Translating Actionable Variants into Evidence-based Practice: The View from TEC

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Overview

- BCBSA Technology Evaluation Center
- Evaluating Evidence
- Value and Affordability
Blue Plans Cover Every Community in the Nation

- 39 Blue Cross and/or Blue Shield Plans
- 99 million members
- Contract with 90% of hospitals, 80% of doctors
- 5-million member FEP Program – Largest private health insurance product in world
- Largest processor of Medicare claims in the nation
- 1985 Technology Evaluation Center (TEC)
Technology Evaluation Center (TEC)

- Rigorous assessment of clinical evidence, systematic review with quality appraisal: Does this technology improve health?
- Independent, expert Medical Advisory Panel
- TEC Assessments 3-year inventory at [www.bcbs.com/tec](http://www.bcbs.com/tec)
- Medical Policy Reference Manual (MPRM): a confidential and proprietary inventory of approximately 350 evidence-based policies, updated annually, that is offered to support Blue Plans’ operations*
- Dedicated professional staff
- Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center [www.ahrq.gov](http://www.ahrq.gov)
- AHRQ Comparative Effectiveness Research EPC cancer and infectious disease

*Note: Each Plan, acting independently, may adopt the MPRM, in whole or in part, modify it, or reject it, in making that Plan’s own medical policy decisions.
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
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)
TEC Focus on Genomics 2008-2010

- EGFR mutations and tyrosine kinase inhibitor therapy in advanced non-small-cell lung cancer (2010)
- Genetic Testing for Familial Hypertrophic Cardiomyopathy (in press)
- Pharmacogenetic Testing to Predict Serious Toxicity from 5-Fluorouracil (2009)
- 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 Evidence

The ACCE evaluation process for genetic testing

From the CDC National Office of Public Health Genomics
http://www.cdc.gov/genomics/genotyping/ACCE/index.htm
Diagnostic Model
a Continuum for Efficacy

- Level 1: Technical efficacy
- Level 2: Diagnostic accuracy efficacy
- Level 3: Diagnostic thinking efficacy
- Level 4: Therapeutic efficacy
- Level 5: Patient outcome efficacy
- Level 6: Societal efficacy

Paraphrased
Pretty Picture
Improved Accuracy
Improved Diagnosis
Improved Treatment
Improved Health
Improved Efficiency


Source: [www.bcbs.com/tec]
Ideal ... Direct Evidence

- Test
  - Treat accordingly
  - Randomize
  - No Test
    - Treat accordingly

- Measure Outcomes
- Compare
- Measure Outcomes
Indirect Evidence:
Genetic test long QT syndrome
(http://www.bcbs.com/blueresources/tec/vols/22/22_09.pdf)

Family history

Suspect LQTS

Performance

LQT test vs. clinical criteria
No true gold standard
LQT test more “sensitive” in 2 series @ n >500

Change Management

LQT-positive start beta-blockers
LQT-negative for all known mutations ↓likelihood LQTS
↓LQTS if LQT-negative for known family mutation

Improve Outcomes (Qualitative Conclusions)

Potential catastrophe untreated
Observational evidence LQTS population
Beta-blocker low-risk intervention

Indirect Evidence:
Genetic test long QT syndrome
(http://www.bcbs.com/blueresources/tec/vols/22/22_09.pdf)
“Prospective-Retrospective” Methodologic Framework (Simon et al.)


- Studies that use a prospectively designed protocol to investigate a candidate predictive marker using archived specimens from a completed prospectively designed RCT that was conducted for a different purpose.

- Typically, the purpose of the original trial would be to test therapeutic efficacy (e.g., tamoxifen vs. no tamoxifen or adjuvant chemotherapy vs. no adjuvant chemotherapy).

- Existing tumor samples could be used to determine whether the candidate marker predicted improved survival (or poorer survival, or no effect) with the treatment of interest.
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

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Value 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

• But no clear cost-effectiveness threshold: can you afford everything that is a “good buy”? 
Projected Spending on Healthcare as Percentage GDP

Source: Congressional Budget Office, 2007 (15).
Summary

• TEC process is evidence based and independent. Genomics is high priority and we seek to complement and collaborate with other organizations.

• Diagnostic technologies raise common questions, whether for diagnostic, prognostic, or predictive use. Critical are when direct or indirect evidence of clinical utility is sufficient and how to be pragmatic and creative in developing good evidence.

• Effectiveness and affordability are pressing issues. All stakeholders need to exercise stewardship for a sustainable healthcare system.