

Evidence Based Guidelines for Genomic Applications in Practice and Prevention

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What is a Clinical Guideline?

- Preformed recommendation issued for the purpose of influencing a decision about a health intervention
- Clinician's need and want authoritative advice

Guidelines Have Always Existed

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

Why Renewed Attention on Guidelines?

- A lot of expert advice has been wrong
- Unacceptable practice variation (cost)
- Literature increasingly complex
- Patient interest in more participation
- Legal pressure
- Availability of more sophisticated methods

Diagnosis of Low Back Pain (courtesy R. Deyo)

- "80% of back pain is caused by weak or tense muscles"
- "the majority of low back pain originates in the sacral ligaments."
- "in more than 50% the facet joint is the site of dysfunction."
- "90 to 95% of back pain is due to discs."
- "An extremely high percentage have fascial problems."
- "50-70% of chronic symptoms are psychological in origin."

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Why are Clinical Guidelines Needed?

- 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?

- 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

- Global subjective judgment
- Explicit and evidence-based

Hallmarks of an Evidence-Based Guideline

- Explicit
- Transparent
- Publicly accountable

General Characteristics that Should be Specified (IOM)

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

Process Characteristics (AHRQ)

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

Desirable Attributes (AHRQ)

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

Validity (AHRQ)

- 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

Evaluation of
Genomic
Applications in
Practice and
Prevention

Parents of EGAPP

- 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

- 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

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

EGAPP Goal

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

Methodology

- 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

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

EGAPP Workplan

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

Brief Reviews

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

EGAPP Timeline & Products

- 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

- 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

- 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

- 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

- 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

- 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

- 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

- 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