View from the Technology Evaluation Center (TEC)

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IOM Genomics Workshop
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Overview

- TEC perspective and process
- Frameworks for assessing diagnostic tests
  - Indirect evidence vs. direct evidence
  - Examples: imaging, genetic testing
  - Predictive, diagnostic, prognostic, pharmacogenomic
  - Quality appraisal of methods, analysis, reporting
- Cost-effectiveness and affordability

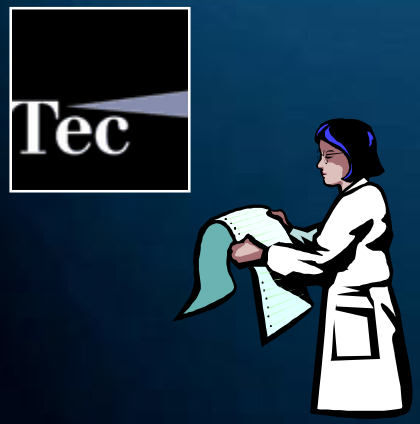
Covering America

Blue Plans cover every community in the nation

- 39 Blue Cross and Blue Shield Plans

- 100 million members
- Largest processor of Medicare claims in the nation
- Contract with 90% of hospitals, 80% of doctors
- 4-million member Federal Employee Program – Largest private health insurance product in world

Technology assessment supports health plans and other stakeholders in developing evidence-based policies



Medical Policy

- Based on scientific evidence
- Costs and coverage NOT considered

Coverage Policy

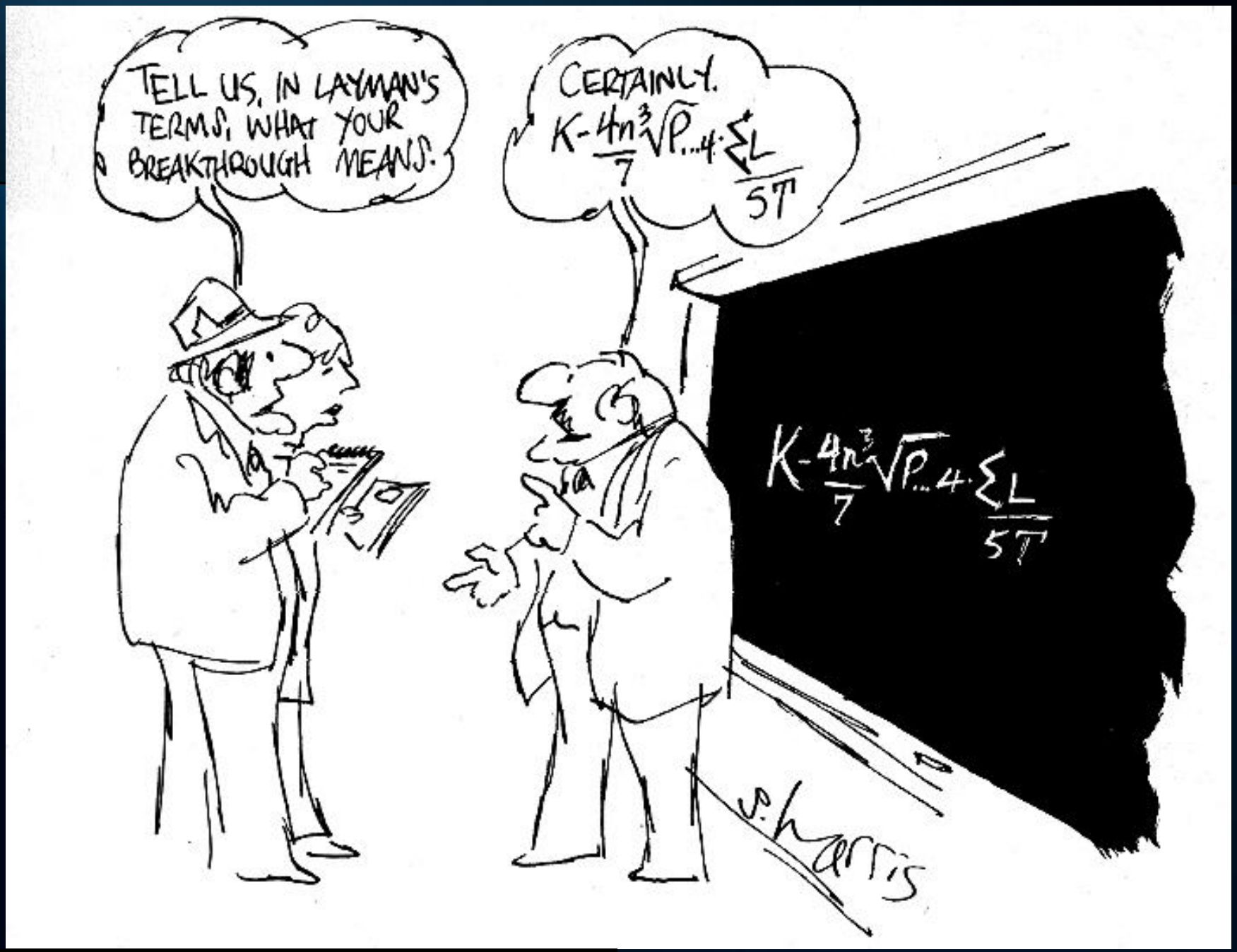
- Determined by purchasers of health plan products
- Cost-effectiveness considered

Payment Policy

Contract between health plans and medical professionals and providers

Technology Evaluation Center

- Rigorous assessment of clinical evidence
- Independent Expert Medical Panel
  - Academic clinical researchers
    (Harvard, Stanford, Johns Hopkins)
  - Specialty society appointees
  - Only 4 of 17 votes are Plan clinicians
- Does this technology improve health?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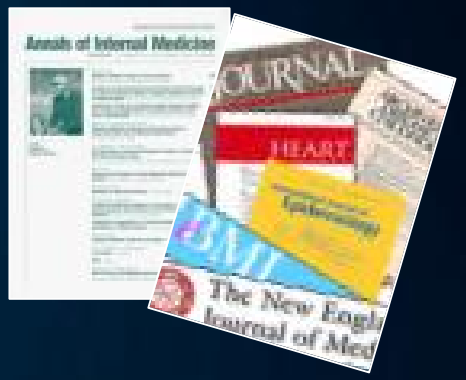
$K-\frac{4n^3}{7}\sqrt{P}...4\cdot\frac{\Sigma L}{5T}$
S. Harris

Technology Evaluation Center



- 300+ technology assessments

  3-year inventory at *www.bcbs.com/tec*

- Articles in prestigious medical journals
  - *Annals of Internal Medicine*
  - *Journal of the National Cancer Institute*
  - *Journal of the American College of Surgeons*

- Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center
  www.ahrq.gov/clinic/epcix.htm

TEC Focus on Genomics

- Gene Expression Profiling of Breast Cancer
- Genetic Testing for Long QT Syndrome
- Horizon Scan: Cardiovascular Pharmacogenomics
- Horizon Scan: Cancer Pharmacogenomics
- Horizon Scan: Genomics of Neurologic Disorders
- Assessing Genomic Biomarkers for Disease Predisposition, Prognosis, or Predicting Response to Therapy

Source: www.bcbs.com/tec

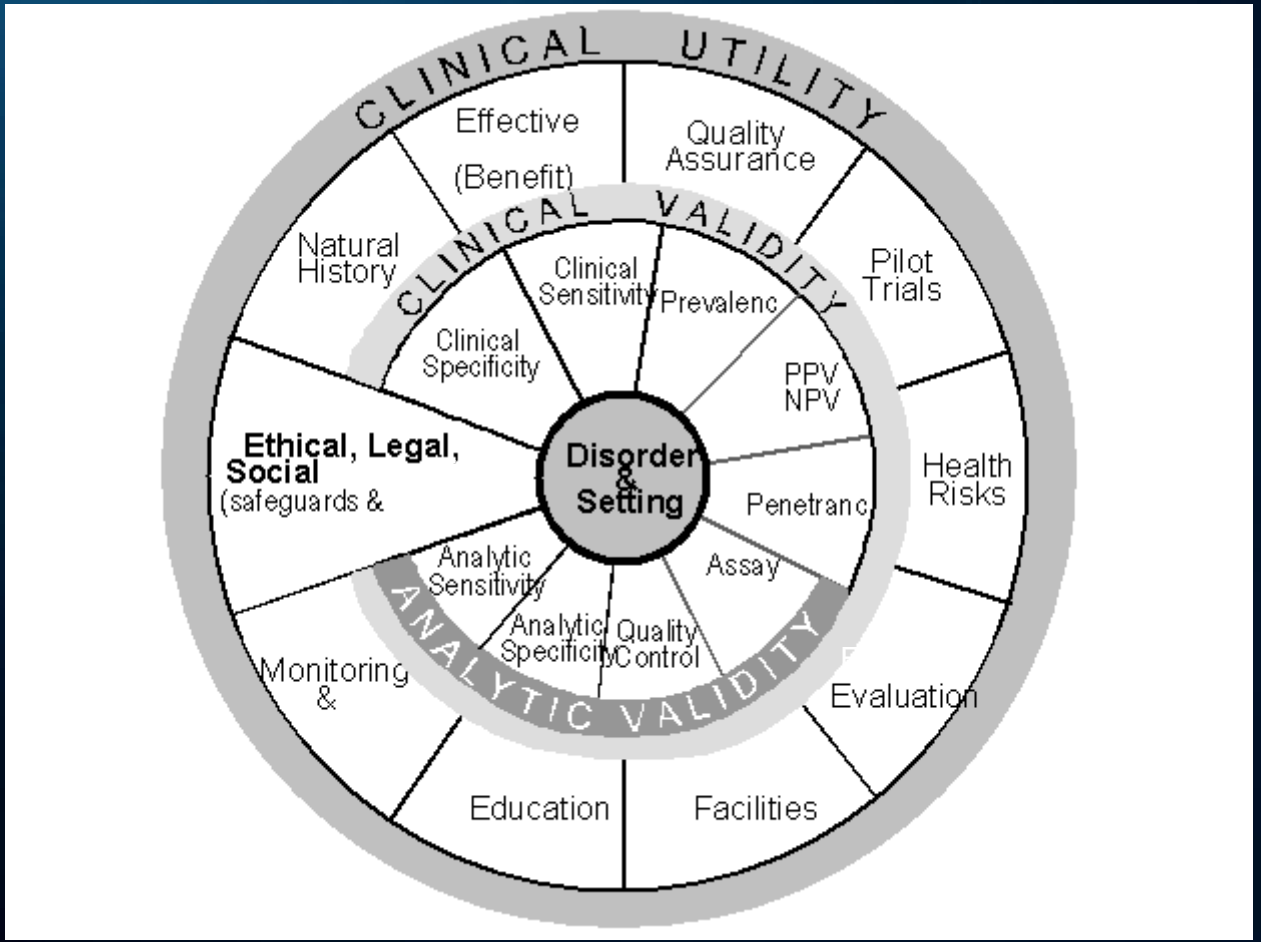
Six-Tiered Model
A Continuum for Efficacy

	Paraphrased
• Level 1: Technical efficacy	Pretty Picture
• Level 2: Diagnostic accuracy efficacy	Improved Accuracy
• Level 3: Diagnostic thinking efficacy	Improved Diagnosis
• Level 4: Therapeutic efficacy	Improved Treatment
• **Level 5: Patient outcome efficacy**	**Improved Health**
• Level 6: Societal efficacy	Improved Efficiency

Fryback & Thornbury (1991) Med Dec Making, 11:88-94

Source: www.bcbs.com/tec

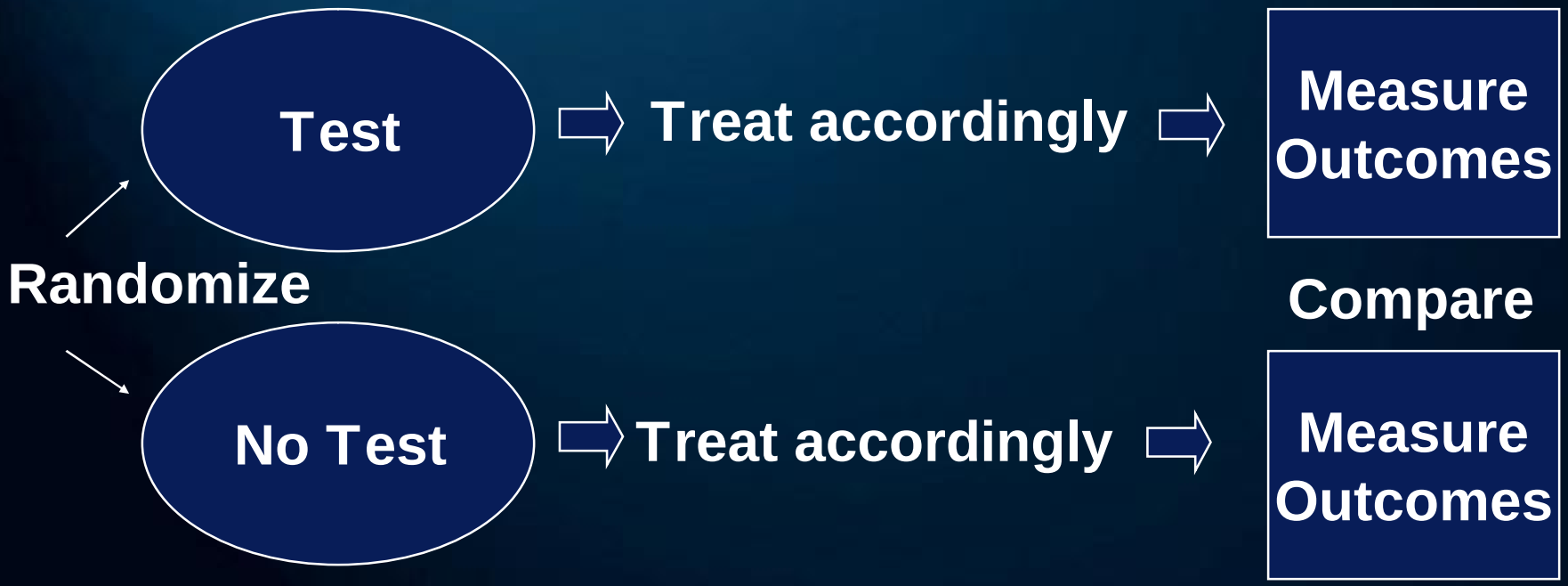
The ACCE evaluation process for genetic testing



From the CDC Office of Genomics and Disease Prevention

http://www.cdc.gov/genomics/gtesting/ACCE.htm

In an ideal world… Direct Evidence



Reality: Indirect Evidence

Patient Populations

Criterion for positive test

Explicit Strategy:
- Avoid other tests
- Avoid invasive procedure
- Change treatment

Balance of Benefits and Harms

Diagnostic study quality

Table 1. Rating the Quality of Studies of Diagnostic Tests (West et al. 2002)

Empirical Basis	
Domain	Essential Element
Study Population	Subjects similar to populations in which the test would be used and with a similar spectrum of disease
Adequate Description of Test	Details of test and its administration sufficient to allow for replication of study
Appropriate Reference Standard	Appropriate reference standard ("gold standard") used for comparison
Blinded Comparison of Test and Reference	Independent, blind interpretation of test and reference
Avoidance of Verification Bias	Decision to perform reference standard not dependent on results of test under study
Best Practices	
Domain	Relevant Element
Appropriate Reference Standard	Reference standard reproducible
Blinded Comparison of Test and Reference	Evaluation of test without knowledge of disease status, if possible

CTA to avoid conventional angiography

Suspected CAD referred for angiography

CTA

Sensitivity
Specificity
PPV
NPV

Test threshold stenosis ≥50%

No Stenosis Avoid Cath

Stenosis
OR
Nondiagnostic: Get Cath

Number of caths avoided?

Effect of false-negative CTA?

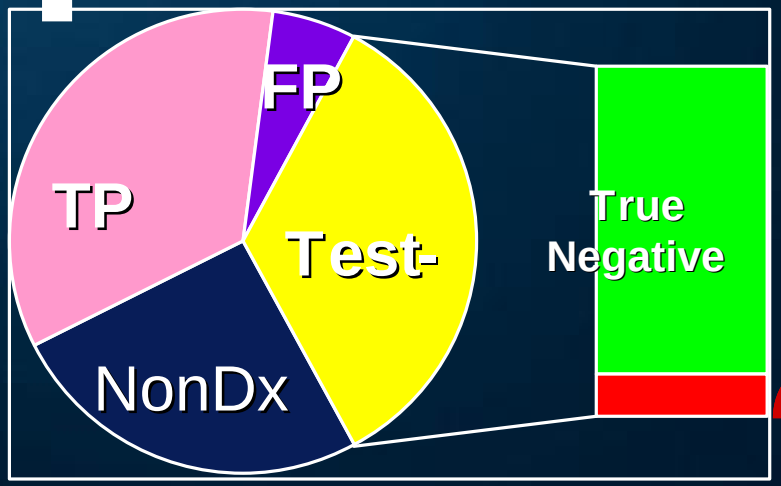
Effect of added radiation?

Effects of extracardiac findings?

What is the balance of benefits and harms?

Cardiac CTA or Angio?

Most patients must get BOTH CTA and angio



10% may be false negative

Patients with Intermediate Risk of CAD

chance of nondiagnostic CTA study

Genetic Test Long QT Syndrome

Family history

Suspect LQTS

LQT test vs. clinical criteria

No true gold standard

LQT test more "sensitive"

LQT+ start beta-blockers

LQT - dx no LQTS

Confidence LQT-known family mutation

Qualitative Conclusions

Beta-blocker low risk intervention

Observational evidence LQTS population

Potential catastrophe untreated

Leap of Inference?

Observational data linking genotype to phenotype

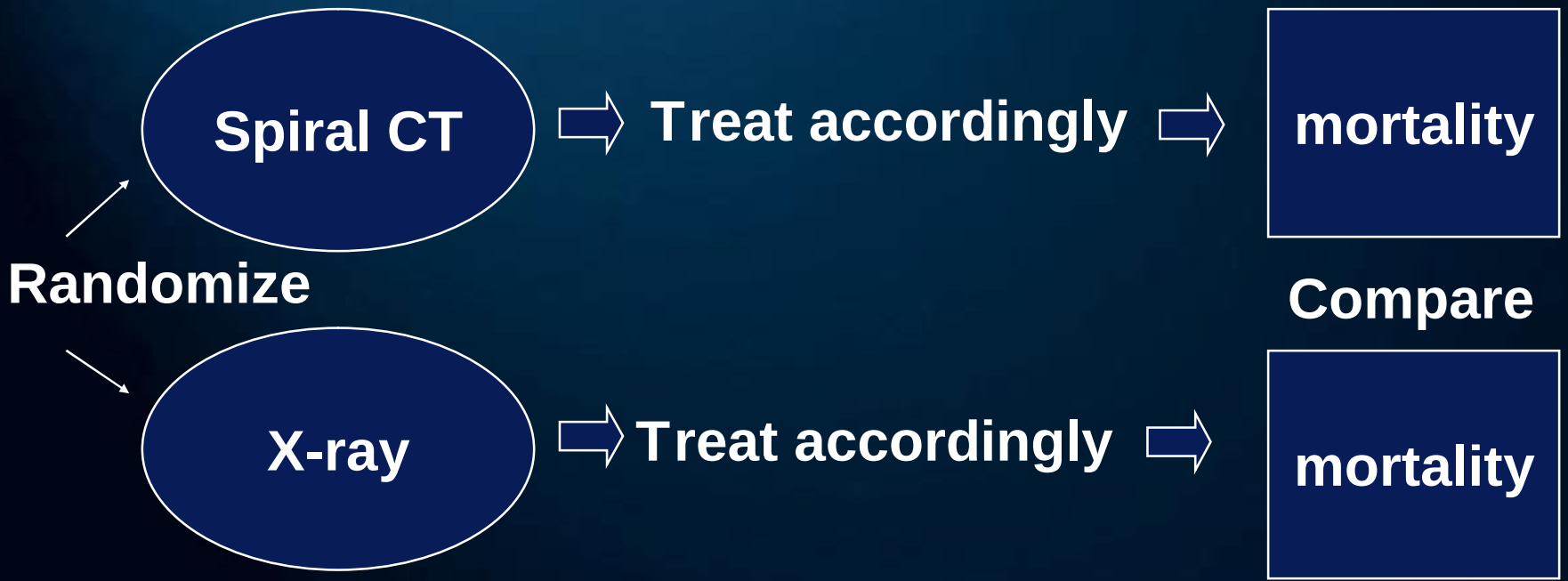
- Retrospective
- Small studies
- Selected patients

- Multigene complexity
- Metabolic complexity
- Gene-environment interaction

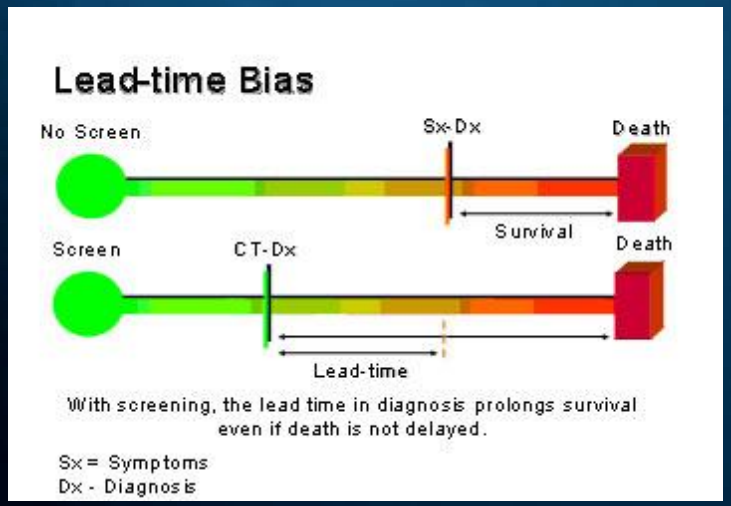
- Rigorous evaluation of utility
- Regulation of genetic testing

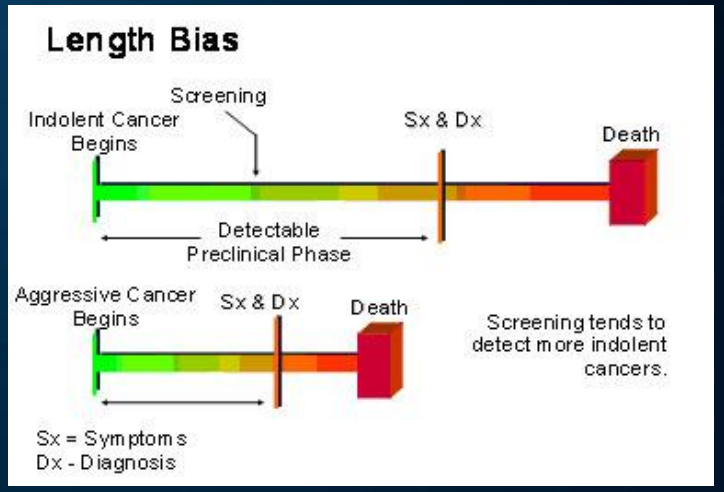
- Personalized medicine
- Cost containment
- Information Infrastructure

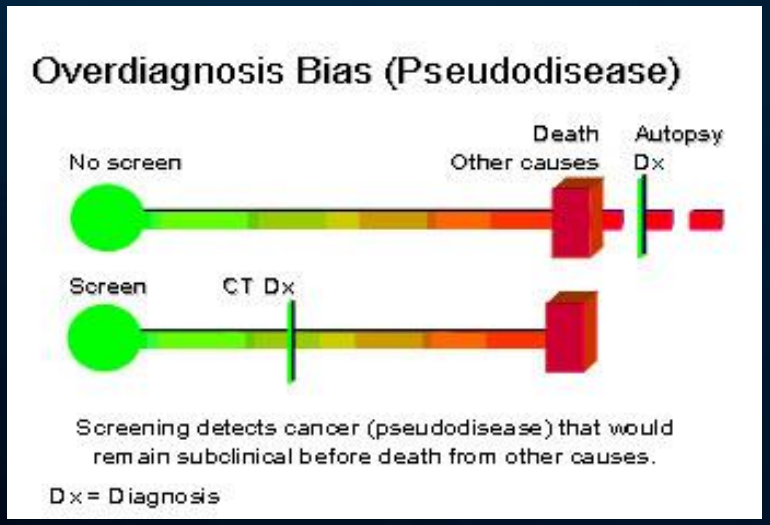
National Lung Screening Trial



Biases in Lung Cancer Screening Effectiveness

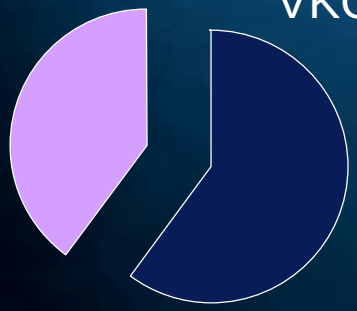






Source: http://www.cancer.gov/nlst/what-is-nlst

Direct evidence for diagnostics: Genotyping for warfarin dose



VKORC1 and CYP2C9 genetic variants account for one-third to one-half of the variability in stable warfarin dose (in European Caucasians)

Need different starting warfarin dose – how different?

Other enzymes

Co-existing disease

Clotting factor genetic variant

Age

Diet

Other drug interactions

Genotyping

Personalized warfarin dose

??????

Prevent clots

Prevent bleeding

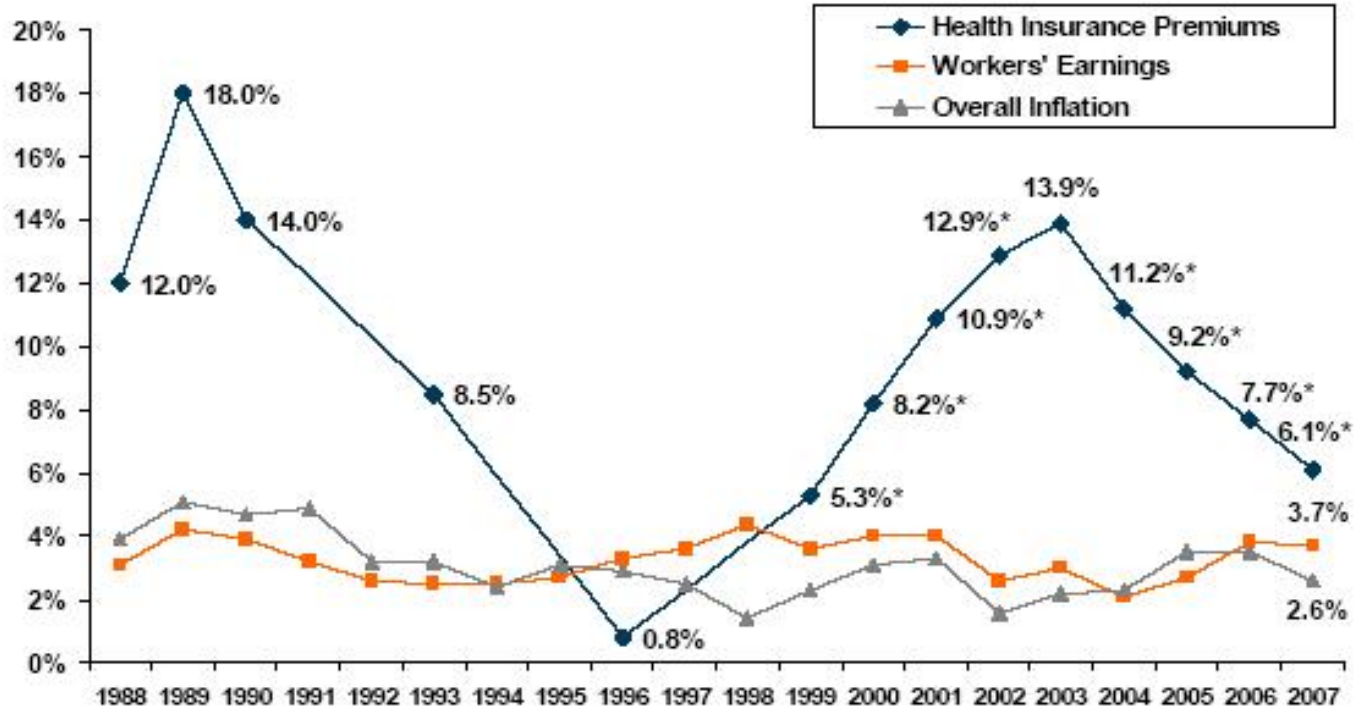
Direct evidence for diagnostics: Genotyping for warfarin dose

- **Prospective trials of dosing algorithms are needed to determine impact of personalized warfarin starting dose on bleeding outcomes compared to standard dosing.**
- **Several trials are underway. Examples:**
  - CReating an Optimal Warfarin Nomogram (CROWN) Trial (NCT00401414)
  - PRospective Evaluation Comparing Initiation of Warfarin StrategiEs (PRECISE) Trial (NCT00377143)
  - Variability in response to warfarin: a prospective analysis of pharmacogenetic and environmental factors (funded by the UK Department of Health)
  - Medco-Mayo Clinic collaboration
  - A large NHLBI study, scheduled to begin next year, will randomize 2000 patients at 15 clinical sites to three approaches to warfarin therapy initiation

Cost, cost-effectiveness and affordability

- Clinical effectiveness is cornerstone of Plan medical and coverage policy
- New technologies may bring small benefit at high cost
- Cost-effectiveness and affordability are pressing issues
- TEC is leading and educating on cost-effectiveness analysis methods
- But no clear cost-effectiveness threshold: can you afford everything that is a “good buy”?

Increases in Health Insurance Premiums Compared to Other Indicators, 1988-2007



*Estimate is statistically different from estimate for the previous year shown (p<.05). No statistical tests are conducted for years prior to 1999.

Note: Data on premium increases reflect the cost of health insurance premiums for a family of four. The average premium increase is weighted by covered workers.

Source: Kaiser/HRET Survey of Employer-Sponsored Health Benefits, 1999-2007; KPMG Survey of Employer-Sponsored Health Benefits, 1993, 1996; The Health Insurance Association of America (HIAA), 1988, 1989, 1990; Bureau of Labor Statistics, Consumer Price Index, U.S. City Average of Annual Inflation (April to April), 1988-2007; Bureau of Labor Statistics, Seasonally Adjusted Data from the Current Employment Statistics Survey, 1988-2007 (April to April).

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Among Firms Offering Health Benefits, Distribution of Firms Offering the Likelihood of Making the Following Changes in the Next Year, 2007

	Very Likely	Somewhat Likely	Not Too Likely	Not At All Likely	Don't Know
Increase the Amount Employees Pay for Health Insurance	21%	24%	21%	33%	<1%
Increase the Amount Employees Pay for Prescription Drugs	11%	30%	31%	26%	2%
Increase the Amount Employees Pay for Deductibles	12%	25%	28%	34%	1%
Increase the Amount Employees Pay for Office Visit Copays or Coinsurance	13%	29%	28%	28%	2%
Introduce Tiered Cost Sharing for Doctor Visits and Hospital Stays	7%	16%	39%	35%	3%
Restrict Employees Eligibility for Coverage	<1%	4%	29%	64%	3%
Drop Coverage Entirely	1%	2%	15%	82%	<1%
Offer HDHP/HRA‡	3%	21%	30%	46%	<1%
Offer HSA Qualified HDHP‡	2%	18%	32%	45%	3%

‡ Among firms not currently offering this type of HDHP/SO.

Source: Kaiser/HRET Survey of Employer-Sponsored Health Benefits, 2007.

Summary

- Health plans want to make evidence-based decisions
- Considerable challenges in obtaining good evidence on outcomes interventions and tests
- Indirect evidence based on performance where evidence chain well understood
- Complex associations and intervening variables call for direct evidence
- Cost-effectiveness and affordability are pressing concerns

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