Characteristics of Evidence For Medicare Coverage of Genetic Testing

Summary of Questions and Discussions Medicare Evidence Development and Coverage Advisory Committee (MEDCAC), February and May 2009

CMS/OCSQ/CAG/DID-DMSS

MEDCAC Meeting: February 25, 2009

DIAGNOSTIC GENETIC TESTS

Purpose of February MEDCAC Meeting

- "CMS wishes to obtain the MEDCAC's recommendation regarding the desirable characteristics of evidence that could be used by the Medicare program to determine whether genetic testing as a laboratory diagnostic service improves health outcomes. "

  – *Source: CMS, December 2008*

Diagnostic Genetic Testing (DGT)

- Purpose of DGT: provide information to make decisions about patient care

- Includes the following aspects:
  - Diagnosis
  - Prognosis
  - Assessing Response to Therapy

Clinical Examples of DGT

DGT Clinical Use:	Summary:
Diagnostic: Huntington's disease	Walker 2007 describes the genetic defect in the HD gene and its use in diagnosis.
Prognostic: Risk of distant recurrence of breast cancer based on gene expression profile	EGAPP 2009 found evidence to support an association between the 'recurrence score' (based on a 21-gene expression profile) and rates of distant metastases at 10 years among women with Stage I or II node-negative estrogen-receptor positive breast cancer treated with tamoxifen.
Assessing response: Colorectal cancer response to chemotherapy	A preliminary clinical opinion of the American Society of Clinical Oncologists reviews the evidence that colorectal cancer patients with mutated *K-ras* have little or no chemotherapeutic response to certain EGFR receptor antagonist agents such as cetuximab or panitumumab.

Invited Guest Speakers: February 2009

- Thomas A. Trikalinos, MD, PhD
  Assistant Director, Tufts-New England Medical Center EPC
  Assistant Professor of Medicine, Tufts University

  "Technology Assessment: Genetic Testing"
  [Sponsor: Agency for Healthcare Research and Quality (AHRQ)]

- Ralph J. Coates, PhD
  Associate Director for Science
  Office of Public Health Genomics, NCCDPHP
  Centers for Disease Control and Prevention (CDC)

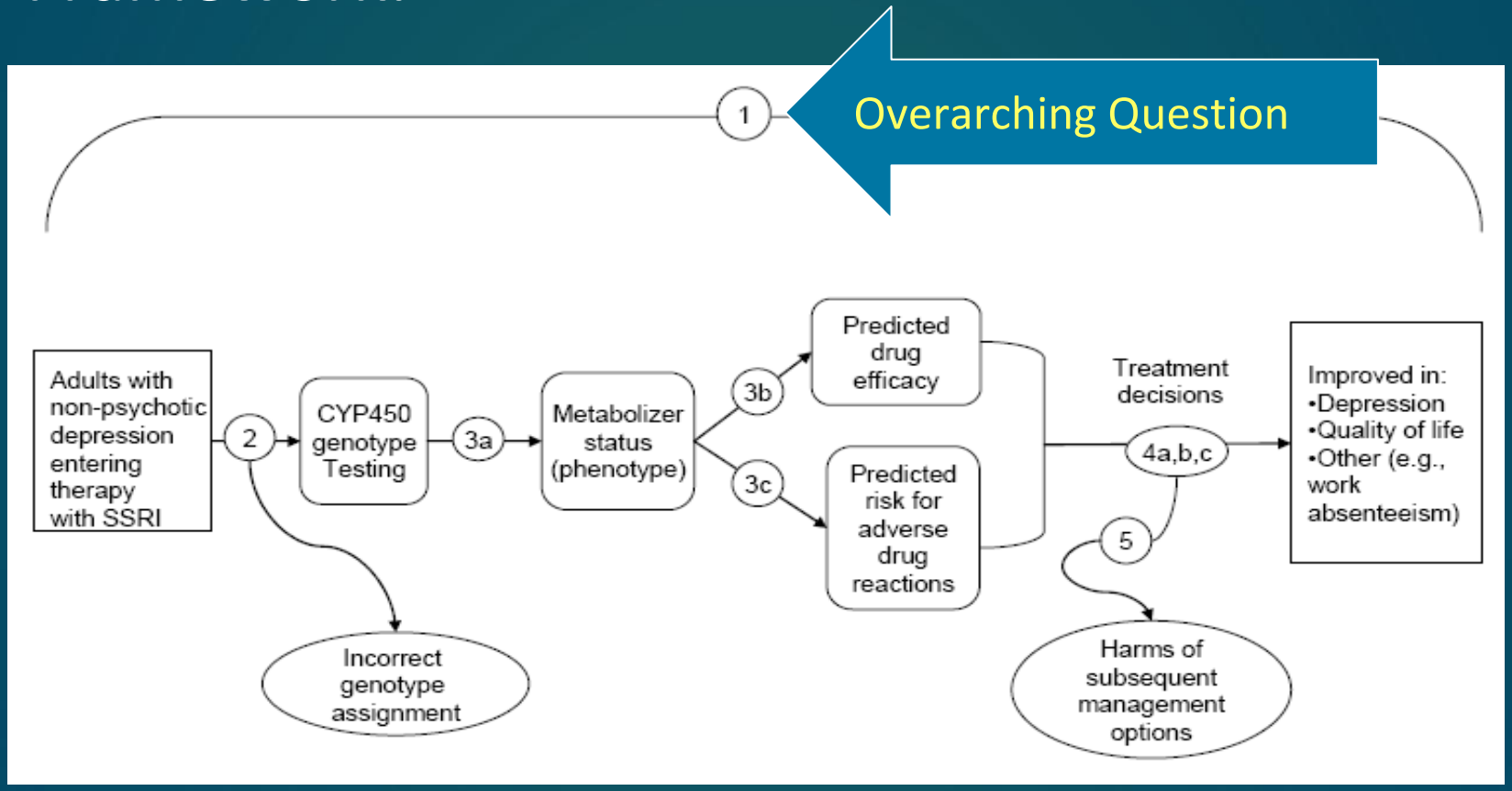
  "EGAPP Methods for Assessing Evidence of Health Improvement from Use of Genomic Tests "

EGAPP ACCE Criteria

- Evaluation of Genetic Applications in Practice and Prevention (EGAPP) Working Group, supported by CDC/NOPHG
- ACCE criteria address:
  - A: Analytic Validity
  - C: Clinical Validity
  - C: Clinical Utility
  - E: Ethical, legal and social implications

EGAPP Review - *CYP450* Example

Framework:



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

EGAPP *CYP450* Evidence Review

Analytic validity

- Sensitivity and specificity 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.

Questions, February 2009

- Q1: "Are the desirable characteristics of evidence for DGT different from the desirable characteristics of diagnostic testing in general?"
- MEDCAC's Response: No
  - Evidence should be rigorous for any diagnostic test
  - EGAPP's ACCE criteria was considered a desirable evidence framework
  - Public is served by robust evidence about DGT
  - Harms as well as benefits of DGT were noted

Questions, February 2009

- Q2: “What are the desirable characteristics of evidence for determining analytical validity of diagnostic genetic tests?”
- MEDCAC’s Response:
  - Relevant factors in the EGAPP’s ACCE criteria were considered to provide a desirable framework for determining analytical validity

Questions, February 2009

- Q3: " … (A)re there meaningful differences in the desirable and/or necessary characteristics of evidence about the effect of DGT on outcomes for …
  - Diagnostic assessment
  - Prognostic assessment
  - Pharmacogenomic assessment?"
- MEDCAC consensus:
  - No difference in characteristics of evidence about DGT – outcome among the paradigms above
  - Panel noted challenge of pharmacogenomic assessment due to genome-disease-drug linkage.

Questions, February 2009

- Q4: MEDCAC panelists were asked how confident they were that methodologically rigorous evidence was sufficient to infer whether DGT improves three types of patient-centered health outcomes, namely:
  a. Change in patient management by physician
  b. Indirect healthcare outcomes (e.g., change in lab result)
  c. Direct healthcare outcome (e.g., mortality, adverse events)

DGT and Evidence of Effectiveness

Outcome	Voting MEDCAC panelists	All MEDCAC panelists
Change in management	2.10	1.79
Indirect healthcare outcome (e.g., lab test value)	3.30	3.00
Direct healthcare outcome (e.g., mortality)	4.80	4.50

Note: MEDCAC panelists' votes from 1 to 5 indicated:

1 – low confidence

5 – high confidence

Questions, February 2009

- Q5: “Are there ethical issues particular to genetic testing that may alter the methodologic rigor of studies of genetic testing?”
- MEDCAC response:
  - Methodologic rigor contributes to ethical rigor
  - A lower methodologic standard would detract from ethical generation of evidence for GT

Questions, February 2009

- Q6: "Does the age of the Medicare beneficiary population present particular challenges that may compromise the generation and/or interpretation of evidence regarding GT?"
- MEDCAC response: No consensus was reached
- Panel members noted:
  - Rarity of Mendelian single-gene disorders in the Medicare beneficiary population
  - Challenges due to prevalence of polypharmacy, multiple comorbidities and competing causes of death for studies of DGT in this population.

Other Comments: February 2009

- The need for additional evidence on DGT and outcomes was mentioned by MEDCAC panelists.
- Several MEDCAC panelists suggested that, using its authority to cover with evidence development, CMS might encourage studies to collect additional evidence about the effect of DGT on patient outcomes in Medicare beneficiaries.

MEDCAC Recommendations About Genetic Test Evidence

- Expectations should be at least as high as for other diagnostic technologies
- Ethical imperative to drive rigorous evidence
  (Ethics cannot be an excuse to accept inadequate evidence; just the opposite.)
- Consider the clinical context
  (How will the test be used with other diagnostic modalities? What are the consequences of misguided treatment or non-treatment?)
- Strong preference for direct patient-centered healthcare outcomes e.g., mortality, functional status, adverse events.

MEDCAC Meeting: May 6, 2009

SCREENING GENETIC TESTS

Purpose of May MEDCAC Meeting

- "This meeting will focus on the desirable characteristics of evidence that are needed to evaluate screening genetic test(s) for Medicare coverage. As such CMS wants to determine whether genetic testing as a laboratory screening service improves health outcomes for the Medicare population."

  – *Source: CMS, 2/2009*

“Screening Test”

- A test to detect a disease in a person without signs or symptoms of that disease.
- Examples:
  - Mammography for breast cancer
  - PSA for prostate cancer
  - FOBT for colorectal cancer

Screening Coverage

- Under Medicare Part B, coverage has been approved for preventive services benefits, including:
  - Screening Pap smears and pelvic exams,
  - screening mammograms,
  - colorectal cancer screening tests,
  - diabetes screening tests, and
  - lipid screening tests.

Screening and MIPPA 2008

- Pursuant to Section 101 of the Medicare Improvements for Patients and Providers Act of 2008 (MIPPA) (Public Law 110-275), effective January 1, 2009, CMS may cover additional preventive services that fulfill certain statutory requirements.

MIPPA Section 101

- A new preventive services benefit may be considered for coverage by HHS ***if*** CMS determines through a National Coverage Determination (NCD) process that
  - It is reasonable and necessary for the **prevention or early detection** of an illness or disability;
  - It is **recommended with grade A or B** rating by the US Preventive Services Task Force (USPSTF); &
  - It is **appropriate for persons eligible for Medicare A/B**.

MIPPA § 101 (continued)

- "... As part of the use of such process *(for making NCDs for a new preventive services benefit not otherwise described in this Title)*,
  - "the Secretary may conduct an assessment of the **relation between predicted outcomes and the expenditures for such service** and
  - "**may take into account the results of such assessment** in making such determination."

Invited Guest Speakers: May 2009

- W. Gregory Feero, MD, PhD
  Chief, Genomic Healthcare Branch
  National Human Genome Research
  National Institute of Health

  "Family History and Screening Genetic Testing"

- Steven Teutsch, MD, MPH
  Chief Science Officer
  LA County Public Health Department

  "Screening Genetic Testing: EGAPP Methods and Recommendations"

EGAPP Methods

ARTICLE

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

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The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative, established by the National Office of Public Health Genomics at the Centers for Disease Control and Prevention, supports the development and implementation of a rigorous, evidence-based process for evaluating genetic tests and other genomic applications for clinical and public health practice in the United States. An independent, non-federal EGAPP Working Group (EWG), a multidisciplinary expert panel selects topics, oversees the systematic review of evidence, and makes recommendations based on that evidence. This article describes the EGAPP processes and details the specific methods and approaches used by the EWG.
***Genet Med* 2009:11(1):3–14.**

***Key Words:** Evidence-based medicine, review, systematic*

The completion of the Human Genome Project has generated

dresses the previously proposed[6,7] components of evaluation: *A*nalytic and *C*linical validity, *C*linical utility and associated *E*thical, legal and social implications. The ACCE Project examined available evidence on five genetic testing applications, providing evidence summaries that could be used by others to formulate recommendations.[13–16] Systematic reviews on genetic tests have also been conducted by other groups.[17–20]

Genetic tests tend to fit less well within "gold-standard" processes for systematic evidence review for several reasons.[21–24] Many genetic disorders are uncommon or rare, making data collection difficult. Even greater challenges are presented by newly emerging genomic tests with potential for wider clinical use, such as genomic profiles that provide information on susceptibility for common complex disorders (e.g., diabetes, heart disease) or drug-related adverse events, and tests for disease prognosis.[25,26] The actions or interventions that are warranted based on test results, and the outcomes of interest, are

Genetics in Medicine 2009;11:3-14

egappreviews.org/workingrp/methods.htm

AHRQ Technology Assessments for Screening (Year/Status)

- Screening Immunoassay Fecal Occult Blood Testing (FOBT) (2003)
- Cost-Effectiveness of Stool DNA Testing to Screen for Colorectal Cancer (2007)
- Cost-Effectiveness of CT Colonography to Screen for Colorectal Cancer (in progress)

Source: http://www.ahrq.gov/clinic/techix.htm

Questions, May 2009

- Q1: “Are there differences in the desirable characteristics of evidence about screening genetic tests versus those of screening tests in general?”

  Discussion

- Q2: “What are the desirable characteristics of evidence for determining the analytical validity of screening genetic tests?”

  Discussion

Questions, May 2009

- Q3A: "Beyond aspects of analytical validity, are there meaningful differences in the desirable and/or necessary characteristics of evidence about the effect of screening genetic testing on outcomes? If yes, please consider question 3 separately for each paradigm."
  - Early detection of disease in an asymptomatic person
  - Early treatment of disease (before signs or symptoms are apparent)
- Q3B: "What comparative data are needed on alternative strategies for screening?"

Questions, May 2009

- Q4: "For each type of outcome below, how confident are you that methodologically rigorous evidence on the outcome is sufficient to infer whether or not screening genetic testing is effective for the prevention or early detection of illness or disability?"

  [Voting question: 1 to 5 indicating lower or higher confidence.]

  a) Additional (confirmatory) diagnostic procedure

  b) Survival

  c) Other patient-focused healthcare outcomes e.g., functional status, incidence of adverse events

Desirable Evidence of SGT Outcomes

Outcome of SGT	Voting members	All panelists
Additional (confirmatory) diagnostic procedures	N/V	N/V
Survival	3.92	3.50
Other patient-focused health outcome (functional status; adverse event incidence)	3.42	3.25

Note: numeric voting from 1 to 5 indicated:

1 – low confidence

5 – high confidence

Questions, May 2009

Q5: "What are the desirable measures of the cost-effectiveness of screening genetic tests for the prevention or early detection of illness or disability?

[Rank a – c as (1=least thru 3=most) as desirable measures; and/or identify other measures that would be appropriate.]

a) Quality-adjusted life years (QALYs) gained due to screening?

b) Decreases in incidence of illness or disability, or net gains in other patient-focused healthcare outcomes?

c) Net changes in lifetime costs of illness or disability?"

Q6: "What are the desirable methodological characteristics of studies of cost-effectiveness for screening genetic tests for the prevention or early detection of illness of disability?"

For discussion.

Desirable Cost-Effectiveness Measures

Measure	Voting members	All panelists
Quality-adjusted life years (QALYs) gained	2.83	2.88
Decreases in incidence of illness or disability, or net gains in other patient-focused healthcare outcomes	2.67	2.75
Net changes in lifetime costs of illness or disability	1.92	2.00

Note: Votes (1 to 3) indicated:

1 – less desirable measure

3 – more desirable measure

Questions, May 2009

Q7: "Are there ethical issues particular to screening genetic testing that may alter the methodologic rigor of studies of genetic testing?"

Please discuss the existence, relevance, and impact of such issues.

Q8: "Does the age of the Medicare beneficiary population present particular challenges that may compromise the generation and/or interpretation of evidence regarding genetic testing?"

Please discuss the existence, relevance, and impact of such challenges.

MEDCAC Recommendations About Screening Genetic Test Evidence

- Expectations should be at least as high as for other diagnostic technologies
- Ethical imperative to drive rigorous evidence (Ethics cannot be an excuse to accept inadequate evidence; just the opposite.)
- Essential to consider evidence of harms from screening, not only benefits (Vulnerability of aged population to harms was emphasized)
- Quality-adjusted life years or decreased incidence of disease were preferred study outcomes.

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