Evidence-Based Practice: What It Is and Why It Matters

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OUTLINE

- What is evidence-based practice?
- The concept of evidence, and its role in decision making
- Challenges in assessing evidence in genetics
- A deeper dive into some tools of the trade
- Examples of understanding evidence in the "real world"
- Why does evidence-based practice matter?
- Resources

What is Evidence-Based Practice?

Evidence-Based Practice (EBP)
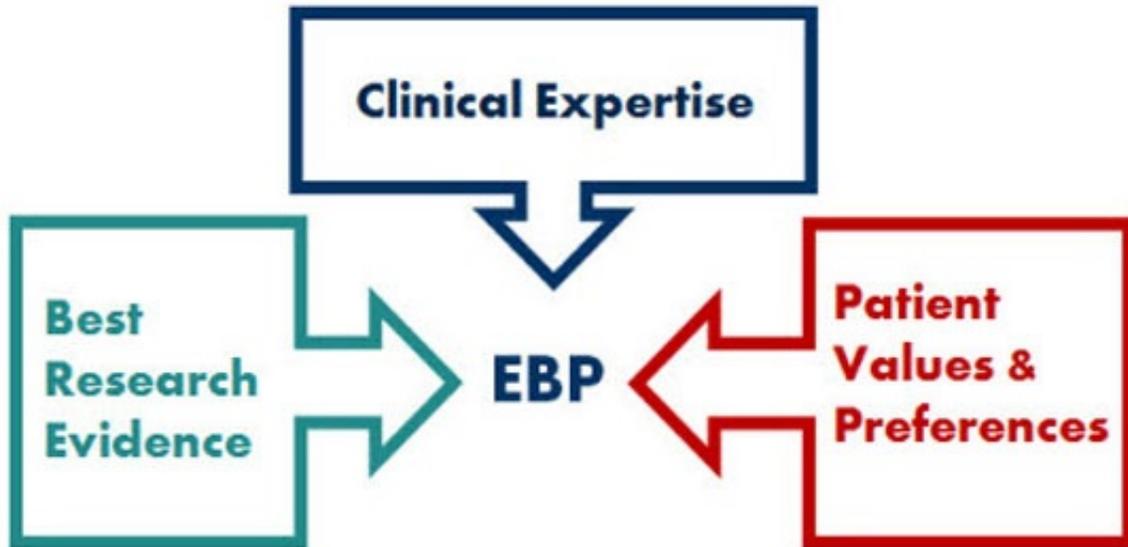
"Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research." Sackett et al., 1996

Fundamental Tenets of Evidence-Based Medicine (EBM)

- Evidence hierarchy as a guide in clinical decision making
- Evidence, on its own, is never sufficient to make a clinical decision

2008

Guyatt *et al*. User's Guides to the Medical Literature. 2nd Edn. 2008

Fundamental Tenets of Evidence-Based Medicine (EBM) cont.

- Awareness of best available evidence required for best decision making

- EBM helps us understand how trustworthy evidence is

- Evidence, on its own, is never sufficient to make a clinical decision
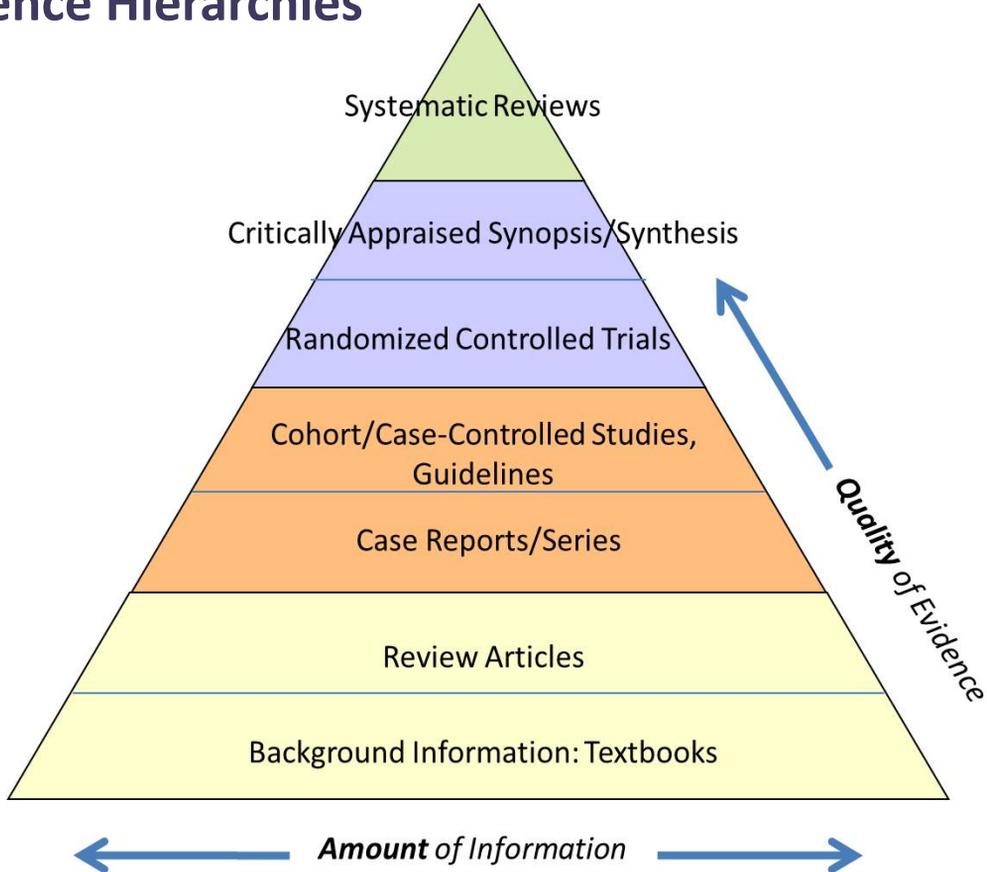
This one didn't change

2015

Guyatt et al. User's Guides to the Medical Literature. 3rd Edn. 2015

Evidence and Decision Making

Evidence Hierarchies

Systematic Reviews

Critically Appraised Synopsis/Synthesis

Randomized Controlled Trials

Cohort/Case-Controlled Studies, Guidelines

Case Reports/Series

Review Articles

Background Information: Textbooks

Quality of Evidence

Amount *of Information*

The Randomized Controlled Trial
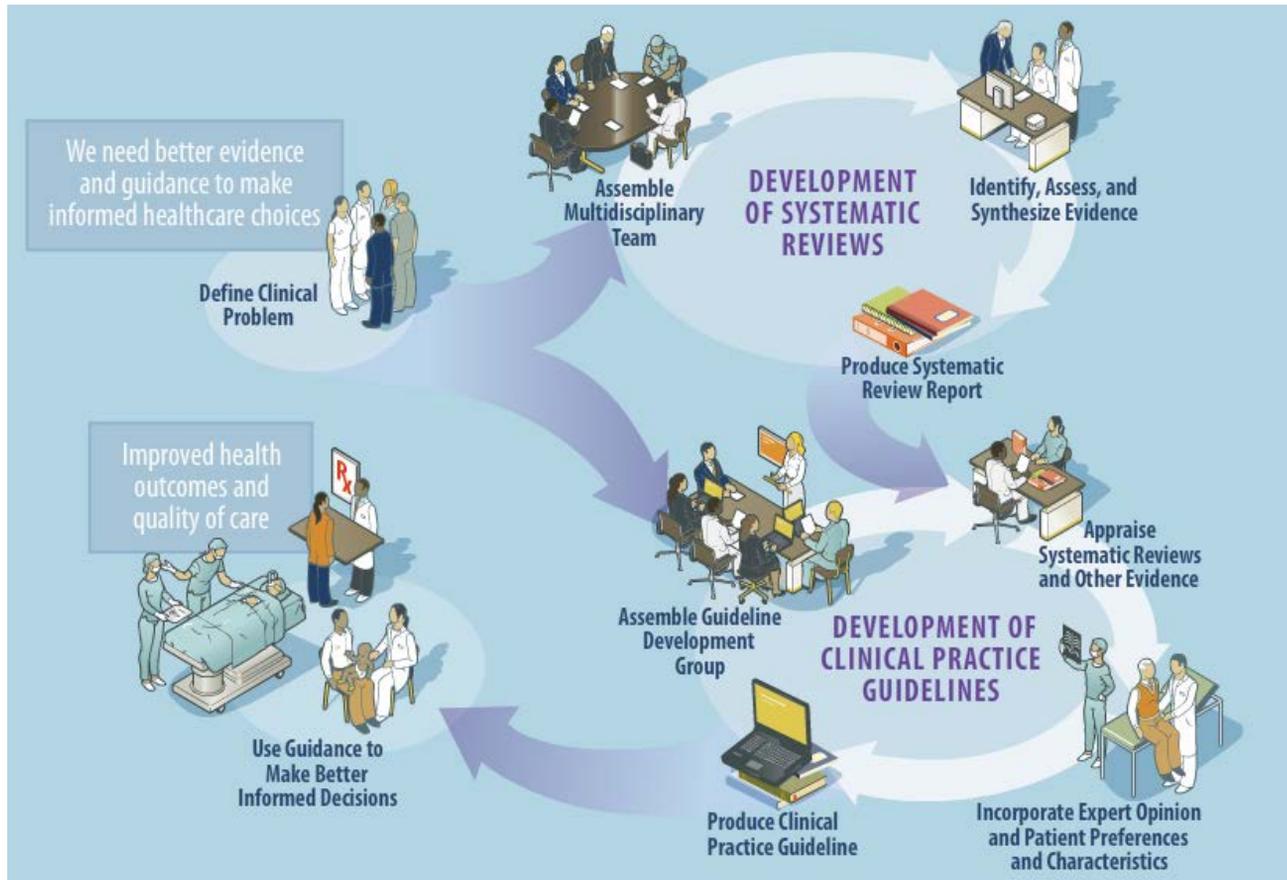

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

A New Hierarchy?

Randomised Control Trials

Cohort Studies

Case Control Studies

Case Series/Reports

Systematic Review/Meta Analysis
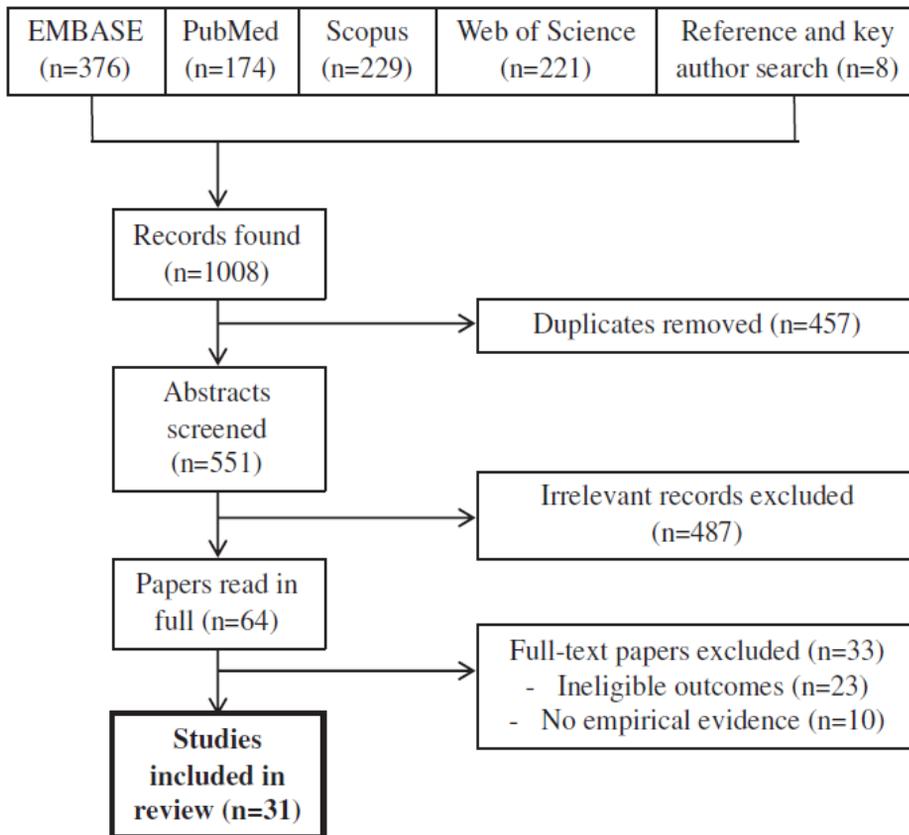
BMJ
Evidence-Based
Medicine

Systematic Reviews to Guidelines

Steps in Systematic Review

- Identify question(s)
- Create protocol
- Define inclusion/exclusion criteria
- Systematic literature search
- Select studies for inclusion
- Extract data
- Assess quality of evidence
- Evaluate risk of bias
- Synthesize results

Systematic Literature Search Flow

Assessing Evidence in Genetics

Organizing the Systematic Review

- Design and organization of systematic reviews can be especially challenging for genetic or genomic-based topics
- Often need to bring together information on
  - Analytic validity
  - Clinical validity
  - Clinical utility
  - Ethical, legal, and social implications
  - Other contextual issues

Analytic Validity

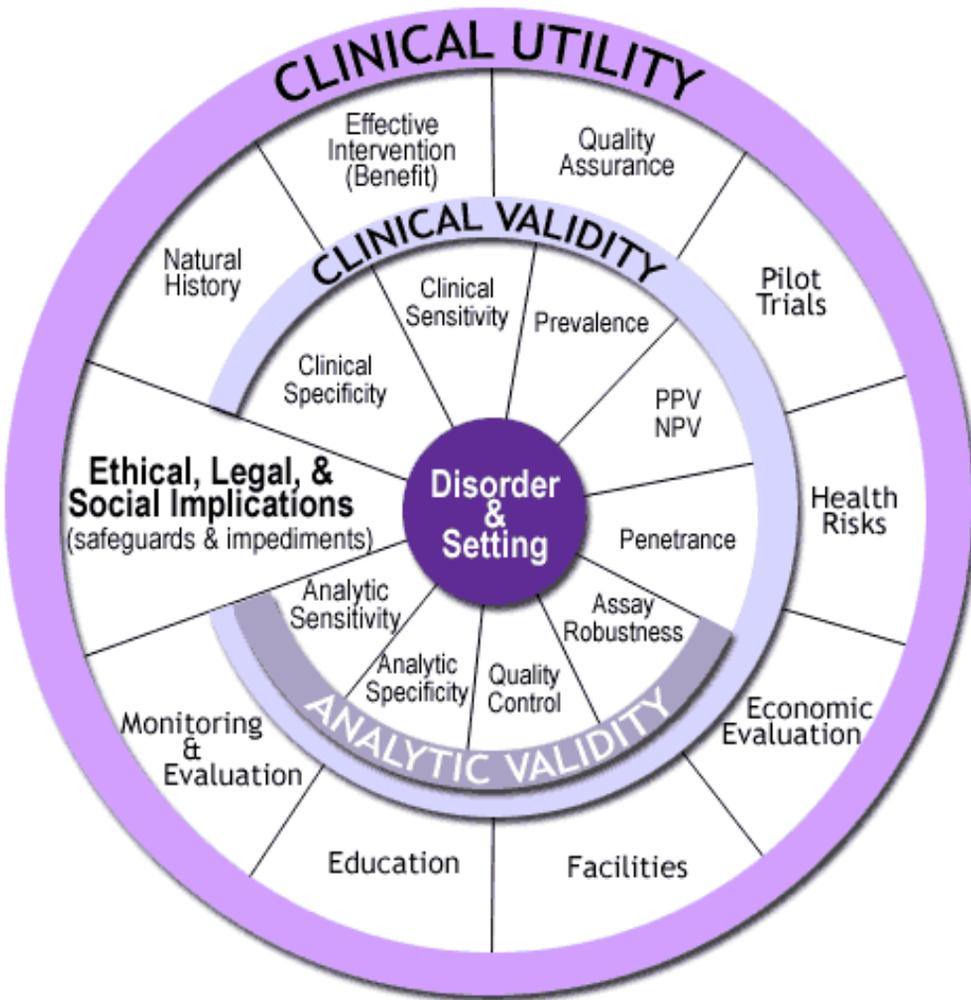- Ability of test to accurately and reliably detect the genotype of interest

Clinical Validity

- Ability of test to detect or predict the clinical disorder (or phenotype) of interest

Clinical Utility

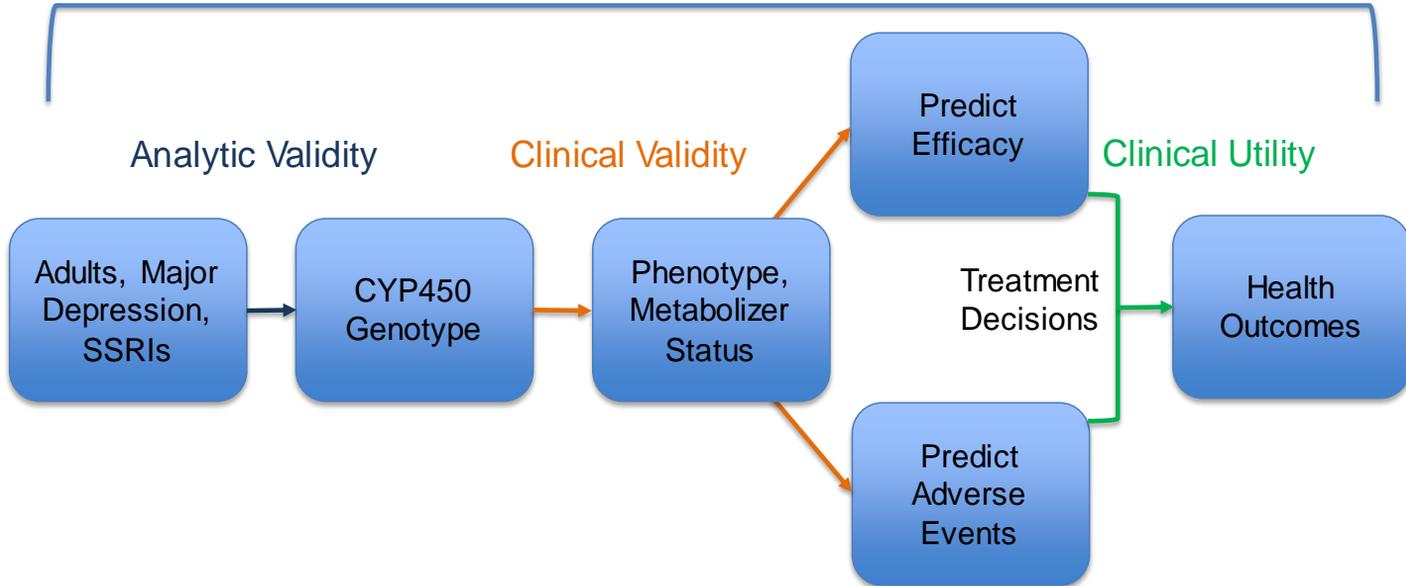- Influence of test on health outcomes; risks vs benefits of introducing test in practice

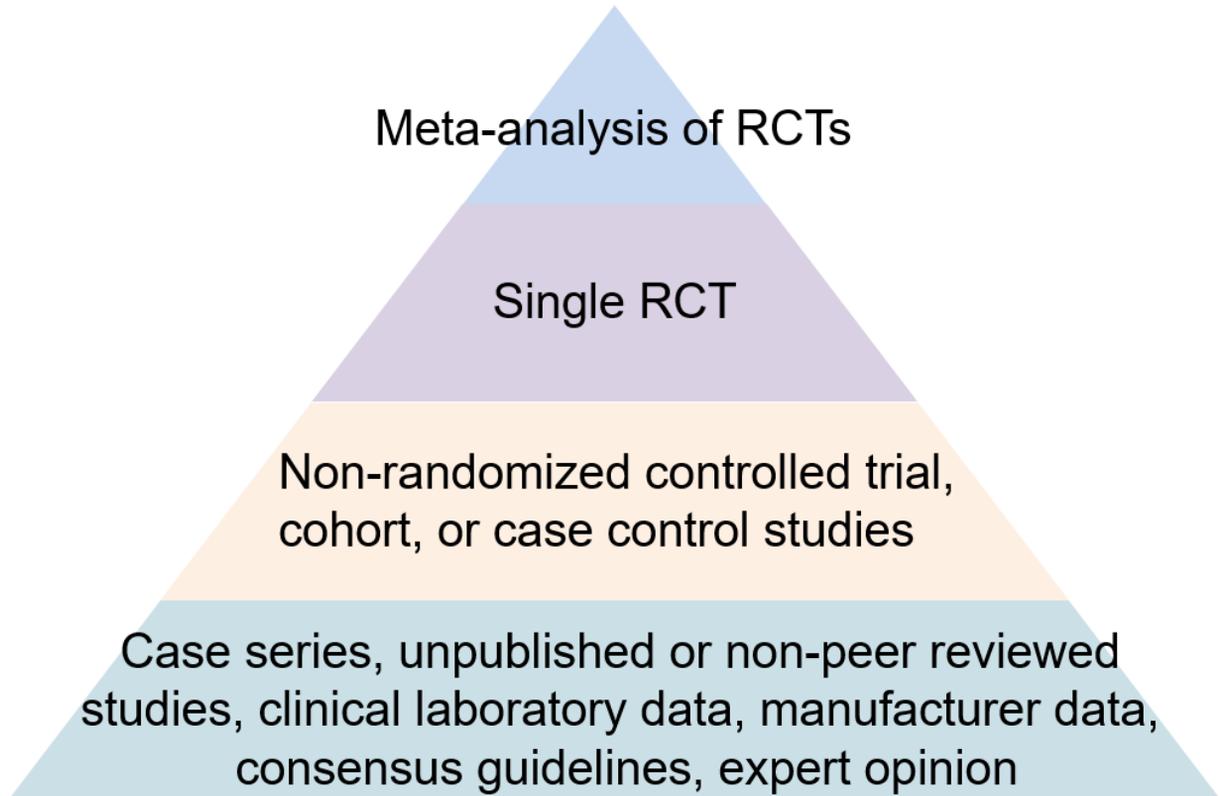| Elements of clinical utility	Explanation
Health outcomes	Health outcomes are outcomes that matter to patients and society: to prevent premature death, to restore or maintain functional health.
Strategy	Outcomes are generated not only by testing only but also by a management strategy that starts with testing but includes all downstream consequences of subsequent clinical management.
Probabilistic	Not all outcomes will be observed in everyone tested; evaluations will be made at the group level and expressed in terms of a distribution of outcomes.
Comparative	Utility is defined relative to a comparator strategy: current best standard practice.

ACCE Model

cdc.gov/genomics/gtesting/acce/

Example Analytic Framework

Overarching Question

Analytic Validity | Clinical Validity | Clinical Utility

Adults, Major Depression, SSRIs → CYP450 Genotype → Phenotype, Metabolizer Status → Predict Efficacy / Predict Adverse Events

Treatment Decisions → Health Outcomes

Clinical Utility

Meta-analysis of RCTs

Single RCT

Non-randomized controlled trial, cohort, or case control studies

Case series, unpublished or non-peer reviewed studies, clinical laboratory data, manufacturer data, consensus guidelines, expert opinion

Clinical Validity

Longitudinal cohort studies,
validated clinical decision rules

Case-control
studies

Case-control (low quality) and cross-sectional
studies, non-validated clinical decision rules

Case series, unpublished or non-peer reviewed studies,
clinical laboratory data, manufacturer data, consensus guidelines,
expert opinion

Analytic Validity

Collaborative study - large panel of well characterized samples, summary data from external proficiency testing schemes, etc.

Other data from proficiency testing schemes, well-designed peer-reviewed studies, expert panel reviewed FDA summaries
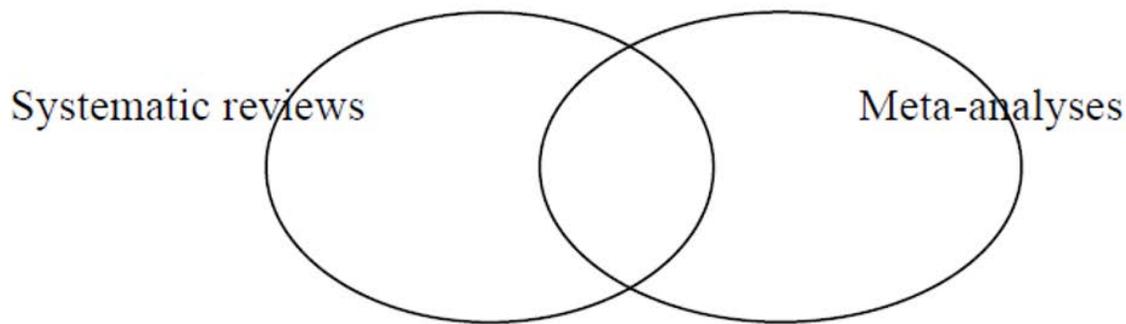
Poorly designed peer-reviewed studies

Unpublished or non-peer reviewed studies, clinical laboratory data, manufacturer data, studies on same method for different target

Meta-Analysis

Systematic Review vs Meta-Analysis

Systematic reviews   Meta-analyses

One slight complication is that these two terms are often used interchangeably, particularly in North America. In this learning material, the term 'systematic review' will refer to the entire process of collecting, reviewing and presenting all available evidence, while the term 'meta-analysis' will refer to the statistical technique involved in extracting and combining data to produce a summary result.

© The Cochrane Collaboration 2002

Objectives of Meta-Analysis

- Summarize results from individual studies
- Analyze differences in results among studies
- Overcome small sample sizes of individual studies to
- detect effects of interest
- analyze end points that require larger sample sizes
- Determine if new studies are needed to investigate an issue
- Generate new hypotheses for future studies

Effect Sizes

| TABLE 1	**COMMON EFFECT SIZE INDICES**[a]	
Index	**Description**[b]	**Effect Size**
Between groups		
Cohen's d[a]	$d = M_1 - M_2 / s$ $M_1 - M_2$ is the difference between the group means (M); s is the standard deviation of either group	Small 0.2 Medium 0.5 Large 0.8 Very large 1.3
Odds ratio (OR)	$\frac{\text{Group 1 odds of outcome}}{\text{Group 2 odds of outcome}}$ If OR = 1, the odds of outcome are equally likely in both groups	Small 1.5 Medium 2 Large 3
Relative risk or risk ratio (RR)	Ratio of probability of outcome in group 1 vs group 2; If RR = 1, the outcome is equally probable in both groups	Small 2 Medium 3 Large 4

Forest Plots
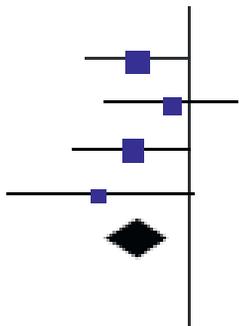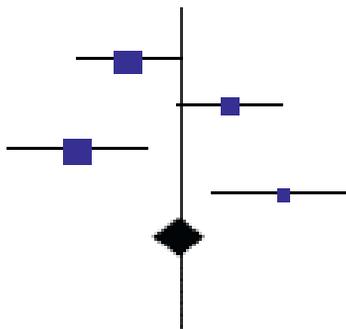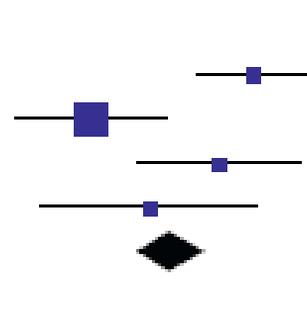
Checking for Potential Bias
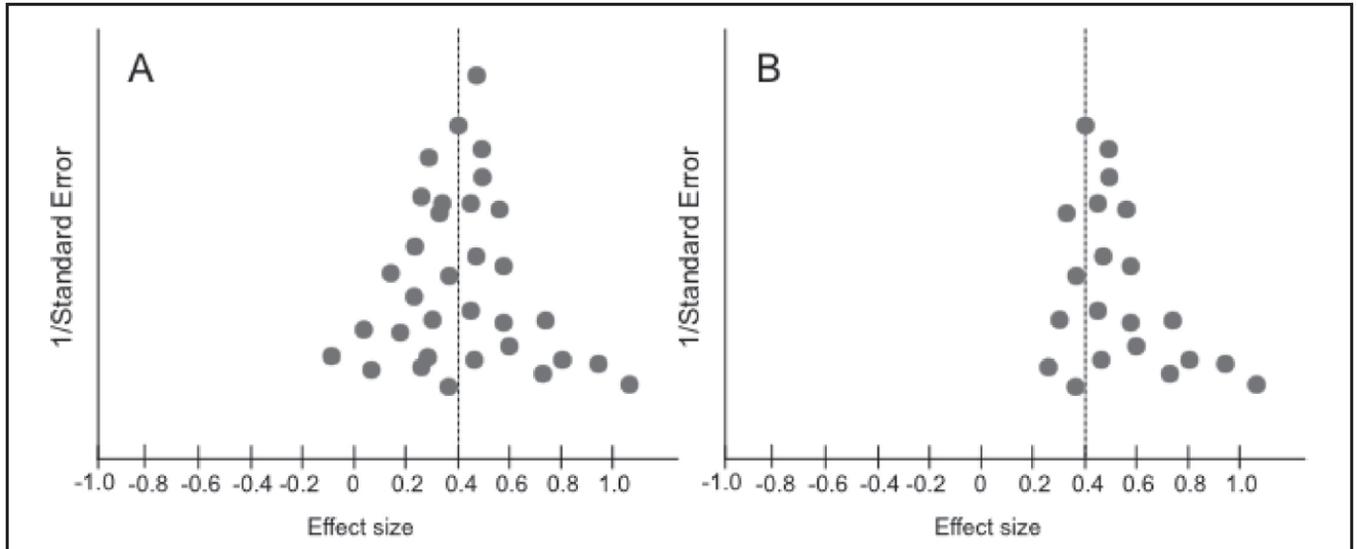
A. Symmetric Funnel Plot

B. Asymmetric Funnel Plot

Sources of Funnel Plot Asymmetry

Selection bias
- Publication bias
- Location biases:
    English language bias
    Citation bias
    Multiple publication bias

True heterogeneity
- Size of effect differs according to study size:
    Intensity of intervention
    Differences in underlying risk

Data irregularities
- Poor methodological design of small studies
- Inadequate analysis
- Fraud

Artefactual
- Choice of effect measure

Chance

Critically Appraising a Meta-Analysis

- Are the study results valid?
- Was a focused and clearly described research question presented?
- Was the literature search both systematic and reproducible?
- Was there a systematic study selection process?
- Characteristics of included studies were provided?
- Was there a quality assessment of included studies?

Critically Appraising a Meta-Analysis (continued)

- Statistical methods for combining studies were adequately reported?

- How heterogeneous were the pooled studies?

- Was there an assessment of publication bias?

- What were the main results of the study?

- What were the practical significance and statistical significance of the main results? What is the likelihood that these results were due to chance?

- Are the results generalizable? To whom are they applicable?

An Evidence Heuristic

An Evidence Heuristic

Prioritizing Genomic Applications for Action by Level of Evidence: A Horizon-Scanning Method

WD Dotson[1], **MP Douglas**[1,2], **K Kolor**[1], **AC Stewart**[1,2], **MS Bowen**[1], **M Gwinn**[1,2], **A Wulf**[1,3], **HM Anders**[1,2], **CQ Chang**[4], **M Clyne**[4,5], **TK Lam**[4], **SD Schully**[4], **M Marrone**[6], **WG Feero**[7], and **MJ Khoury**[1,4]

Levels of Evidence

- Tier 1 –base of synthesized evidence supporting implementation in practice

- Tier 2 – synthesized evidence not adequate to support routine implantation in practice; may still be useful in selective use strategies/decision making

- Tier 3 – synthesized evidence supporting recommendations against use, or no relevant synthesized evidence

Association Rules

Green	• FDA label requires use of test to inform choice or dose of a drug • CMS covers testing • Clinical practice guideline based on systematic review supports testing	Tier 1
Yellow	• FDA label mentions biomarker* • CMS coverage with evidence development • Clinical practice guideline, not based on systematic review, supports use of test • Clinical practice guideline finds insufficient evidence but does not discourage use of test • Systematic review, without clinical practice guideline, supports use of test • Systematic review finds insufficient evidence but does not discourage use of test • Clinical practice guideline recommends dosage adjustment, but does not address testing	Tier 2
Red	• FDA label cautions against use • CMS decision against coverage • Clinical practice guideline recommends against use of test • Clinical practice guideline finds insufficient evidence and discourages use of test • Systematic review recommends against use • Systematic review finds insufficient evidence and discourages use • Evidence availble only from published studies without systematic reviews, clinical practice guidelines, FDA label or CMS labels coverage decision	Tier 3

What is Practical in Public Health?

Public Health Genomics Knowledge Base (v4.0)	Tier Table Database

Disease/Disorder	Test to be Assessed	Intended Use
Lynch syndrome	Various strategies	Screening, cascade testing of relatives
Hereditary breast and ovarian cancer	Family history of known breast/ovarian cancer with deleterious BRCA mutation	Risk prediction; referral to counseling for BRCA genetic testing
Familial hypercholesterolemia (FH)	DNA testing and LDL-C concentration measurement	Cascade testing of relatives of people diagnosed with FH

Examples

Understanding Evidence in the "Real World"

Example: Importance of Understanding the Questions

The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis

Gareth J Hollands,[1] David P French,[2] Simon J Griffin,[3] A Toby Prevost,[4] Stephen Sutton,[3] Sarah King,[1] Theresa M Marteau[1]

WHAT THIS STUDY ADDS

The results of this updated systematic review with meta-analysis using Cochrane methods suggest that communicating DNA based disease risk estimates has little or no impact on risk-reducing health behaviour

Existing evidence does not support expectations that such interventions could play a major role in motivating behaviour change to improve population health

Some Limitations

- Pooled the results of small studies, with separate meta-analyses for
  - Diet
  - Smoking cessation
  - Physical activity
- What about differences between the genetic tests?

Example: Conflicting Results

Challenges and Limitations in the Interpretation of Systematic Reviews: Making Sense of Clopidogrel and CYP2C19 Pharmacogenetics
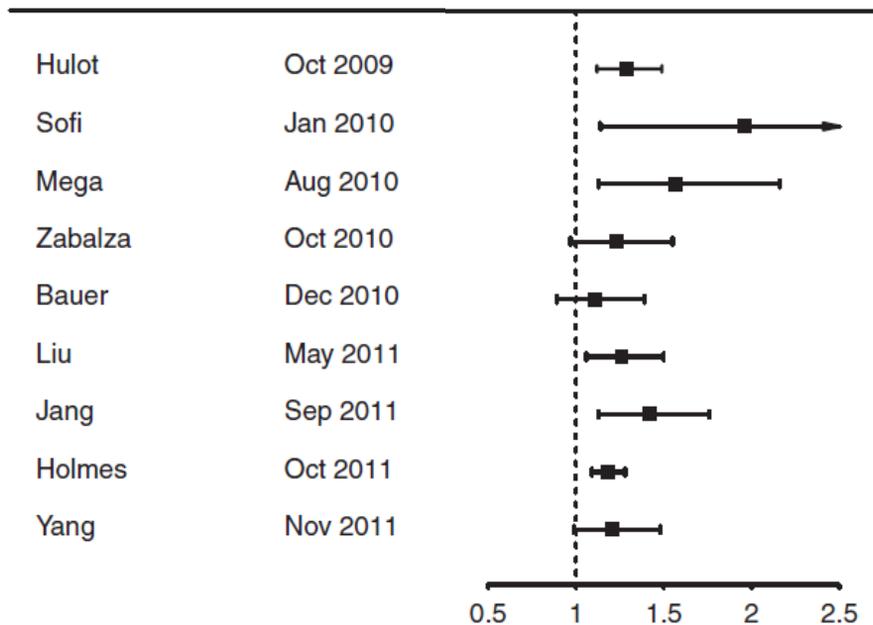
Why Does EBP Matter?

Evidence-Based Practice

- Enables evidence-informed, standardized protocols, not "cookbook" health care
- Affords transparent pathways to improving
  - Diagnosis
  - Treatment
  - Health outcomes

Some Resources

Sources of Systematic Reviews

- Advisory Committee on Heritable Disorders in Newborns and Children
- Agency for Healthcare Research & Quality (AHRQ)
- Cochrane Collaboration
- Health Technology Assessment International (HTAi)

Sources of Practice Guidelines

- American College of Medical Genetics and Genomics (ACMG)
- American College of Obstetricians and Gynecologists (ACOG)
- National Society of Genetic Counselors (NSGC)
- US Preventive Services Task Force (USPSTF)

Thank you!

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For more information, contact CDC
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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.