Best Approaches to Validate LDTs and Develop Clinical Evidence

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FOLEY HOAG LLP
Driving Business Advantage

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Coordinated Talks

- Best Approaches to Validate LDTs and Develop Clinical Evidence

- Negotiating the Payer's Maze: Essential Steps to Achieve Coverage and Reimbursement

Goals

- **Understand the difference between analytic validity, clinical validity, clinical utility**
- **Understand the Fryback/Thornbury approach to test evidence**
- **Understand the rapidly evolving "tech assessment industry" in the U.S.**
- **Understand the role of economic data in payer decision making**

  - ✓ *Be able to discuss and assess a candidate diagnostic test in a rationale framework*
  - ✓ *Understand the lay of the land well enough to engage and "fire test" consultants as needed*
  - ✓ *Understand when to "pull the trigger" on clinical launch and payer meetings*

Delivering Affordable Cancer Care in the 21st Century:
Workshop Summary

GENOME-BASED DIAGNOSTICS
Clarifying Pathways to Clinical Use

WORKSHOP SUMMARY

Evolution of Translational Omics

Lessons Learned and the Path Forward

Genome-Based Diagnostics: Clarifying Pathways to Clinical Use

Workshop Summary

PERSPECTIVES ON
BIOMARKER AND
SURROGATE ENDPOINT
EVALUATION

Roundtable on Translating Genomic-Based Research for Health

Assessing the Economics of Genomic Medicine: A Workshop

Evidence for Clinical Utility of Molecular Diagnostics in Oncology: A Workshop

Integrating Large-Scale Genomic Information into Clinical Practice

Workshop Summary

Generating Evidence for Genomic Diagnostic Test Development:

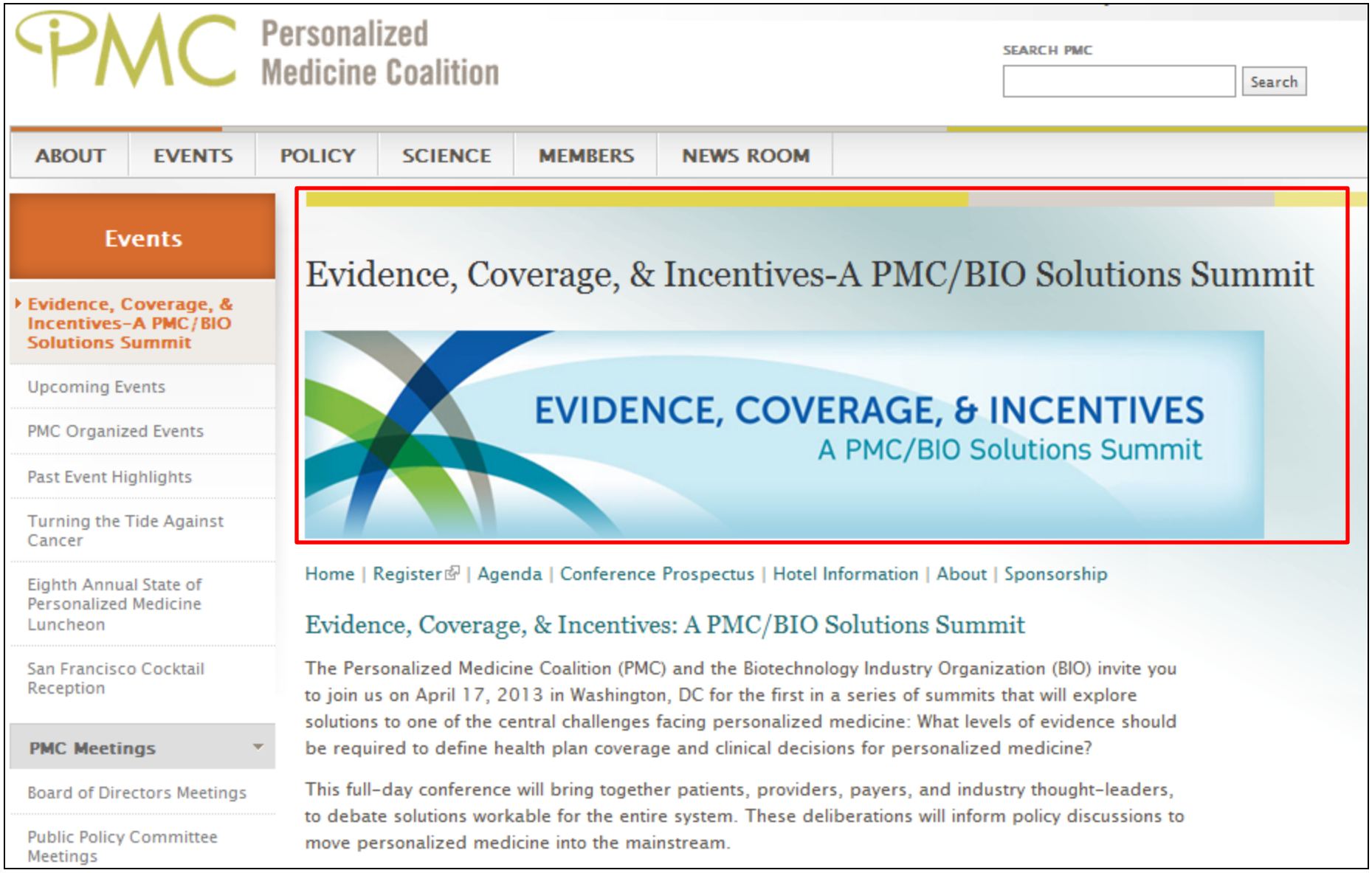
Workshop Summary

Genome-Based Therapeutics: Targeted Drug Discovery and Development

PERSPECTIVES ON
BIOMARKER AND
SURROGATE ENDPOINT
EVALUATION

Discussion Forum Summary

April 17, 2013



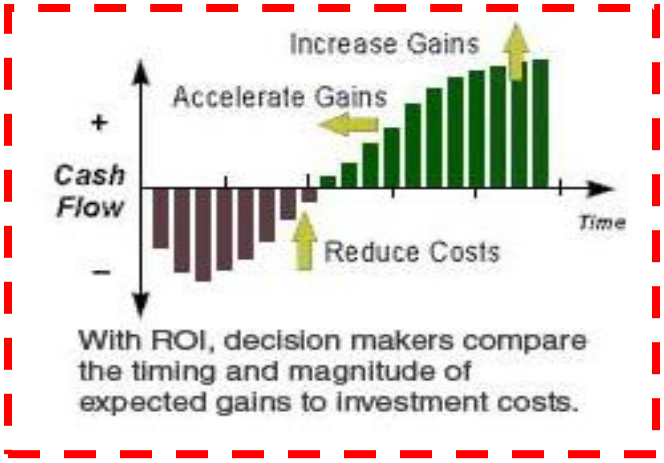
Many facets of commercializing a test

- What is the I.P.?
- What is the marketplace?
- What clinical need am I filling?
- Will the coding and fee schedule system work against me?
- Is the solution this test provides understandable?
- Does this test have enemies?
- Is it clearly better than stuff that is cheap or free?
- What has to be demonstrated and what can be assumed?
- What is the ROI of my investment and my expected return?
- How does this fit with what my lab does / can do?
- Who will be the new entrants that are predictable?
- What is the go-to-market and clinical adoption time line?
- Will I run afoul of the FDA? How about just New York State and Palmetto MOLDX?

“B-school 101”

With ROI, decision makers compare the timing and magnitude of expected gains to investment costs.

Significant Holes in Any of These Makes ROI Hard to Assess !



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http://www.business-case-analysis.com/return-on-investment.html

Personalized diagnostics: the struggle for position

For several major cancers, drug selection already pivots on biomarker results (e.g., trastuzumab for breast cancer, and gefitinib and erlotinib for lung cancer). Fast-paced advances in genomic and proteomic laboratory technologies could enable the widespread use of molecular testing before therapy selection in any field of medicine. This article describes two potentially large obstructions to such innovation. First, laboratory tests have traditionally been commodities with low prices, prices that matched the resources required to operate the laboratory technology itself. Assuming that the marginal costs of molecular laboratory technology will fall, there will be a widening chasm between estimated test revenue and the costs of innovative and definitive clinical trials, and regulatory approval for new tests. Without corrective action, even cost-saving laboratory tests could be in shortfall, because they will not be created through upfront investment. Second, it is argued that while diagnostic tests, drugs and surgical procedures should meet a fundamental standard for payer coverage ('will health outcomes be improved?'), molecular diagnostics could require different analysis pathways than those that are used to evaluate interventions.

KEYWORDS: biomarkers · business model · drug development · drug–test codevelopment · payer

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The technologies that support innovation in healthcare delivery have evolved rapidly over the past 20 years. Advances in electronics and

However, the conclusion that
of molecular diagnostics from be
is easy would be completely wro

CHAPTER

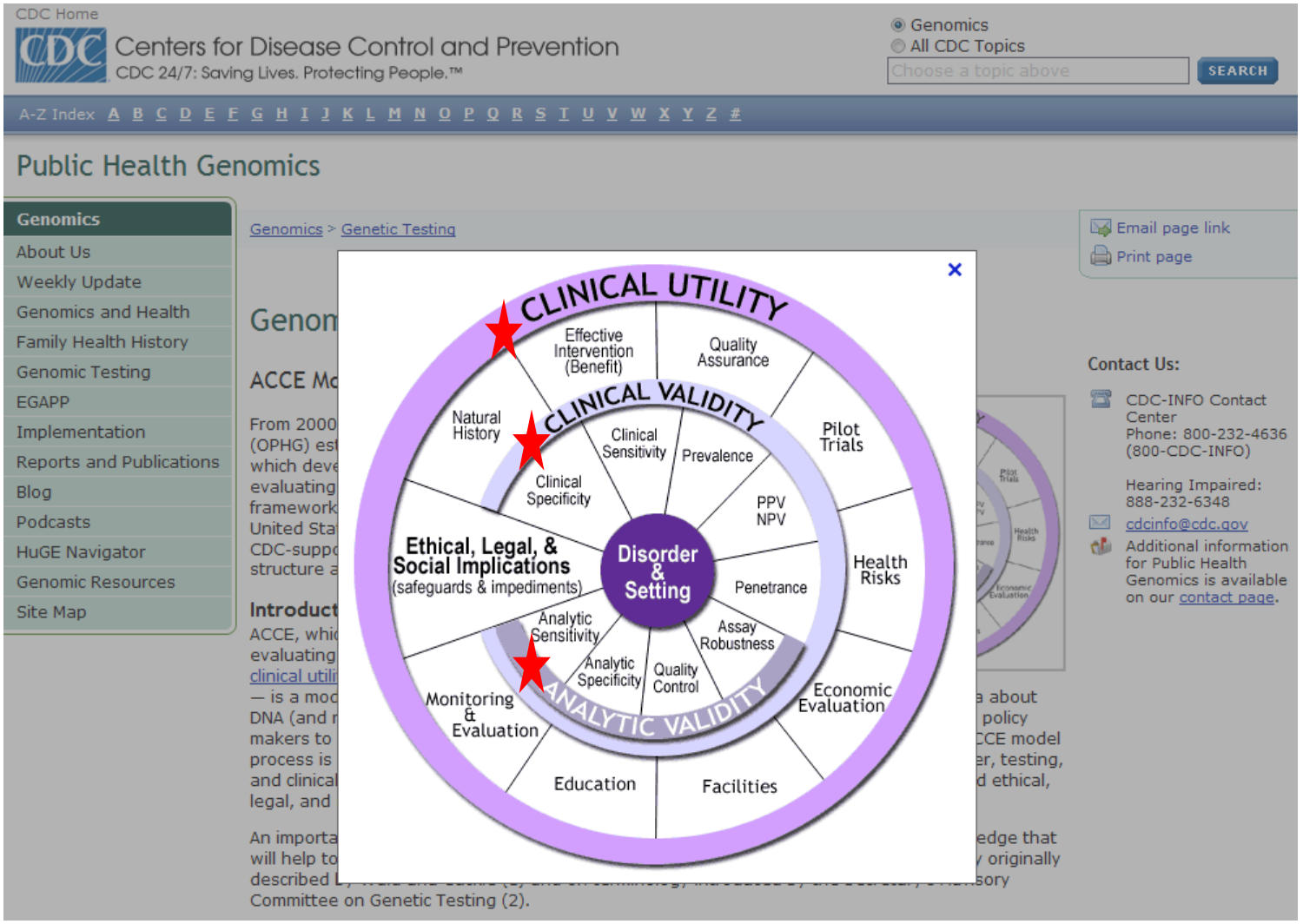
Reimbursement Issues in Genomic and Personalized Medicine

Bruce Quinn, Robert Giffin, and Sean Tunis

INTRODUCTION

Genomics and personalized medicine hold great promise for improving clinical care. Fulfilling this promise depends on practical aspects of economics and technology. New molecular can be quite difficult to conduct. Greater certainty about the type of evidence required for test reimbursement will allow diagnostic test developers and clinical researchers to better focus their research efforts on generating the required stud-

Origins from CDC

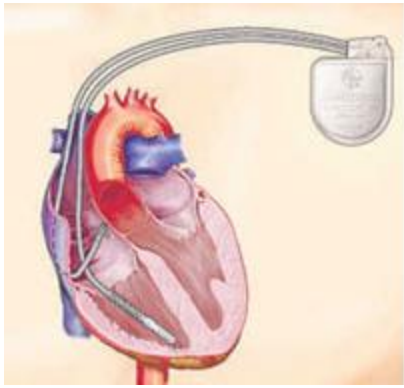


2000-2004 http://www.cdc.gov/genomics/gtesting/ACCE/

Concept	Definitions
Analytical Validity	**What actually happens in the laboratory** **"Inside the test tube"** • Sensitivity – ng/ml • Specificity - cross reactivity • Assay robustness
Clinical Validity	**The correlation between the inside of the test tube and the patient** • Gold standard disease state • Less-than-gold standard test • Patient population? Spectrum effects • FP/FN rates (varies with population) • CLINICAL sensitivity and specificity (developed for binary tests!)
Clinical Utility	**Most definitions are "tautologies"** **"Clinical utility is the usefulness of the test in patient care"** • How is the patient different in a pathway WITH and WITHOUT the test?

Not entirely unique to diagnostics

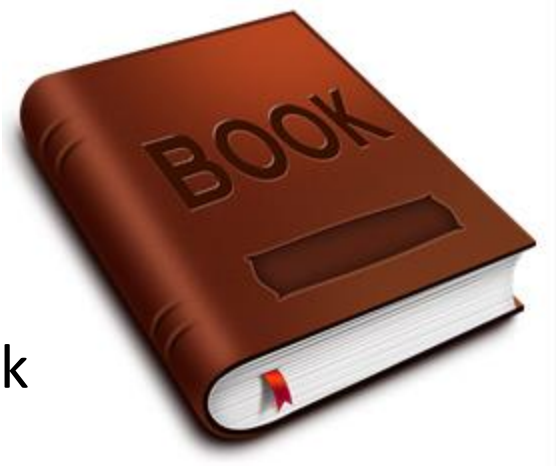
- Medtronics Implantable Cardiac Defibrillator (ICD)



- **Analytical Validity**
  - Battery life, wires, reproducibility of the shock
- **Clinical Validity**
  - When the patient has this EKG the device delivers this shock 97% of the time
- **Clinical Utility**
  - How often does this prevent death by re-starting the heart?

Not entirely unique to diagnostics

- **Book**



- **Analytical Validity**
  - Weight, thickness of paper, chemistry of ink
- **Clinical Validity**
  - Language written in, are facts correct
- **Clinical Utility**
  - What is it about? Do I need this book? How will this book help me?

Concept	Definitions
Analytical Validity	What actually happens in the laboratory "Inside the test tube" • Sensitivity – ng/ml • Specificity - cross reactivity • Assay robustness
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Clinical Utility	Most definitions are "tautologies" "Clinical utility is the usefulness of the test in patient care" • How is the patient different in a care patient WITH and WITHOUT the test?

Concept	Issues
Analytical Validity	Easy enough to explain, but: • **Not always clear what the correct "standards" are** • **Readers confuse "analytical" chemistry validity with clinical validity, in part due to synonyms** • **Most medical reviewers are not laboratorians**
Clinical Validity	**Very complicated in some cases** • Gold standard disease state **may be fuzzy** • Less-than-gold standard test **or no gold standard (Tumor of Unknown Origin gene panel tests)** • Patient population? **Age, race, disease severity** • Spectrum effects **really can GREATLY impact validity** • FP/FN **rates (Varies with population; most familiar are problems with screening tests)** • CLINICAL sensitivity and specificity **-- developed for binary tests with "gold standards" and poorly suited for prognostic tests**
Clinical Utility	Most definitions are "tautologies" "Clinical utility is the usefulness of the test in patient care" • How is the patient different in a care patient WITH and WITHOUT the test? • **"Outcomes" or QALYs or Value/Dollar or other metrics (less pain, or, futile surgery avoided, or… – completely different all)**

Concept	Issues
Analytical Validity	**These are just abstract nouns.** **By themselves, they are not enough to be an "instruction book" for** • **How to validate the test** • **How to prove or explain the validity** • **How to assess the test for a coverage decision !**
Clinical Validity	
Clinical Utility	

Fryback and Thornbury 1991

Medical Decision Making

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The Efficacy of Diagnostic Imaging

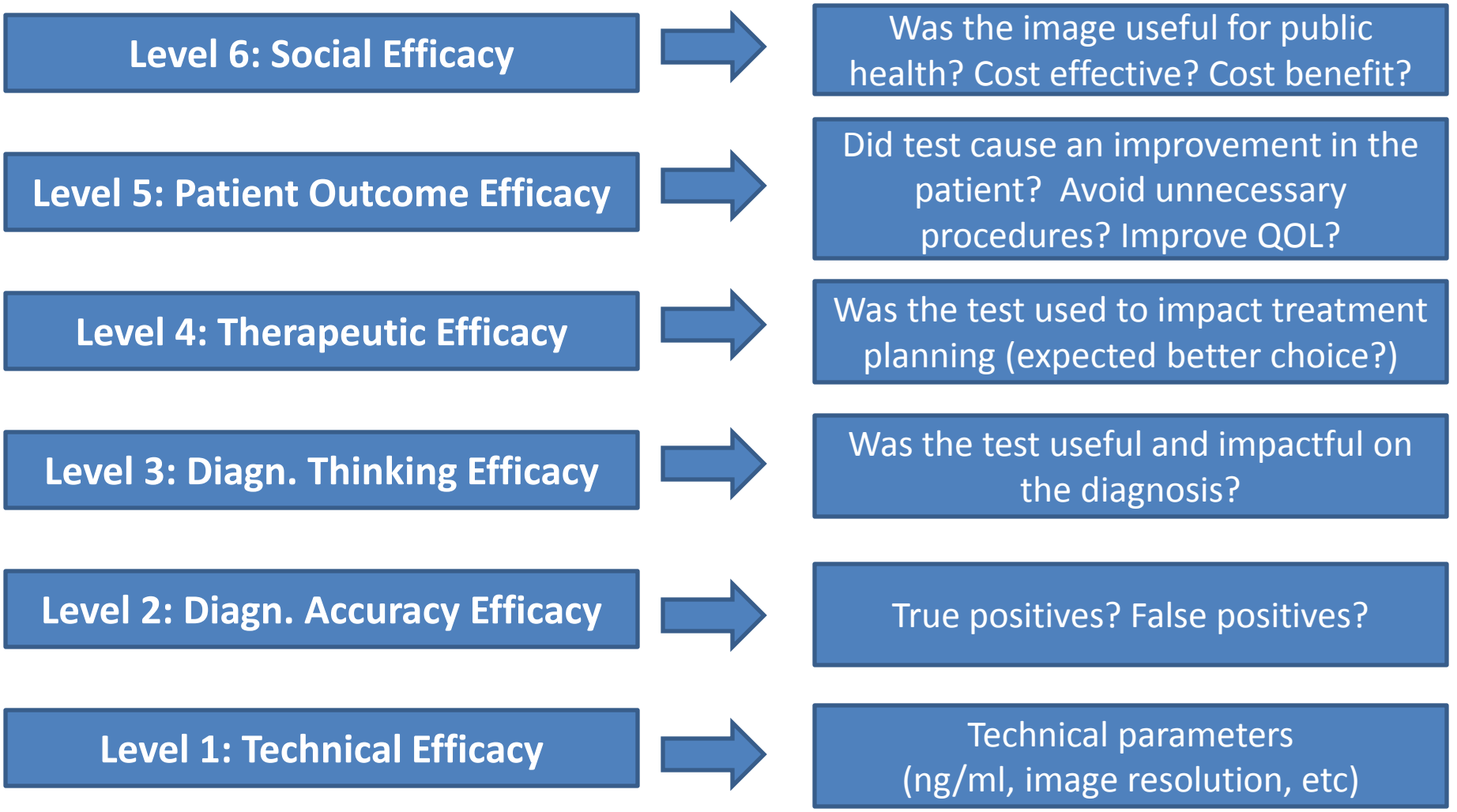
Dennis G. Fryback, PhD

John R. Thornbury, MD

Abstract

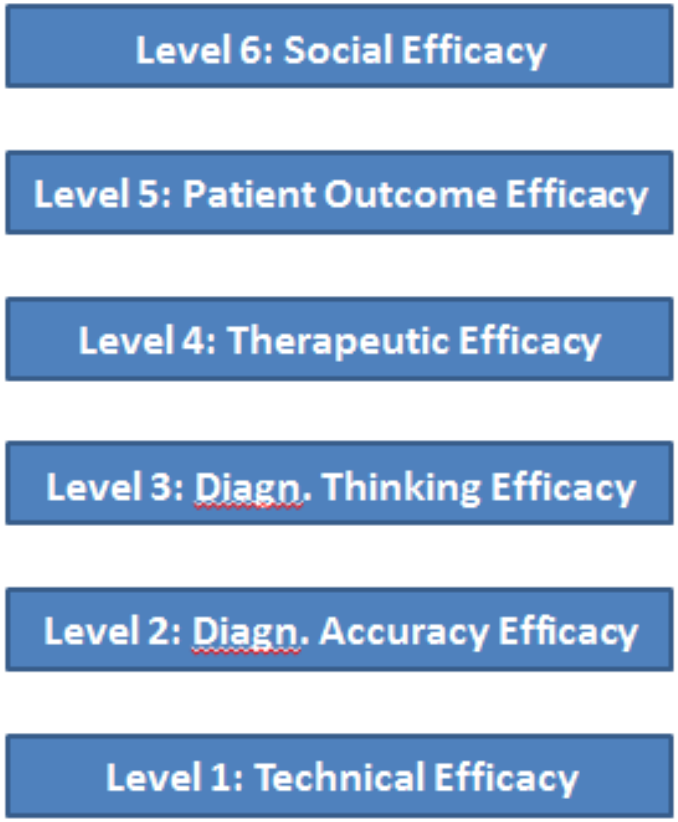
The authors discuss the assessment of the contribution of diagnostic imaging to the patient management process. A hierarchical model of efficacy is presented as an organizing structure for appraisal of the literature on efficacy of imaging. Demonstration of efficacy at each lower level in this hierarchy is logically necessary, but not sufficient, to assure efficacy at higher levels. Level 1 concerns technical quality of the images; Level 2 addresses diagnostic ac curacy, sensitivity, and specificity associated with interpretation of the images. Next, Level 3 focuses on whether the information produces change in the referring physician's diagnostic thinking. Such a change is a logical prerequisite for Level 4 efficacy, which concerns effect on the patient management plan. Level 5 efficacy studies measure (or compute) effect of the information on patient outcomes. Finally, at Level 6, analyses examine societal costs and benefits of a diagnostic imaging technology. The pioneering contributions of Dr. Lee B. Lusted in the study of diagnostic imaging efficacy are highlighted.

Fryback and Thornbury 1991



http://www.sciencedirect.com/science/article/pii/S0212698209001116

Fryback and Thornbury 1991



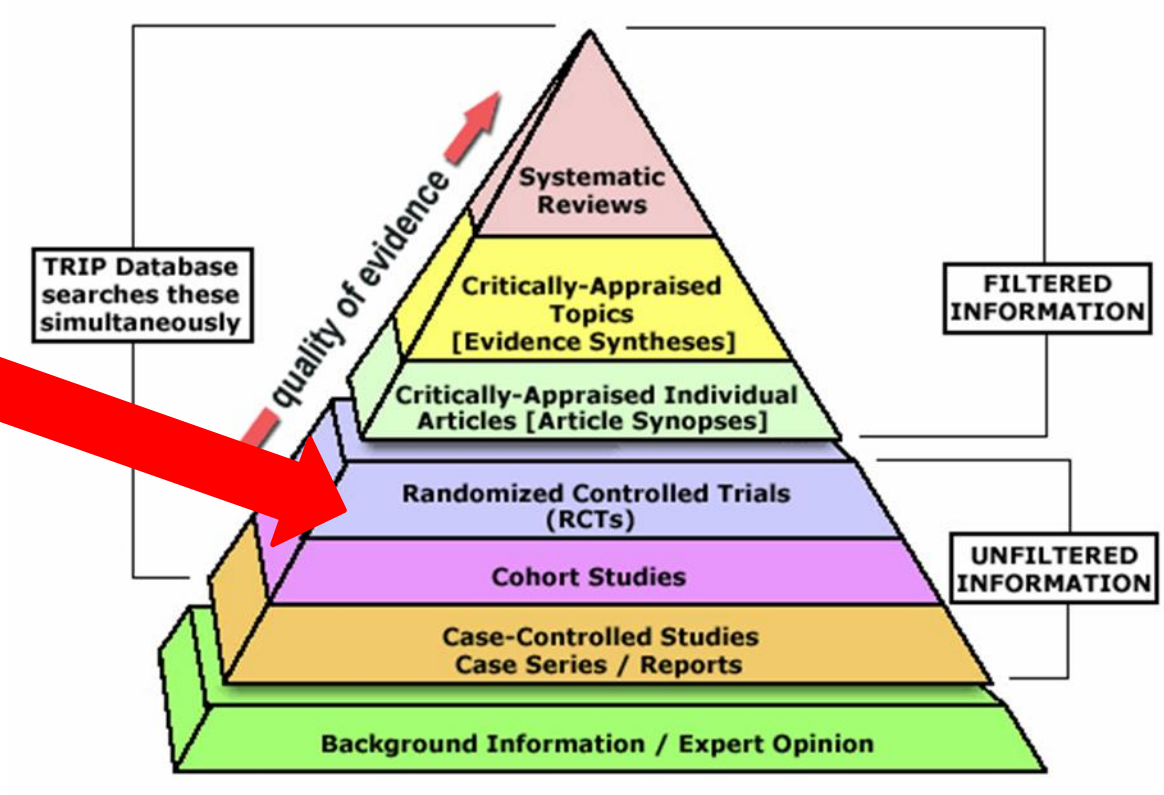
- Cited by Medicare in National Coverage Decisions for over a decade!
- People can usually agree on what the evidence is
- People will differ on what can be *reasonably confidently* ***inferred*** (nearer the top)

- **The level of "barrier" and "pushback" against "just inferring utility" can be very high**

http://www.sciencedirect.com/science/article/pii/S0212698209001116

Fryback and Thornbury vs "Levels of Evidence"

- Level 6: Social Efficacy
- Level 5: Patient Outcome Efficacy
- Level 4: Therapeutic Efficacy
- Level 3: Diagn. Thinking Efficacy
- Level 2: Diagn. Accuracy Efficacy
- Level 1: Technical Efficacy



People usually imagine that lack of RCTs is lack of investment or lack of effort.

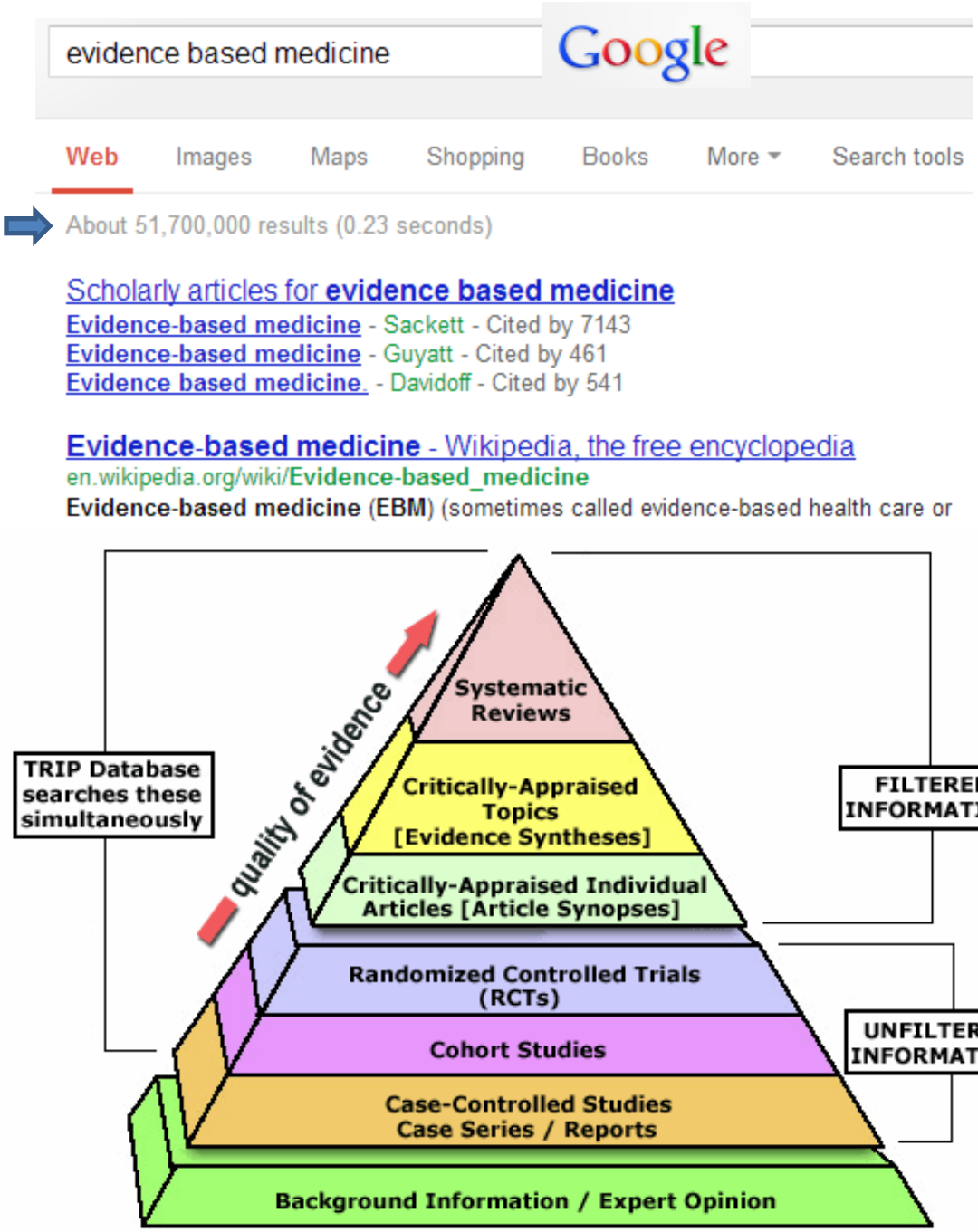
However, with DIAGNOSTIC TESTS, patients are usually very unwilling to be randomized to a worse diagnostic test in the middle of their real world illness planning. Many examples.

http://www.sciencedirect.com/science/article/pii/S0212698209001116

Evaluating and Developing Data *while* Thinking Ahead to the Technology Assessment:

A Crucial Skill!!

- **Health technology assessments are seen as a rational way to control technology growth.**
- In the field of diagnostics – among the fastest changing technologies – the health technology assessments may systematically under-value new diagnostic tests.



Eisenhower warns us of the **military industrial complex**. - YouTube

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The NEW ENGLAND JOURNAL of MEDICINE

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The New
Health Technology Assessment /
Industrial Complex

Evidence-based Medicine Toolkit

SECOND EDITION

ICER

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

IQWiG

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

CMTP

Center for Medical Technology Policy

Scottish Medicines Consortium

EVIDENCE-BASED MEDICINE

How to practice and teach it

NHS

National Institute for Health and Clinical Excellence

eunethta

HISTORY

In 2004 the European Commission and Council of Ministers targeted Health Technology Assessment (HTA) as "a political priority", recognising "(...)an urgent need for establishing a sustainable European network on HTA".

AHRQ Agency for Healthcare Research and Quality

Advancing Excellence in Health Care

CTAF

CALIFORNIA TECHNOLOGY ASSESSMENT FORUM℠

Health Technology Assessment Review

Review of Health Technology Assessment in Australia (HTA Review)

Technology Evaluation Center (TEC)

Hayes

Transforming Healthcare with Evidence

The HTA Industry

- Pharma, Medical Devices, and Diagnostics are all complaining about the Health Technology Assessment "Industry"
  - Too big
  - Vague standards
  - Reviewer lack subject matter competence
    - Poor understanding of "Fit for Purpose"

Next slide:

- Although not endorsed officially, I believe if you can sit down and effectively answer the "Frueh Questions" you will get pretty far

“Frueh Questions”

- Who should be tested and under what circumstances?
- What does the test tell us?
- Can we act on the information provided by the test?
- Will we act on the information provided by the test?
- Does the outcome change, in a way we find value in?
- Can we afford it? (Is it a *reasonable* value?)

http://www.thirdrockventures.com/team_entrepreneur.php

Presented at GTC Biomarker Conference, San Francisco, February 2013 Quoted with permission.

Economic Evaluation Studies

- If you can't clearly infer the impact on patient management, it's hard to do economic evaluation
  - Exception: You are replacing $100 test with new, equivalent, $50 test

- Long history of payers being "dubious" of pharmacoeconomic arguments
- One problem with Diagnostic models:
  - Created high "artificial world" (SimCity)
  - Pretend that "value" exists in a vacuum with no competitors
  - Example:
    - Prozac is proven to have a clear pharmacoeconomic value of $500 per month
    - Data is absolutely solid
    - The day it goes generic it is now $5 a month
    - So: "Value Diagnostics" do not exist in a vacuum
  - Two basic formats are "cost per QALY or event" and "Budget Impact Model" (pm/pm for health plan)

- Dr Bob McDonald will talk about what payers do with these after you have finished them

Best Approaches to Validate LDTs and Develop Clinical Evidence…

THANK YOU !

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