adults showed that, compared with EMs, *CYP2C19* PMs had significantly reduced metabolic function and significantly lower plasma concentrations of drug metabolites. In PMs, the parent drug had longer half-life and reduced clearance, compared with EMs.[32,33,35] A fourth study of paroxetine in healthy adults found reduced metabolic function in *CYP2D6* PMs compared with EMs.[34] One multiple dose study of paroxetine reported a nonsignificant difference in median plasma concentration between homozygous wild-type EMs and heterozygous EMs (e.g., one active allele and one inactive allele).[36]
- In contrast, results of 11 heterogeneous studies evaluating genotype and SSRI blood levels in patients taking steady state doses of SSRIs were mixed. Some showed significant differences between SSRI levels in *CYP2D6* and *CYP2C19* (and *CYP2C9*, where tested) EMs versus PMs, and some did not.

Association of genotype with clinical response. Only five studies evaluated the relationship between CYP450 genotype and clinical response in patients with depression receiving ongoing SSRI treatment.[40,42,48–50]

- One study found no difference in the proportion of responders among *CYP2D6* EMs, IMs, and PMs treated with fluvoxamine.[48]
- Another study found that SSRI plasma concentrations varied significantly between metabolizer categories, but that SSRI levels did not predict response.[40]
- A study in patients treated with paroxetine found no differences in depression scores between two groups, *CYP2D6* UMs + EMs versus PMs + IMs.[42]
- One retrospective analysis and one study involving active screening found a significantly higher prevalence of UMs in patients not responding to SSRI drugs than in the general population.[49,50] Results are limited by the lack of a within-study comparison population.

Association of genotype with adverse drug reactions. Nine studies relating CYP450 genotypes and SSRI adverse effects were identified; however, three studies only reported adverse effects in CYP450 PMs as a secondary finding.[33,40,51] Nausea was the most common adverse effect reported.

- Four studies found no association between genotype and adverse drug reactions. Three of these studies reported no differences in rates of adverse effects between *CYP2D6* PMs and EMs,[48,49,52] whereas the fourth reported no differences in adverse effects between the combined PM + IM and EM + UM groups.[42] (Groups were combined because of small numbers; whether this masked an effect could not be addressed.)
- In one study the *CYP2D6* genotype predicted a greater prevalence of gastrointestinal adverse effects in PMs compared with EMs.[53]
- Two studies found a significantly higher prevalence of PMs among depressed nonresponders treated with antidepressants (including SSRIs) with adverse effects than in the general population.[49,54] One of these studies also reported a significantly greater frequency of PMs among those with adverse effects when compared with a random group of depressed patients.[54]

Limitations. In general, studies of clinical validity were limited by inadequate power; some grouped results for different SSRIs even though metabolism may differ, and some did not specify exclusion criteria. In terms of quality assessment, utilizing criteria and a scale developed by the Oxford Centre for Evidence-based Medicine that ranges from 1 to 5 (where 1 is highest quality), the vast majority of these studies were rated 3 or 4.[1] Although some reported on race/ethnicity of patients, most provided no information on other variables such as diet or other medications, which could influence metabolism, and did not account for other genetic factors that may influence SSRI tolerability (e.g., genetic variations in serotonin transporter proteins or serotonin receptor proteins).

Conclusions. Some studies of a single SSRI dose in healthy patients suggest a significant association between CYP450 genotypic metabolizer status and circulating SSRI levels. However, this relationship was not supported by similar studies of patients taking maintenance doses of SSRI. Studies did not consistently identify a significant association between CYP450 genotype and clinical response to SSRI treatment or adverse events. Studies were generally small and of poor quality. The evidence is insufficient to support clinical validity.

Clinical utility

The clinical utility of a genetic test is the likelihood that using the test to guide drug choice or dose will significantly improve patient outcomes. No studies addressed the influence of CYP450 genotyping results on SSRI prescribing decisions. No studies used CYP450 genotyping to guide SSRI choice or dose and studied subsequent patient outcomes.

Conclusions. No evidence exists to support clinical utility.

Research gaps

EGAPP found the research literature insufficient in many respects, and examining the deficiencies can be helpful in designing studies that could fill the gaps.

- Currently, the evidence is insufficient to conclude that there is a relationship between genotype and clinical response. Therefore, conclusive evidence of clinical validity is required from well-designed studies.
- If conclusive evidence of clinical validity is acquired, then prospective studies of CYP450 genotyping and its relationship to clinical outcomes are needed to answer the overarching question and address clinical utility. Best evidence would come from adequately powered, randomized controlled clinical trials that compare patient outcomes when treatment is informed by genotyping tests versus empirical treatment. Because depression is prevalent and is an important public health issue, and because SSRIs are widely prescribed, such trials are feasible and essential to determine best management practices with respect to CYP450 testing.
- Alternatively, prospective studies could address more limited clinical scenarios, such as the potential value of using CYP450 testing to manage the subset of patients with depression who have a history of poor response to SSRIs or other antidepressant drugs or who have experienced adverse drug reactions.
- All studies need to incorporate information on potential confounding variables to reduce the likelihood of bias. For example, medications that inhibit or induce certain CYP450 enzymes, including some SSRIs themselves, can affect metabolism of CYP450 metabolized drugs, and may themselves vary in activity by CYP450 genotype.
- Prospective studies of patient outcomes should blind both patients and the clinicians reporting outcomes to genotyping results.
- Studies should examine specific SSRIs individually; SSRIs are not all metabolized the same way and different CYP450 polymorphisms may affect some more than others.
- Introduction of tests should be accompanied by key measurements supporting the analytic sensitivity and specificity, repeatability, and robustness of the proposed method. Analytic predictive values of the tests should be based on genotype, rather than allele frequencies.
- General studies are needed to address issues that include the acceptability of pharmacogenetic testing to individuals with depression, perceptions of risks and benefits, psychological outcomes of testing including access, informed consent, the potential for discrimination, implications for family members, and the possibility that polymorphisms related to drug response could later be determined to be related to disease susceptibility.

Recommendations of other groups

EGAPP did not find recommendations from other groups regarding CYP450 testing in patients with depression.

Contextual issues important to the recommendation

There is insufficient evidence on clinical validity and utility to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for nonpsychotic depression. Thus, additional contextual issues were taken into account in the final EGAPP recommendation statement. Contextual factors could be considered to suggest potential benefits and harms of CYP450 testing, but there is little direct evidence of many of these factors.

Contextual factors that suggest potential benefits of CYP450 testing:

- Depression is a major health problem in the United States, with very large direct and indirect costs and impact on quality of life.
- SSRIs are the most commonly used approach to treating depression, and most experts consider SSRIs to be the treatment of choice.
- Empirical SSRI treatment for depression has varied effectiveness.
- Nonadherence to treatment is a major concern and many individuals drop out from treatment because of lack of effectiveness of SSRIs.

Contextual factors that suggest potential harms of CYP450 testing:

- Utilization of genetic testing for CYP450 polymorphisms and impact on physician decision-making with regard to use of SSRIs is not known.
- In the absence of evidence supporting clinical utility, widespread use of CYP450 genetic testing is potentially costly and may not lead to changes in treatment that improve patient outcomes.
- There have not been any published cost-effectiveness analyses. The costs of testing and follow-up are not known, although the test itself is relatively inexpensive.

Potential harms may include increased cost without impact on clinical decision-making or improvement in patient outcomes, less effective treatment with SSRI drugs, or inappropriate use of genotype information in the management of other drugs metabolized by CYP450 enzymes.

It is important to understand that although evidence for the existence of such harms was not found, the potential for their occurrence is nevertheless real. The need to consider potential harms in formulating this recommendation also emphasizes the need for direct evidence on their existence and magnitude.

This recommendation statement is a product of the independent EGAPP Working Group. Although the Centers for Disease Control and Prevention (CDC) provides support to the EGAPP Working Group, including staff support in the preparation of this document, recommendations made by the EGAPP Working Group should not be construed as official positions of the CDC or the U.S. Department of Health and Human Services.

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