Complete Summary

GUIDELINE TITLE

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

BIBLIOGRAPHIC SOURCE(S)

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. Genet Med 2007 Dec;9(12):819-25. [54 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Non-psychotic depression

GUIDELINE CATEGORY

Technology Assessment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Medical Genetics
Pharmacology
Psychiatry

INTENDED USERS

Health Care Providers
Health Plans
Managed Care Organizations
Physicians

GUIDELINE OBJECTIVE(S)

To provide recommendations regarding cytochrome P450 genetic testing in adult patients with non-psychotic depression beginning treatment with selective serotonin reuptake inhibitors (SSRIs), and to summarize the supporting scientific evidence

TARGET POPULATION

Adults with non-psychotic depression for whom selective serotonin reuptake inhibitor (SSRI) therapy is being considered

Note: The review does not address patients in other possible clinical scenarios (e.g., patients with repeated poor response to antidepressant therapy).

INTERVENTIONS AND PRACTICES CONSIDERED

Cytochrome P450 (CYP450) polymorphism testing (genetic testing)

MAJOR OUTCOMES CONSIDERED

Analytic Validity

- Analytic sensitivity and specificity of cytochrome P450 (CYP450) polymorphism tests
- Precision and robustness of CYP450 tests
- Confidence intervals on performance estimates

Clinical Validity

- Association of genotype with circulating levels of drug and drug metabolites
- Association of genotype with clinical response, including time lost from work, school or other pursuits and quality of life
- Association of genotype with adverse drug reactions

Clinical Utility

- Influence of CYP450 genotyping results on selective serotonin reuptake inhibitor (SSRI) prescribing decisions
- Patient outcomes following use of CYP450 genotyping to guide SSRI choice or dose

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): An evidence review commissioned by the Evaluation of Genomic applications in Practice and Prevention (EGAPP) and funded by the Centers for Disease Control and Prevention (CDC) was prepared by the Duke University Evidence-Based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ) (see the "Availability of Companion Documents" field).

Development of Research Questions

Working with AHRQ, CDC, and members of the project's technical expert panel, the Duke EPC developed the following key research questions:

- **Question 1**: Does testing for cytochrome P450 (CYP450) polymorphisms in adults entering selective serotonin reuptake inhibitor (SSRI) treatment for non-psychotic depression lead to improvement in outcomes, or are testing results useful in medical, personal, or public health decision-making? (overarching question)
- **Question 2**: What is the analytic validity of tests that identify key CYP450 polymorphisms?
- **Question 3a**: How well do particular CYP450 genotypes predict metabolism of particular SSRIs? Do factors such as race/ethnicity, diet, or other medications, affect this association?
- **Question 3b**: How well does CYP450 testing predict drug efficacy? Do factors such as race/ethnicity, diet, or other medications, affect this association?
- **Question 3c**: How well does CYP450 testing predict adverse drug reactions? Do factors such as race/ethnicity, diet, or other medications, affect this association?
- **Question 4a**: Does CYP450 testing influence depression management decisions by patients and providers in ways that could improve or worsen outcomes?
- **Question 4b**: Does the identification of the CYP450 genotypes in adults entering SSRI treatment for non-psychotic depression lead to improved clinical outcomes compared to not testing?
- **Question 4c**: Are the testing results useful in medical, personal or public health decision-making?

- **Question 5**: What are the harms associated with testing for CYP450 polymorphisms and subsequent management options?

Literature Search

The EPC searched MEDLINE® (1966 to May 2006), the Cochrane Database of Abstracts of Reviews of Effects (DARE), PsychInfo, HealthSTAR, and CINAHL. Searches of these databases were supplemented by reviews of the reference lists contained in all included articles and in relevant review articles. Documents from the U.S. Food and Drug Administration (FDA) that could be publicly accessed were also included. The searches yielded a total of 1,200 citations.

Selection of Evidence

Pairs of researchers independently reviewed each abstract and selected 140 for full-text review. Project-specific inclusion/exclusion criteria were developed, and both researchers were required to agree on inclusion status at the full-text stage. A total of 37 articles were included for data abstraction.

Three progressively stricter screening opportunities were used for each article (abstract screening, full-text article review, data abstraction review), as were involvement of three individuals (two investigators and a copy-editor) in each data abstraction; and agreement of at least two investigators on all included studies.

NUMBER OF SOURCE DOCUMENTS

Questions 1, 4a, 4b, 4c, and 5: No studies were identified that directly addressed any aspect of these questions.

Question 2: 12 published articles and 2 documents from the U.S. Food and Drug Administration (FDA) Web site that described methods for CYP450 genotyping.

Question 3a: 16 studies met inclusion criteria, of which 5 were conducted in healthy adults after a single dose of a selective serotonin reuptake inhibitor (SSRI).

Question 3b: 5 studies were identified, 3 of which involved cohorts of depressed patients in antidepressant treatment.

Question 3c: 9 studies, 3 of which reported adverse effects in CYP450 poor metabolizers (PMs) only as a secondary finding, were identified.

See "Description of Methods to Collect/ Select the Evidence" field for the questions.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The EGAPP Working Group has developed criteria for assessing the quality of the body of evidence for the individual components of evaluation, analytic validity, clinical validity, and clinical utility. The adequacy of information to answer the key questions related to each evaluation component is classified as Convincing, Adequate, or Inadequate.

Based on the available evidence, the overall level of certainty is categorized as follows:

- *High* - Consistent, generalizable results from well-designed and well-conducted studies make it unlikely that conclusions will change based on the results of future studies.
- *Moderate* - Limitations in quantity, quality, consistency or generalizability of available data reduce confidence in the results, and as further information becomes available, the estimate or effect may change sufficiently to alter the conclusion.
- *Low* - Data that are insufficient or of poor quality, results not consistent or generalizable, or lack of information on important outcomes, result in conclusions that may be likely to change based on results of future studies.

Teutsch SM, Bradley LA, Palomaki GE, Haddow JE, Piper M, Calonge N, Dotson WD, Douglas MP, Berg AO, on behalf of the EGAPP Working Group. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: Methods of the EGAPP Working Group. Genetics in Medicine, manuscript in press.

METHODS USED TO ANALYZE THE EVIDENCE

Decision Analysis
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): An evidence review was prepared by the Duke University Evidence-Based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ) (see the "Availability of Companion Documents" field).

Data Abstraction and Development of Evidence Tables

The Duke research team developed data abstraction forms/evidence table templates for abstracting data for the various key questions (Appendix C in the Evidence Review [see the "Availability of Companion Documents" field]). Based on clinical expertise, a pair of researchers was assigned to the research questions to abstract data from the eligible articles. One of the pair abstracted the data, and the second researcher over-read the article and the accompanying abstraction to check for accuracy and completeness. The completed evidence tables are provided in Appendix D in the Evidence Review (see the "Availability of Companion Documents" field).

Quality Assessment Criteria

At the data abstraction stage, the abstracting researcher was asked to evaluate each included article for methodological quality. For Question 2 regarding analytic validity, EPC staff assessed quality of studies based on questions in the Analytic validity, Clinical validity, Clinical utility and associated Ethical, legal and social implications (ACCE) model for evaluation of genetic testing (Appendix E in the Evidence Review [see the "Availability of Companion Documents" field). For all other questions for which we could identify data, EPC staff intended to use the quality assessment criteria developed by the Tufts-New England Medical Center Evidence-based Practice Center for an evidence report on "Effects of Omega-3 Fatty Acids on Cardiovascular Disease." However, these criteria require the study to be either a randomized controlled trial, longitudinal cohort study, or case-control study, and none of the studies identified for this report had these study designs. Therefore, EPC staff elected to use criteria developed by the Oxford Centre for Evidence-based Medicine (Appendix E in the Evidence Review [see the "Availability of Companion Documents" field) to evaluate individual studies based on type of the study (therapy vs. prognosis vs. prevalence) and strength of study design, with numerical scores ranging between 1 and 5 (including 1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, 5). The overall strength of recommendation for each question was then graded for each question as A, B, C, or D according to criteria that take into account the quality of individual studies identified for each question. The quality assessment scores for individual studies are reported in the relevant evidence tables. Because numerical value may not convey details about quality assessment, methodological issues pertaining to studies relevant to individual questions are addressed in the discussion of results for each question.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Balance Sheets
Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC): An evidence review commissioned by the Evaluation of Genomic applications in Practice and Prevention (EGAPP) and funded by the Centers for Disease Control and Prevention (CDC) was prepared by the Duke University Evidence-Based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ) (see the "Availability of Companion Documents" field).

The EGAPP Working Group (EWG) members and technical consultants reviewed the evidence report and additional sources of information as needed, and considered the quality of the evidence and the identified gaps in knowledge, the final EGAPP recommendation statement was formulated using a priori criteria based on certainty of evidence and magnitude of net benefit, along with consideration of contextual factors.

Teutsch SM, Bradley LA, Palomaki GE, Haddow JE, Piper M, Calonge N, Dotson WD, Douglas MP, Berg AO, on behalf of the EGAPP Working Group. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: Methods of the EGAPP Working Group. Genetics in Medicine, manuscript in press.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (EWG) uses the following standard terminology in recommendation statements:

- **Recommend For**
- **Recommend Against**
- **Insufficient Evidence**

Based on existing evidence, consideration of contextual issues or results of modeling, Insufficient Evidence may be qualified as:

Neutral - Not possible to predict with current evidence

Discouraging - Use discouraged until specific gaps in knowledge are filled, or it is considered unlikely that the application will meet evidentiary standards even with further study

Encouraging - Likely to meet evidentiary standards with further studies, or it is reasonable to use in limited situations based on existing evidence while additional evidence is gathered

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COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Evidence Report

Based on Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) protocols, the draft evidence report was reviewed by a panel of experts. Reviewer comments and suggestions were considered in finalizing the evidence report.

Recommendation Statement

After the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (EWG) receives the final evidence report, a writing team begins development of the recommendation statement. Technical comments on the final evidence report are solicited from test developers and considered by the writing

team. Following internal review and acceptance by the EWG, the draft recommendation statement is distributed to selected external peer reviewers, selected from organizations and individuals expected to be impacted by the recommendation (e.g., health care providers/payers, professional organizations, consumers). Primary objectives of the external peer review process are to ensure the accuracy and completeness of the evidence summarized in the recommendation statement, improve the clarity and organization of information, soliciting feedback from different perspectives, identify contextual issues that need to be addressed or clarified, and avoid unintended consequences. Following approval by the EWG, final drafts of EGAPP recommendation statements are submitted for publication.*

Relevant recommendations from other organizations are also routinely sought, but were not found on CYP450 testing in patients with non-psychotic depression.

*Teutsch SM, Bradley LA, Palomaki GE, Haddow JE, Piper M, Calonge N, Dotson WD, Douglas MP, Berg AO, on behalf of the EGAPP Working Group. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: Methods of the EGAPP Working Group. Genetics in Medicine, manuscript in press.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Summary of Recommendation

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found insufficient evidence to support a recommendation for or against use of cytochrome P450 (CYP450) testing in adults beginning selective serotonin reuptake inhibitor (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.

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 non-psychotic 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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Potential Benefits of Implementing the Recommendations

- Provide objective information to improve professional and consumer understanding on the use of CYP450 in this clinical scenario.
- Inform a translational research agenda by identifying gaps in knowledge that might be addressed in future research.

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This recommendation statement is a product of the independent Evaluation of Genomic Applications in Practice and Prevention (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.
- The literature review revealed a paucity of high-quality studies addressing the key questions. No prospective studies of cytochrome P450 genotyping and its

relationships to clinical outcomes were found. In general, most of the available evidence included small, poor-quality studies examining prevalence rates of certain genotypes in a sample or examining the correlation between various genotypes and limited clinical outcome, such as response or adverse effects. There were no randomized studies of alternative testing strategies.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. Genet Med 2007 Dec;9(12):819-25. [54 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007 Dec

GUIDELINE DEVELOPER(S)

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

GUIDELINE DEVELOPER COMMENT

This recommendation statement is a product of the independent, non-federal Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group.

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative is a project developed by the National Office of Public Health Genomics (NOPHG) at the Centers for Disease Control and Prevention (CDC) 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.

SOURCE(S) OF FUNDING

United States Government

GUIDELINE COMMITTEE

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

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Group Members: Alfred O. Berg, MD, MPH (University of Washington) (Chair); Margaret Piper, PhD, MPH (Blue Cross/Blue Shield Association Technology Evaluation Center); Katrina Armstrong, MD, MSCE (University of Pennsylvania School of Medicine); Jeffrey Botkin, MD, MPH (University of Utah); Ned Calonge, MD, MPH (Colorado Department of Public Health and Environment); James Haddow, MD (Women and Infants' Hospital); Maxine Hayes, MD, MPH (Washington State Department of Health); Celia Kaye, MD, PhD (University of Colorado School of Medicine); Kathryn A. Phillips, PhD (University of California, San Francisco); Carolyn Sue Richards, PhD, FACMG (Oregon Health & Science University); Joan A. Scott, MS, CGC (Johns Hopkins University); Ora L. Strickland, PhD, DSc (Hon.), RN, FAAN (Emory University); Steven Teutsch, MD, MPH (Merck & Co.)

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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. 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.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Genetics in Medicine Journal.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Matchar DB, Thakur Me, Grossman I, McCrory DC, Orlando LA, Steffens DC, Goldstein DB, Cline KE, Gray RN. Testing for cytochrome P450 polymorphisms in adults with non-psychotic depression treated with selective serotonin reuptake inhibitors (SSRIs). Evidence Report/Technology Assessment No. 146. (Prepared by the Duke Evidence-based Practice Center under Contract no. 290-02-0025.) AHRQ Publication No. 07-E002. Rockville (MD): Agency for Healthcare Research and Quality. 2007 Jan. 157 p. Electronic copies: Available from the AHRQ Web site.
- Review of evidence for genetic testing for CYP450 polymorphisms in management of patients with nonpsychotic depression with selective serotonin reuptake inhibitors. Genet Med. 2007 Dec;9(12):826-35.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on May 8, 2008. The information was verified by the guideline developer on June 6, 2008.

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