

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

A CDC Perspective on Clinical Evaluation of Biomarkers

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Centers for Disease Control and Prevention (CDC)

October 6, 2008, Hinxton, UK



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://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?

**U.S. Institute of Medicine: Building a Better Delivery System, NAS,
2005; NY Times, 1/8/2008; McGlynn NEJM 2003;248:2635; Shuster
Milbank Quarterly 2005; 83:243; Schroeder NEJM 2007;357:1221F8.**



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/

EGAPP Working Group: www.egappreviews.org

Teutsch SM et al. *Genetics In Medicine* 2008;10(10):
available online at: www.geneticsinmedicine.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*

1997 U.S. National Institutes of Health – Department of Energy*Task Force Report *Promoting Safe & Effective Genetic Testing*

(*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

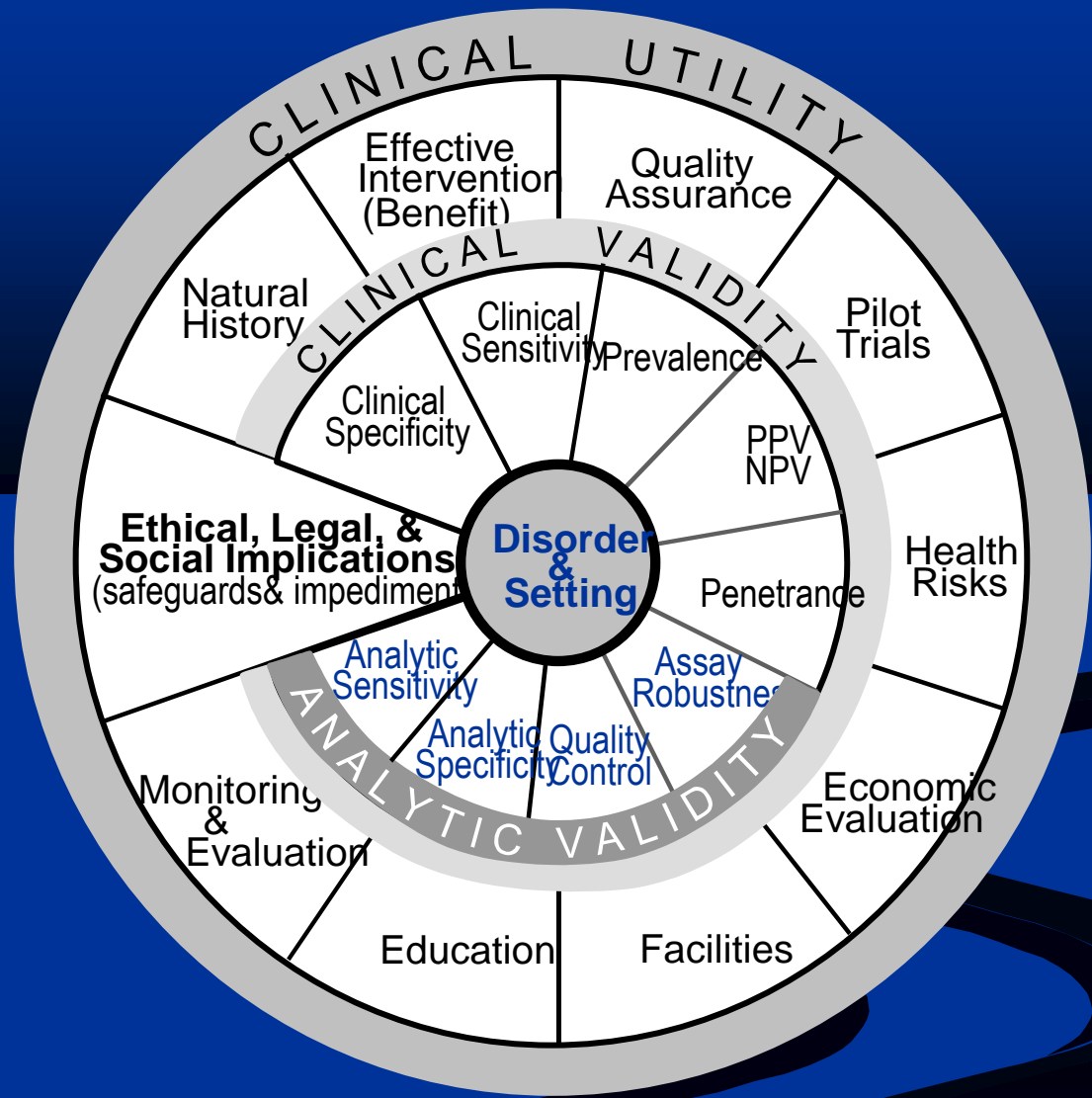
2008 SACGHS Draft Report:

Oversight of Genetic Tests

<http://www4.od.nih.gov/oba/sacghs.htm>



CDC ACCE Model Project (2000-2004)



44 questions
for biomarker
evaluation

Haddow JE, Palomaki GE. ACCE 2003.

www.cdc.gov/genomics/gtesting/ACCE/



CDC EGAPP Initiative 2003 – Present

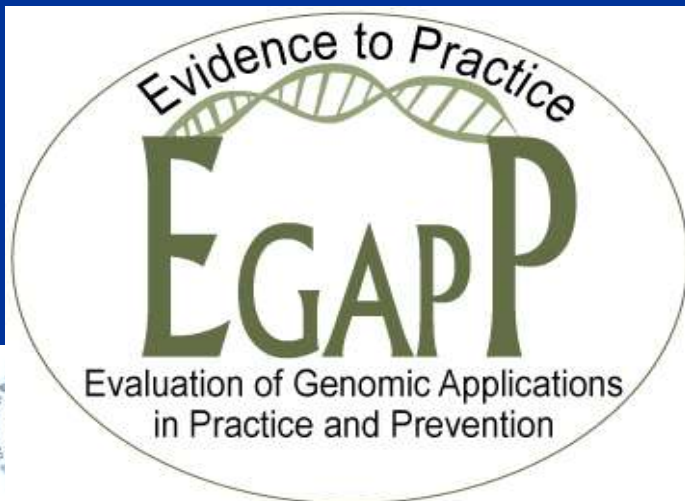
Evaluation of
Genomic
Applications in
Practice and
Prevention

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/qtesting/

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.ahrq.gov/clinic/uspstf07/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.ahrq.gov/clinic/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 overall balance of benefits & harms

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

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

www.cdc.gov/genomics/qtesting/

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/qtesting

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/qtesting/

www.egappreviews.org/



EGAPP Methods Paper Publication

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: Methods of the EGAPP Working Group

Steven M. Teutsch MD, MPH, Linda A. Bradley, PhD, Ned Calonge, MD, MPH, et al. on behalf of the EGAPP Working Group. *Genetics in Medicine*. 2008;10(10): available online at www.geneticsinmedicine.org/ (Electronically published ahead of print)



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?

Teutsch SM et al. *Genetics In Medicine* 2008;10(10):
available online at: 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)

Teutsch SM et al. *Genetics In Medicine* 2008;10(10):
available online at: www.geneticsinmedicine.org/



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

Teutsch SM et al. *Genetics In Medicine* 2008;10(10):
available online at: www.geneticsinmedicine.org/



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/



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

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December 2007 • Vol. 9 • No. 12

EGAPP recommendation statement

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

EGAPP Working Group *Genet Med* 2007;9(12):819-25. & www.egappreviews.org/

EGAPP Review - CYP450 Example

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)

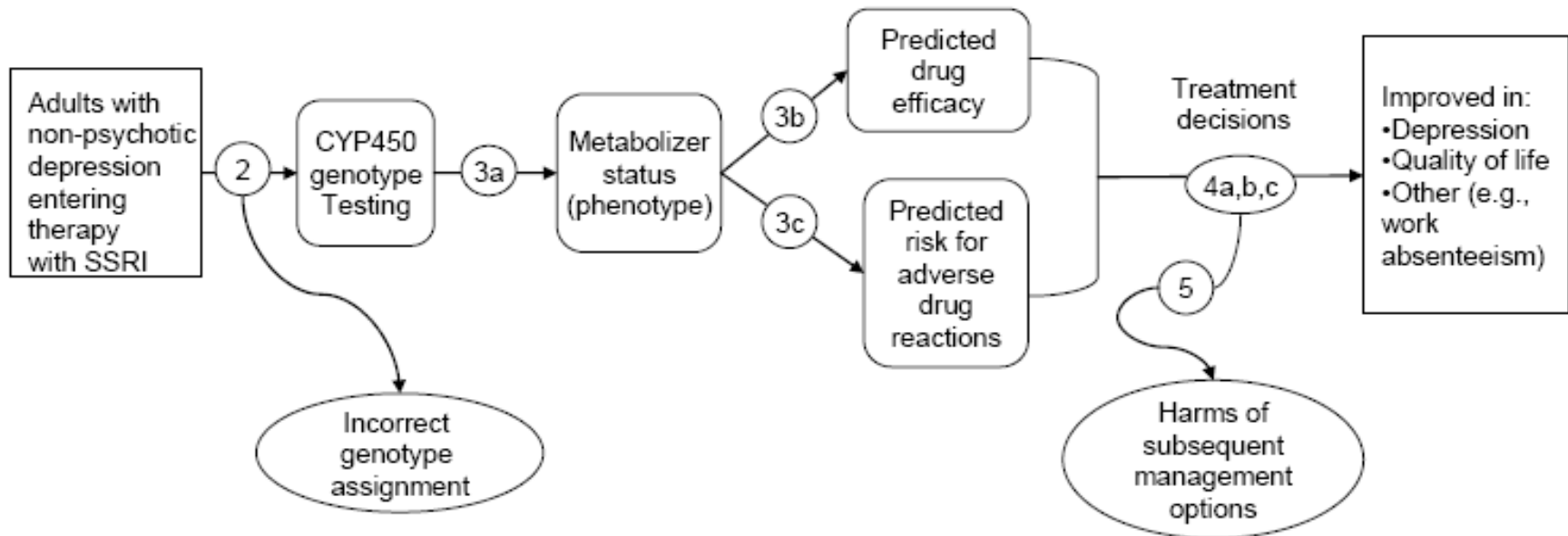
EGAPP Working Group Genet Med 2007;9(12):819-25.



EGAPP Review - CYP450 Example

Overarching Question

Analytic Framework:



EGAPP Working Group Genet Med 2007;9(12):819-25.

EGAPP Review - CYP450 Example

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 Working Group Genet Med 2007;9(12):819-25.



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?

EGAPP Working Group Genet Med 2007;9(12):819-25.



EGAPP Review CYP450- Evidence

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

EGAPP Working Group Genet Med 2007;9(12):819-25.



EGAPP Working Group CYP450 Recommendation

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

www.egappreviews.org/ (Gen Med 2007;9(12):819-285)



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

Katsanis SH et al. Science 2008;321:769-770



EGAPP Reviews & Recommendations In Press 2008

DNA testing strategies aimed at reducing morbidity & mortality from Lynch Syndrome

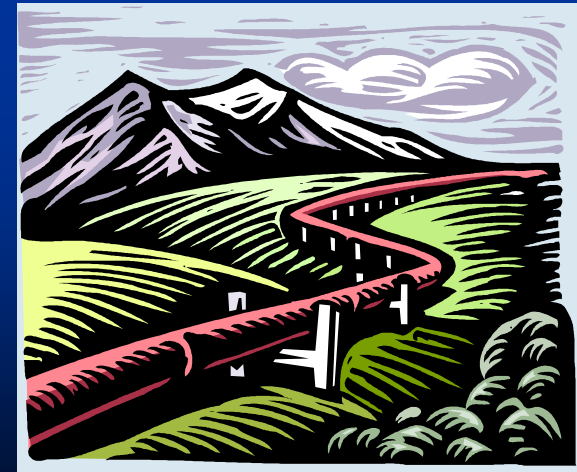
Can UGT1A1 genotyping reduce morbidity & mortality in patients with metastatic colorectal cancer treated with Irinotecan?

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

CDC-Supported Approach to Biomarker Evaluation

Major challenges:

Rapidly evolving field, large numbers of new tests

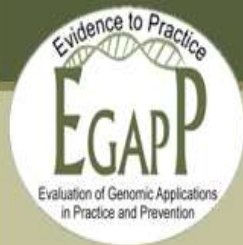
Complexity of markers, tests, test uses

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

Additional Information & Reviews available at www.egappreviews.org



Evaluation of Genomic Applications in Practice and Prevention



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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](#).

CDC-Supported Approach to the Evaluation of Biomarkers

CDC Public Health Genomics

www.cdc.gov/genomics/

EGAPP

www.cdc.gov/genomics/gtesting/

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

