

# Clinical Guidelines and Genetic Tests

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# What is a Clinical Guideline?

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- Preformed recommendation issued for the purpose of influencing a decision about a health intervention

# Guidelines Have Always Existed

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- Professors
- Textbooks
- Journal articles
- Editorials
- Consensus panels
- Insurance decisions
- Community standards

# Why Renewed Attention on Guidelines?

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- Many guidelines have been wrong
- Unacceptable practice variation (cost)
- Literature increasingly complex
- Patient interest in more participation
- Legal pressure
- Availability of more sophisticated methods

# Why are Clinical Guidelines Needed?

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- No one can keep up
- Make sense out of voluminous literature
- Deal with complex decisions
- Improve quality of decision making
- Provide justification to patients, payers, legal system

# How Are Guidelines Useful?

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- Transmit medical knowledge
- Assist patient and physician decisions
- A way to set clinical norms
- Quality improvement
- Privileging and credentialing
- Payment and cost control
- Medicolegal evaluation

# Approaches to Guidelines

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- Global subjective judgment
- Explicit and evidence-based

# Hallmarks of an Evidence-Based Guideline

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- Explicit
- Transparent
- Publicly accountable



# General Characteristics that Should be Specified (IOM)

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- Clinical condition
- Health practice
- Target population
- Health care setting
- Type of clinician
- Purpose
- Source and sponsorship

# Process Characteristics (AHRQ)

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- Panel selection
- Problem specification
- Literature search strategy
- Literature analysis
- Evidence summarization
- Recommendation rationale
- Clinical outcomes
- Sensitive to cost and practicality

# Desirable Attributes (AHRQ)

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- Valid
- Reliable
- Applicable
- Flexible
- Clear
- Multidisciplinary
- Reviewed
- Documented

# Validity (AHRQ)

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- Projected health outcomes
- Projected costs
- Evidence/policy rationale
- Evidence-based
- Literature review
- Literature evaluation
- Strength of evidence

# EGAPP — A Model Project from the Centers for Disease Control and Prevention

**E**valuation of  
**G**enomic  
**A**pplications in  
**P**ractice and  
**P**revention

# Parents of EGAPP

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- Growing availability and promotion of genetic tests
- Clinician need for authoritative advice
- Natural evolution of "evidence-based" processes used previously (example of US Preventive Services Task Force)

# Challenges to Using EBM Methods for Genetic Tests

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- Many conditions are uncommon or rare
- Interventions and clinical outcomes are not well defined
- Tests have inadequate sensitivity and specificity in unselected populations, with poor predictive value
- Tests are proposed and marketed based on descriptive evidence and pathophysiological reasoning, with no clinical trials
- Overlay of advocacy from industry and patient interest groups

# EGAPP Background

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- CDC principal sponsor
- Non regulatory
- Independent, non-federal, multidisciplinary
- Minimize conflicts of interest
- Evidence-based, transparent, and publicly accountable



# EGAPP Goal

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- Establish and evaluate a systematic and sustainable mechanism for pre- and post-market assessment of genomic applications in the United States

# Methodology

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- Topic selection
- Analytic framework, explicit search strategy, quality assessment, strength of evidence
- Attention to analytic and clinical validity
- Specification of clinical outcomes

# Categories of Outcome

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- Diagnostic thinking/health information impact
- Therapeutic choice
- Patient outcomes impact
- Familial and societal impact

# EGAPP Workplan

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- Develop methods
  - Select topics
  - Define relevant clinical outcomes
  - Methods: conduct reviews, make recommendations
- Test methods
  - CYP450
  - HNPCC
  - Ovarian cancer screening

# Brief Reviews

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- Limited data available
- Not covering all components
- Narrow scope
- Not in depth
- More like technology assessment
- First review UGT1A1

# EGAPP Timeline & Products

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- 3-year project, extended to 4 (5?)
  - Midway through year 3
- Products
  - 3-5 major reviews
  - 2-3 brief reviews
  - Methods
  - Evaluation

# Testing for CYP450 Clinical Scenario

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

# Testing for CYP450 Methods

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- Analytic framework
- Key questions
- Explicit search strategy, standard abstract, full text, two reviews
- Assessments of quality
- Evidence tables where possible



# Testing for CYP450

## Key Questions

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- Does testing improve outcomes?
- Test characteristics
- Correlations of tests with metabolism, efficacy, adverse effects
- Effects on management, clinical outcomes, decision-making
- Harms associated with testing

# Testing for CYP450

## Preliminary Observations

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- Some data on sensitivity and specificity
- No studies linking testing to clinical outcomes
- Small, poor-quality cohort studies predominate
- No comparisons of alternative testing strategies
- Failure to account for all relevant genotypes

# Other Topics in Review

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- Tests for ovarian cancer
- HNPCC for patients with colorectal cancer
- UGT1A1 for patients treated with irinotecan for colorectal cancer
- Gene expression profiling in breast cancer
- Genomic profiling for cardiovascular disease
- CYP450 profiling for pain management

# Genetic Testing

## Apparent Gaps in Evidence

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- Prevalence in general population
- Penetrance
- Clinical trials comparing testing and intervention strategies
- Assessment of all relevant outcomes
- Attention to benefits as well as harms
- Cost and feasibility

# Personal Observations

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- A large and growing number of tests marketed in the United States to consumers and clinicians
- A national attitude that more is always better and that technology is always good
- An environment hostile toward regulation
- Potential for benefits and harms
- Limited evidence