Evaluating the Evidence for Clinical Utility
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Institute of Medicine
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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
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](http://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

- Pharmacogenomics of Cancer (2007)
- Cardiovascular Pharmacogenetics (2007)
- Pharmacogenomics of EGFR-Targeted Therapy (2007)
- Fecal DNA for Colon Cancer Screening (2006)
- Gene Expression Profiling for Breast Cancer (2005)
- 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)
EGFR mutations and tyrosine kinase inhibitor therapy in advanced non-small-cell lung cancer (in press)


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)

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 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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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) $\rightarrow$ reclassification (using test result) $\rightarrow$ 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

<table>
<thead>
<tr>
<th>Classification by NCCN</th>
<th>Reclassification by Oncotype DX</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (8%)</td>
<td>Low</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Intermed</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>3</td>
</tr>
<tr>
<td>High (92%)</td>
<td>Low</td>
<td>301</td>
</tr>
<tr>
<td></td>
<td>Intermed</td>
<td>137</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>178</td>
</tr>
</tbody>
</table>
Genetic Test Long QT Syndrome

Family history; suspect LQTS


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

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
• TEC Assessment 2010
  – 13 studies link response to erlotinib to *EGFR* mutation status
    • 9 - nonconcurrent prospective
      
      | Mutation + | Median ORR (%) | Median PFS (mos.) | OS (mos.) |
      |------------|----------------|-------------------|-----------|
      | 45         | 12.5           | 21                |

      | Wild Type  | 5              | 2.5               | 8         |

  • 4 - one armed prospective enrichment
      
      | 3 - Mutation + | Median ORR (%) | Median PFS (mos.) | OS (mos.) |
      | 40-70         | 8-14           | 16-29             |

      | 1 - Wild Type | 3.3            | 2                 | 9         |
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