BlueCross BlueShield Association

An Association of Independent Blue Cross and Blue Shield Plans

A Blue Cross and Blue Shield Association Presentation

Evaluating the Evidence for Clinical Utility

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Roundtable on Translating Genomic-Based Research for Health
Workshop on Evidence Generation for Genomic Diagnostic Test Development

November 16, 2010

Presentation Overview

- BCBSA Technology Evaluation Center (TEC)
- Technology Evaluation Criteria
- Framework for Evaluating Genetic Test Evidence
- Focus on Improving Patient Outcomes
- What kind of evidence does not vs. does meet TEC criteria?
  - Oncotype Dx 2005 → 2007
  - Genetic testing for Long QT Syndrome
  - *(KRAS* mutation testing to predict response to EGFR inhibitors)
  - *EGFR* mutation testing to predict response to erlotinib 2007 → 2010

Technology Evaluation Center

TEC's mission is to provide healthcare decision makers with timely, objective and scientifically rigorous assessments that synthesize the available evidence on the diagnosis, treatment, management and prevention of disease.

- 1985 BCBSA Technology Evaluation Criteria
- 1993 Collaboration with Kaiser Permanente

  External Medical Advisory Panel
- 1997 AHRQ Evidence-based Practice Center
- 2003 Evidence-based medicine public resource (www.bcbs.com/tec)

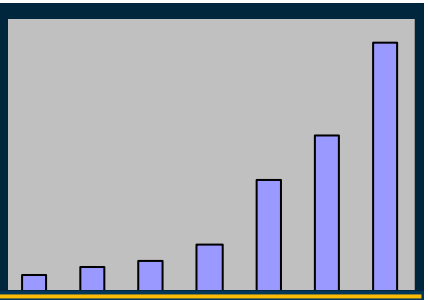
Technology Evaluation Criteria

1. The technology must have final approval from the appropriate government regulatory bodies.
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
3. The technology must improve the net health outcome.
4. The technology must be as beneficial as any established alternatives
5. The improvement must be attainable outside the investigational setting.

TEC Focus on Genomics 1997-2007

- Gene Expression Profiling for Breast Cancer - Update (2007)
- Pharmacogenomics of Cancer (2007)
- Cardiovascular Pharmacogenetics (2007)
- Use of GeneSearch Breast Lymph Node Assay (2007)
- Pharmacogenomics of EGFR-Targeted Therapy (2007)
- Fecal DNA for Colon Cancer Screening (2006)
- Gene Expression Profiling for Breast Cancer (2005)
- Genotyping for Cytochrome P450 Polymorphismss (2004)
- HFE Gene Mutations and Hereditary Hemochromatosis (2001)
- Alzheimer's Disease: ApoE Epsilon 4 Allele (1999)
- Inherited Susceptibility to Colorectal Cancer (1998)
- Inherited BRCA1 or BRCA2 Mutations (1997)
- Germline Mutations of the *RET* Proto-Oncogene in Medullary Carcinoma of the Thyroid (1997)

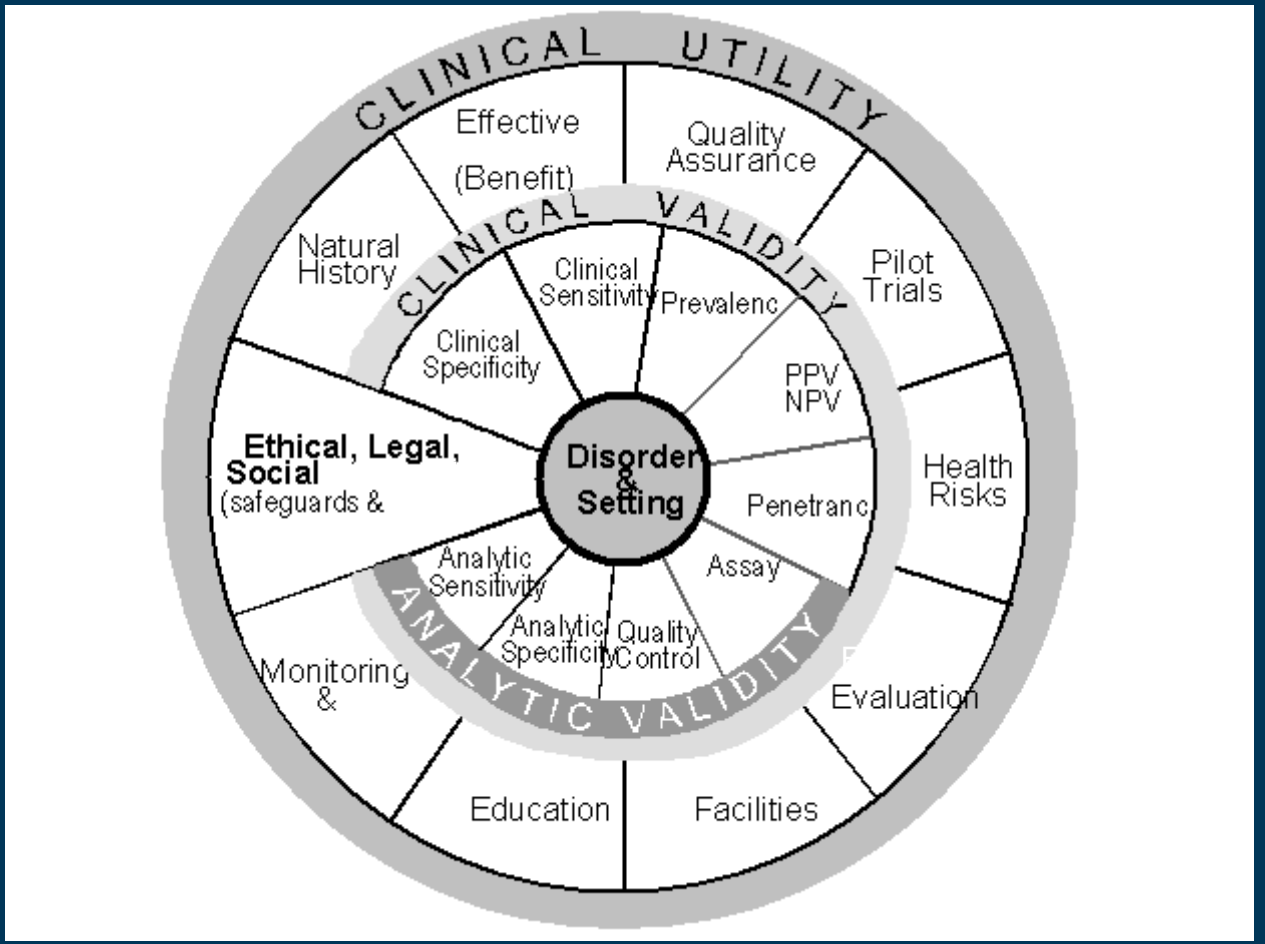
TEC Focus on Genomics 2008-2010



- EGFR mutations and tyrosine kinase inhibitor therapy in advanced non-small-cell lung cancer (in press)
- Gene Expression Profiling in Women with Lymph-Node-Positive Breast Cancer (2010)
- Genetic Testing for Familial Hypertrophic Cardiomyopathy (2010)
- Pharmacogenetic Testing to Predict Serious Toxicity from 5-Fluorouracil (2010)
- Special Report: Molecular karyotyping by aCGH (2008)
- Special Report: Genetics of Prostate Cancer (2008)
- *KRAS* testing for anti-EGFR treatment in colorectal cancer (2008)
- Pharmacogenomics-Based Treatment of *Helicobacter Pylori* (2008)
- CYP2D6 Pharmacogenomics of Tamoxifen Treatment (2008)
- Genetic Testing for Long QT Syndrome (2008)

Framework for Evaluating Genetic Test Evidence

The ACCE evaluation process for genetic testing



From the CDC National Office of Public Health Genomics
http://www.cdc.gov/genomics/gtesting/ACCE/index.htm

Assessment of Genetic Tests: Types of Evidence

- Clinical validity: Association of test result with outcome; e.g.:
  - Diagnosis of disease
  - Predicting cancer recurrence in the absence of treatment (prognosis)
  - Predicting drug response or adverse events (pharmacogenomics)
  - Expressed by OR, RR, HR, Logistic regression or by test descriptors (clinical sensitivity, specificity; predictive value)
  - Describes significance for populations

★ • Clinical utility: Describes the impact of the test on patient management and outcomes compared to usual care
  - Describes significance for individual patient decision-making

- (Analytic validity)

Measures of Association Not Enough

- Clinical purpose of test is to discriminate between outcomes for individual patients, e.g.:
  - Disease vs. no disease
  - Future cancer recurrence vs. no recurrence
  - Future drug-related adverse event vs. none
- Measures of association only quantify discrimination between populations with vs. without the outcome

Margaret Pepe et al. (2004)
Limitations of the Odds Ratio in Gauging the Performance of a Diagnostic, Prognostic, or Screening Marker

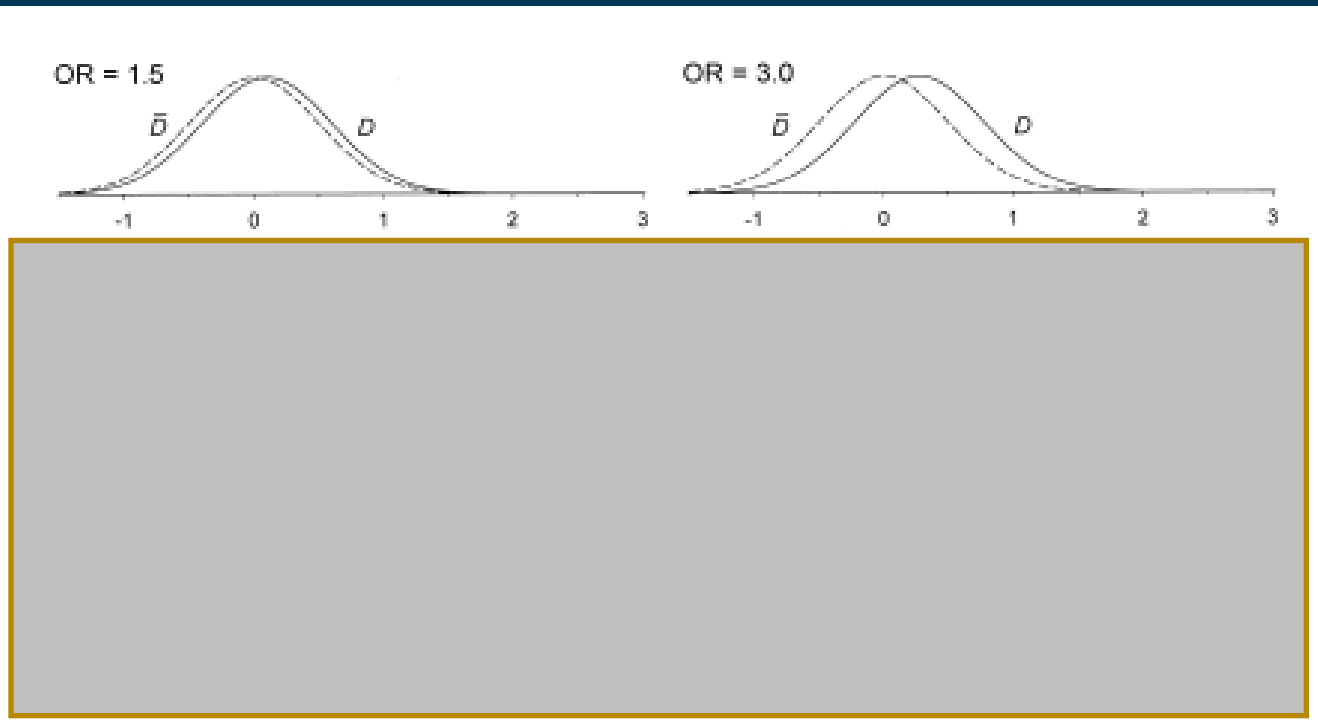


FIGURE 2. Probability distributions of a marker, X, in cases (solid curves) and controls (dashed curves) consistent with the logistic model $\text{logit}P(D = 1|X) = \alpha + \beta X$. It has been assumed that X has a mean of 0 and a standard deviation of 0.5 in controls so that a unit increase represents the difference between the 84th and 16th percentiles of X in controls. The marker is normally distributed, with the same variance in cases. The odds ratio (OR) per unit increase in X is shown.

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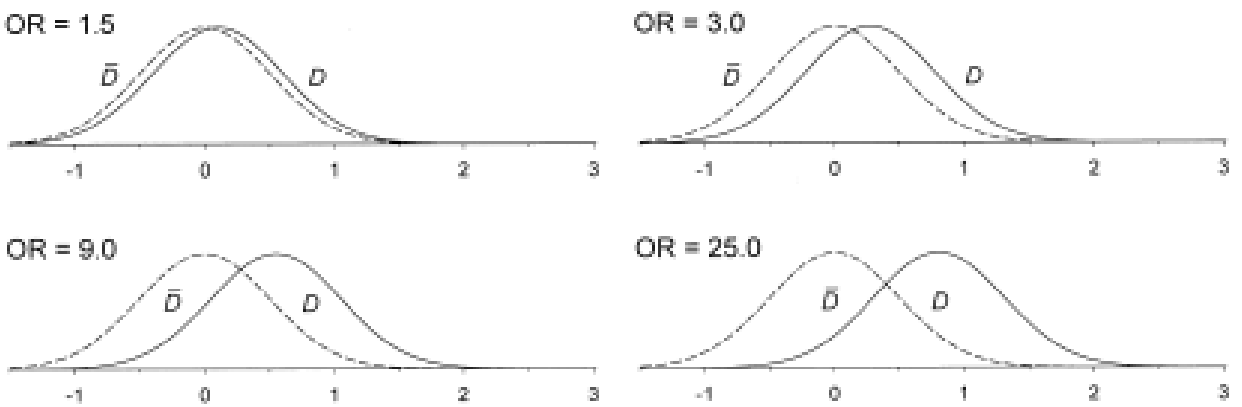

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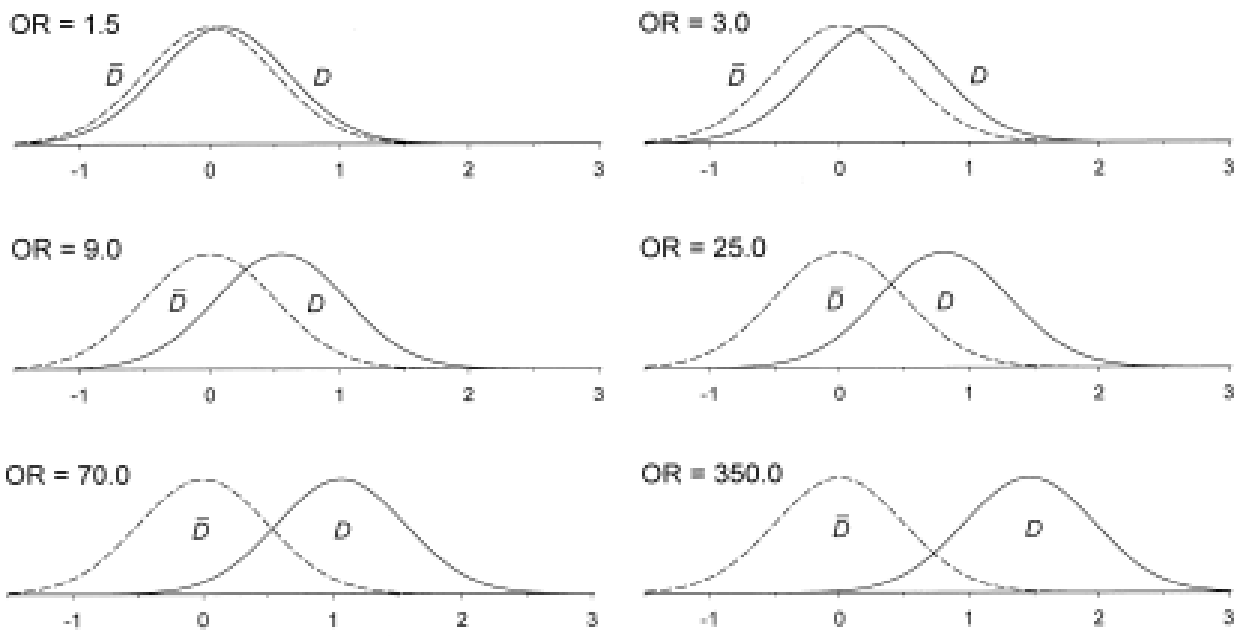

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Clinical Utility

- Does use of the test change individual patient management and improve outcomes compared to usual care?
- In other words, what is the incremental value of adding the test to usual clinical practice (measured in terms of outcomes)?
- Study design
  - Direct evidence (Ideal): RCT of using the test vs. not using the test to direct management in the population of interest and comparing outcomes
    - Not always possible
    - Expect for large affected population, public health impact, short-term outcomes
  - Indirect evidence chain
    - E.g. U.S. Preventive Services Task Force (USPSTF) Update on Methods: http://www.ahrq.gov/clinic/uspstf07/methods/benefit.htm
    - E.g. EGAPP reviews http://www.egappreviews.org/workingrp/reports.htm

Clinical Utility: Incremental Value

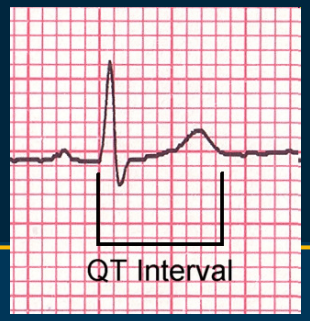
- Analysis of incremental value
  - A test should meaningfully improve discriminatory ability when added to existing predictors, or demonstrate superior discrimination alone if intended to replace those currently used
  - Easiest to evaluate when test results are classified in a manner that informs decision-making (high risk, low risk)
    - *c*-statistic=area under the receiver operator curve (ROC)
      - May be difficult to determine if improvement in *c*-statistic is clinically meaningful with regard to treatment decisions
    - Classification (by usual methods) → reclassification (using test result) → quantify improvement e.g. "net reclassification improvement" (Pencina et al. *Stat Med*, 2008;27:157)
      - Correct and incorrect re-classifications have different consequences

Example 1: Oncotype DX (node-negative)

- Nonconcurrent prospective evaluation of banked specimens from prospective, already completed clinical trials
  - E.g. Oncotype Dx - NSABP trials of TAM, TAM + chemo
  - NEJM 2004: Established relationship between Recurrence Score and distant disease recurrence within 10 years (clinical validity)
  - NEJM 2006: Established relationship between Recurrence Score and likelihood of benefit from chemotherapy (clinical validity)
- Key: Reclassification, Net reclassification index

Classification by NCCN	**Reclassification by Oncotype DX**		**(95% CI)**
Low (8%)	Low	38	100 (NR)
	Intermed	12	80 (59–100)
	High	3	56 (13–100)
High (92%)	Low	301	93 (89–96)
	Intermed	137	86 (80–92)
	High	178	70 (62–77)

Genetic Test Long QT Syndrome



Family history; suspect LQTS

Indirect evidence:
http://www.bcbs.com/blueresources/tec/vols/22/22_09.html

LQT test vs. clinical criteria

No true gold standard

LQT test more "sensitive"

⇨

LQT-pos start beta-blockers

LQT-neg; diagnose no LQTS

Confident LQT-neg; known family mutation

⇨

Qualitative Conclusions

Beta-blocker low risk intervention

Observational evidence LQTS population

Potential catastrophe untreated

KRAS Mutations and EGFR Inhibitor Therapy

- Cetuximab and panitumumab are monoclonal antibodies that bind to the epidermal growth factor receptor (EGFR), preventing activation of downstream signaling pathways vital for cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.
- RAS proteins act as a binary switch between the cell surface EGFR and downstream signaling pathways.
- The *KRAS* gene can harbor oncogenic mutations that result in a constitutively activated protein, independent of EGFR ligand binding, rendering antibodies to the upstream EGFR ineffective.
- Do patients with mutated *KRAS* respond to EGFR inhibitors?

KRAS Mutations and EGFR Inhibitor Therapy in Metastatic CRC

- **Five randomized, controlled trials: subgroup analyses of the efficacy of EGFR inhibitors in patients with wild-type versus mutated *KRAS*. Data consistently show a lack of clinical response to cetuximab and panitumumab in metastatic CRC patients with mutated *KRAS*.**
- **Five single-arm studies retrospectively analyzed *KRAS* mutation status and tumor response rate in patients with metastatic CRC:**

Table 6. Single-Arm Studies Showing Objective Response Rate (n [%]) to Anti-EGFR Monoclonal Antibodies in Chemotherapy Refractory Metastatic Colorectal Cancer

Study	Treatment	Total Patients (Wildtype: Mutated)	Wild Type n (%)	Mutated n (%)
Lievre et al. 2008	C ± CT	89 (65:24)	26 (40)	0 (0)
De Roock et al. 2008	C ± CT	108 (66:42)	27 (41)	0 (0)
Khambata-Ford et al. 2007	C	80 (50:30)	5 (10)	0 (0)
Di Fiore et al. 2007	C + CT	59 (43:16)	13 (28)	0 (0)
Benvenuti et al. 2007	P or C or C + CT	48 (32:16)	10 (31)	1 (6)

C: cetuximab; CT: chemotherapy; P: panitumumab

EGFR Mutations and Tyrosine Kinase Inhibitor Therapy in Advanced NSCLC

- Gefitinib (not available in U.S.) and Erlotinib inhibit EGFR activation
- In 2004, somatic gain-of-function mutations in the TK domain of the EGFR gene were identified in tumor samples from patients who had objective responses
- Can EGFR mutations predict response prospectively?
- TEC Assessment 2007: Retrospective analysis of completed trials
  - Gefitinib; EGFR PPV ~ 72%, NPV ~ 89%
  - (Erlotinib; EGFR PPV ~ 34%, NPV ~ 88%)
  - Some patients with wild-type EGFR did respond (median objective response rate =11%)
  - Conclusion: Test does not reliably identify nonresponders

EGFR Mutations and Tyrosine Kinase Inhibitor Therapy in Advanced NSCLC

- TEC Assessment 2010
  - 13 studies link response to erlotinib to *EGFR* mutation status
    - 9 - nonconcurrent prospective

	Median ORR (%)	M edian PFS (mos.)	OS (mos.)
Mutation +	45	12.5	21
Wild Type	5	2.5	8

    - 4 - one armed prospective enrichment

	Median ORR (%)	M edian PFS (mos.)	OS (mos.)
3 - Mutation +	40-70	8-14	16-29
1 - Wild Type	3.3	2	9

EGFR Mutations and Tyrosine Kinase Inhibitor Therapy in Advanced NSCLC

- Patients with *EGFR* mutations treated with erlotinib also demonstrate improved outcomes as compared to similar patients treated with standard chemotherapy
- Conclusions:
  - EGFR mutation positive patients ideal candidates for erlotinib
  - Wild type patients best served by other therapeutic options
- EGFR mutation testing to predict response to erlotinib treatment meets TEC criteria

Evidence: Putting the Pieces Together

NEW TESTS

EVIDENCE

CLINICAL APPLICATIONS → IMPROVED OUTCOMES