OECD Workshop: Policy Issues For the Development and Use of Biomarkers in Health

A CDC Perspective on Clinical Evaluation of Biomarkers

Ralph J. Coates, PhD
National Office of Public Health Genomics, NCCDPHP
Coordinating Center for Health Promotion
Centers for Disease Control and Prevention (CDC)
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CDC Perspectives Based on the Analytic Paper for OECD

Clinical Evaluation of Biomarkers

Ron Zimmern & Carol Wright
PHGC Foundation
UK
Need for Evaluation of Biomarkers

Large numbers of biomarker tests available
Over 1,600 genetic tests
Rapidly developing research, numbers increasing
Potential for wide range of applications for common disorders, wide range of uses
Potential for substantial population health impact
Unanswered questions about validity & utility
In U.S., tests being marketed widely
uncertain guidance, oversight & regulation

www.cdc.gov/genomics/gtesting.htm/
http://www4.od.nih.gov/oba/sacghs.htm
Need for Evaluation of Biomarkers

Clinician & policymaker interest in when tests ready for use & how

Public interest in more knowledge & participation in healthcare decision-making

Natural evolution of "evidence-based" processes to address biomarkers, genomics

Opportunity to facilitate consensus on standards and criteria for validity & utility of applications & to improve patient outcomes through translation of new technology

www.cdc.gov/genomics/gtesting.htm/
http://www4.od.nih.gov/oba/sacghs.htm
In U.S., Additional Reasons for Evaluation

Appropriate Translation for Use

Healthcare Spending High, Exceeded Record
$US 2 Trillion in 2006. ~16% of GDP

U.S. behind many advanced countries in health status

~55% of Americans receive recommended care for acute or chronic conditions

~20%-30% receive contraindicated care

~50% receive recommended preventive care

30-40% of dollars spent on overuse, underuse, misuse of services; duplication; system failures & inefficiency

For biomarkers, how to assure appropriate use?

Need for Evaluation of Biomarkers

Balance of benefits/harms in population unknown

Need to establish evidence on validity and utility of genetic tests before wide use

Need to provide accurate & objective information healthcare professionals, public, & policymakers to help determine which biomarkers are safe and effective & to provide guidance on their appropriate use

www.cdc.gov/genomics/gtesting.htm/
http://www4.od.nih.gov/oba/sacghs.htm
Types of Biomarkers (OECD)

Clinical: signs used in disease diagnosis
Cellular: cellular variations, imaging
Molecular:

Genomic: DNA profiles, SNPs
  e.g., pharmacogenomic
Transcriptomic: RNA expression
Proteomic: protein profiles
Metabolomic: intermediates & products of metabolism

Baucher M-A. Introduction to biomarkers and policy issues. OECD, 2008
CDC Perspective on Biomarker Evaluation

Shaped by experience with evaluations of Genomic, Transcriptomic & Proteomic markers, including Pharmacogenomics

Discussed in the OECD paper “Clinical Evaluation of Biomarkers”

ACCE Framework

EGAPP

CDC EGAPP: [www.cdc.gov/genomics/gtesting.htm](http://www.cdc.gov/genomics/gtesting.htm)

EGAPP Working Group: [www.egappreviews.org](http://www.egappreviews.org)

Evolution of CDC-Supported Approach

Developed in response to a number of U.S. reports on genomics 1994-2008

1994  U.S. Institute of Medicine, National Academy of Sciences Report  *Assessing Genetic Risks*


(*NIH & DOE Co-Sponsored Human Genome Project, sequencing the first human genome)*
Evolution of CDC-Supported Approach

2000  U.S. Department of Health and Human Services Secretary’s Advisory Committee on Genetics Testing (SACGT) Report

*Enhancing the Oversight of Genetic Tests*

2005  Secretary’s Advisory Committee on Genetics Health & Society (SACGHS) Report:

*Coverage & Reimbursement*

2008  SACGHS Draft Report:

*Oversight of Genetic Tests*

CDC ACCE Model Project (2000-2004)

44 questions for biomarker evaluation

www.cdc.gov/genomics/gtesting/ACCE/
**CDC EGAPP Initiative 2003 – Present**

| Evaluation of Genomic Applications in Practice and Prevention | Purpose: Establish and test a systematic, evidence-based process for evaluating genetic tests and other applications of genomic technology in transition from research to practice |

www.egappreviews.org/
cdc.gov/genomics/gtesting/
EGAPP

Non-regulatory CDC-supported initiative
Develop process for evaluation
Evidence-based, transparent, publicly accountable
Integrate existing processes for evaluation
Minimize conflicts of interest
Independent, non-federal, multidisciplinary
  Working Group to make recommendations
Steering Committee of federal agencies
Stakeholder Group for consultation, evaluation

cdc.gov/genomics/gtesting/
Teutsch SM et al. Genetics In Medicine 2008;10(10):
available online at: www.geneticsinmedicine.org/
EGAPP Approach: Build on methods from other organizations, processes

U.S. Preventive Services Task Force
www.ahrg.gov/clinic/usostf07/methods/benefit.htm

Centre for Evidence-Based Medicine
http://www.cebm.net/

QUADAS
[BMC Medical Research Methodology 2003, 3:25]
www.biomedcentral.com/1471-2288/3/25

U.S. Agency for Healthcare Research & Quality Evidence-based Practice Center Program
www.ahrg.gov/clinc/epc/

Others
cdc.gov/genomics/gtesting/
Teutsch SM et al. Genetics In Medicine 2008;10(10):
available online at: www.geneticsinmedicine.org/
EGAPP Approach: Use common processes for developing evidence-based guidelines

Published, transparent methods for reviewing evidence and making recommendations on the overall balance of benefits & harms.

Systematic reviews by “disinterested,” experienced reviewers using explicit, standardized procedures.

Use of evidence from a range of publications, information sources, & study designs with explicit evaluation and grading of quality of the evidence.

www.cdc.gov/genomics/gtesting/
www.egappreviews.org/
EGAPP Approach: Use common processes of developing evidence-based guidelines

Use of content technical experts as consultants to assure substantive expertise in defining questions, identifying evidence, but not as decision-makers

Peer review of evidence reviews & recommendations by experts, agencies & stakeholders

www.cdc.gov/genomics/gtesting
www.egappeviews.org/
EGAPP Approach: Use common processes for developing evidence-based guidelines

Final evaluation & recommendations from independent panel primarily from academia with expertise in evaluation, healthcare & evidence-based practice, with no conflicts of interest

www.cdc.gov/genomics/gtesting/
www.egappreviews.org/
The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: Methods of the EGAPP Working Group

EGAPP Evaluation Method

Step 1 Define the Disorder & Setting:

a. Characterize medical disorder
   Defined by clinical characteristics, not test
   For pharmacogenomics, may be reduction of
   adverse events, optimizing treatment, or
   targeting patients who will benefit

b. Characterize biomarker, e.g., which specific
   DNA mutations?

available online at: [www.geneticsinmedicine.org/](http://www.geneticsinmedicine.org/)
EGAPP Evaluation Method

Step 1. Define the Disorder & Setting (cont.):

c. Characterize clinical scenario
- Primary or specialty care or direct to consumer?
- Diagnosis, screening, or treatment?
- Preliminary tests, evaluations required?
  (e.g., family history)

EGAPP Evaluation Method

Step 2. Evaluate Analytic Validity
Ability of test to accurately and reliably detect marker of interest in clinical lab setting in population of interest

Step 3. Evaluate Clinical Validity
Ability to accurately and reliably predict the clinically defined disorder or phenotype of interest, including sensitivity, specificity, predictive values


EGAPP Evaluation Method

Step 4. Evaluate Clinical Utility
Evidence of improved measurable clinical outcomes, added value in patient or clinical decision-making, overall balance of benefits & harms from test use and use of interventions based on the test

Step 5. Assess Contextual Factors
Clinical factors (prevalence & severity of disorder, therapeutic alternatives); diagnostic alternatives; availability & use of test; economic issues; ethical, legal, and social issues

Teutsch SM et al. Genetics In Medicine 2008;20:
available online at: www.geneticsinmedicine.org/
EGAPP Working Group - Independent Panel - Responsibilities

- Develop methods for evidence reviews & recommendations
- Develop topics for review
- Oversee evidence reviews
- Develop recommendations based on the evidence
- Consult with CDC on other EGAPP processes and activities

www.cdc.gov/genomics/gtesting.htm/
EGAPP Working Group
Areas of expertise

Evidence-based medicine
Clinical epidemiology
Medical practice
Laboratory medicine
Public health practice
Genetics
Health economics
Decision analysis
Outcomes research

www.cdc.gov/genomics/gtesting.htm/
EGAPP Steering Committee

Members representing USDHHS:
Food & Drug Administration
Centers for Medicare & Medicaid Services
Agency for Healthcare Research & Quality
Health Resources & Services Administration
HHS Personalized Medicine Office
HHS Secretary’s Advisory Committee on Genetics, Health & Society
National Institutes of Health
Veterans Administration
Centers for Disease Control & Prevention

www.cdc.gov/genomics/gtesting.htm/
EGAPP Stakeholder Group

Healthcare providers
In vitro diagnostic and biotech industry
Public health professionals
Healthcare payers/plans
Policymakers & Media science writers
Consumer advocacy groups
Researchers & Funding agencies
Educators & Communicators
IT (EMR/HIT) developers

www.cdc.gov/genomics/gtesting.htm/
EGAPP Stakeholder Group

Roles

Build partnerships to promote translation
Promote evidence-based processes
Communication to stakeholders & key audiences
Facilitate development of informatics, decision support tools
Participate in EGAPP evaluation
Consultation to EGAPP WG and CDC

www.cdc.gov/genomics/gtesting.htm/
First EGAPP Recommendation

Review of evidence for genetic testing for CYP450 polymorphisms in management of patients with nonpsychotic depression with selective serotonin reuptake inhibitors

Magda Haine, MD1, Iris Grossman, PhD2, Douglas C. McCray, MD, MHS3, Lori A. Orlando, MD, MHS2, David C. Serfas, MD, MHS2, Kathryn E. Goin, MHS2, Rebecca A. Gray, DPhil4, Jennifer Parmer, MD5, Georgette Deluca, MD1, Cara O'Brien, MD3, Gregory Samsa, PhD3, David N. Goldsmith, PhD5, and David E. Marchion, MD5

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

www.egappreviews.org/
Key Questions:

Overarching question (1): Does testing for CYP450 polymorphisms in adults entering treatment with selective serotonin reuptake inhibitors (SSRI) for non-psychotic depression lead to improvement in outcomes, or are testing results useful in medical, personal, or public health decision making?

(SSRI’s: fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram, escitalopram)

Overarching Question

Analytic Framework:

1. Adults with non-psychotic depression entering therapy with SSRI
   2. CYP450 genotype Testing
      3a. Metabolizer status (phenotype)
      3b. Predicted drug efficacy
      3c. Predicted risk for adverse drug reactions
   4a,b,c. Treatment decisions
   5. Harms of subsequent management options
      • Improved in:
        • Depression
        • Quality of life
        • Other (e.g., work absenteeism)

Incorrect genotype assignment
Key Questions (continued):

**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?

**Question 3b:** How well does CYP450 testing predict drug efficacy?

**Question 3c:** How well does CYP450 testing predict adverse drug reactions?

(3a-c) Do factors such as race/ethnicity, diet, or other medications, affect any of these associations?

EGAPP Review - CYP450 Example

Key Questions (continued):

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?

Analytic validity
Accuracy and reliability appear high

Clinical validity
No consistent association between CYP450 genotype and drug levels, clinical response to SSRI treatment, or adverse side effects

Clinical Utility
No studies used CYP450 genotyping to guide SSRI choice or dose and studied subsequent patient outcomes

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 contextual issues, EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed.

Practice Changes Given Recommendation?

Interest in media, support from many, including EGAPP Stakeholder Group

CYP 450 Testing available for patients with depression over the internet:

http://www.healthanddna.com/drug-safety/depression.html

http://www.dnadirect.com/patients/tests/drug_response/drugs_to_test_for.jsp

And other sources

Katsanis SH et al. Science 2008;320:53-55
EGAPP Reviews & Recommendations
In Press 2008

DNA testing strategies aimed at reducing morbidity & mortality from Lynch Syndrome
Can UGT1A1 genotyping reduce morbiity & mortality in patients with metastatic colorectal cancer treated with Irinotecan?
Can tumor gene expression profiling improve outcomes in patients with breast cancer?
Available at www.egappreviews.org
publications in Genetics in Medicine
EGAPP Reviews
In Process

Multi-gene panel testing in the general population to assess risk of cardiovascular disease and identify prevention strategies
Factor V Leiden testing in individuals with a family history or suspicion of thrombophilia for prevention & management
TCF7L2 testing in the general population for Type 2 diabetes risk prediction & assessment

Information at www.egappreviews.org
CDC-Supported Approach to Biomarker Evaluation

Successfully used for genomic markers, including pharmacogenomic markers; transcriptomic markers & proteomic markers

May be generalizable to evaluation of clinical, cellular, & metabolomic markers

This type of process is feasible
Major challenges:
- Rapidly evolving field, large numbers of new tests
- Complexity of markers, tests, test uses
- Lack of consensus on needs for evaluation, & the process, methods
- Lack of consensus on roles of test developers, government, researchers, stakeholders in addressing issues
- Substantial issues, limited resources
Evaluation of Genomic Applications in Practice and Prevention (EGAPP) is an initiative launched in 2004 to support a coordinated, systematic 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.

The EGAPP Working Group was established in 2005 to support the development of a systematic process for assessing the available evidence regarding the validity and utility of rapidly emerging genetic tests for clinical practice. This independent, multidisciplinary panel prioritizes and selects tests, reviews CDC-commissioned evidence reports and other contextual factors, highlights critical knowledge gaps, and provides guidance on appropriate use of genetic tests in specific clinical scenarios.

**What’s New**

EGAPP Working Group Releases First Recommendation Statement on Genetic Testing. The recommendation statement appears in the December issue of *Genetics in Medicine*.

- See the [Working Group announcement](#).
- Read the [Genetics In Medicine press release](#).
Contact information: RCoates@cdc.gov
The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention