COLLABORATIVE DEVELOPMENT OF EVIDENTIARY STANDARDS FOR CLINICAL UTILITY OF MDx

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The Potential

• Widespread recognition that genomics, MDx may have transformational impact over next several decades
• Genomic tests and molecular diagnostics currently apply to 2% of population, with potential to rise to 60% (UHC, 2012)
• Life sciences market of $42 billion by 2015, 10% annual growth (PWC, 2011)
Current Reality – According to EGAPP
(Teutsch et al, Genet Med, 2008)

• “Of most concern, the number and quality of studies are limited. Test applications are being proposed and marketed based on descriptive evidence and pathophysiologic reasoning, often lacking well-designed clinical trials or observational studies to establish validity and utility, but advocated by industry and patient interest groups”
Reasons for Inadequate Evidence

• Technology changes rapidly, existing hierarchy of evidence is inherently much slower
• Diagnostic business model does not generate enough money to pay for high quality studies
• Lack of clarity about regulatory requirements
• Lack of clarity about evidentiary standards for reimbursement, clinical guidelines.
SACGHS recommendation

- “Information on clinical utility is critical for managing patients, developing professional guidelines, and making coverage decisions.”
- “HHS should create a public private entity of stakeholders to...establish evidentiary standards and levels of certainty required for different situations”
A Fundamental Trade-off

• In defining the evidence “goal line” for MDx, there is a need to find the right balance of:
  – Internal validity
  – External validity / generalizability
  – Feasibility, Cost and Timeliness
Effectiveness Guidance Documents

• Specific recommendations for study design reflecting information needs of patients, clinicians, payers
• Targeted to public/private sector clinical researchers
• Describe study designs that provide “reasonable confidence of improved health outcomes”
• Balance internal validity with generalizability, feasibility, timeliness and cost
• Multi-stakeholder collaborative process
MDx EGD Process Overview

**Define Project Scope**
- Conduct Literature Review
- Protocol Development for Qualitative Interviews
- Institutional Review Board (IRB) Review
- Review interviews to identify key issues and themes
- *Conduct Key Informant Interviews*
- Identify additional experts (Snowball Sampling)
- Identify Key Methodological Issues Related to Clinical Validity & Clinical Utility
- Draft major issues and recommendations
- Develop Delphi survey for TWG members
- TWG meetings to develop consensus on issues and draft recommendations
- MDAG & IOM workshops to obtain stakeholder input & refine recommendations
- Final Effectiveness Guidance Document (EGD) on Molecular Diagnostics for Solid Tumors

Project Initiation: July 2010
Target Completion: December 2012
# Technical Working Group on Clinical Utility of MDx in Oncology

<table>
<thead>
<tr>
<th>TWG Member Name</th>
<th>Stakeholder Category</th>
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Draft Recommendations – Clinical Validity examples

Recommendations

• Clinical validation (CV) studies must be conducted in populations adequately reflecting the patient population intended to be seen in actual clinical practice.

• Appropriate metrics to demonstrate strength of an association between MDx test and a disease state include clinical sensitivity, clinical specificity, PPV and NPV.

Rationale

• While use of less representative population is often justified early in test development, not sufficient for CV studies.

• ROC curves and AUC curves can be used in tandem with other techniques, but are not independently sufficient. Odds ratios, hazard ratios, and regression coefficients are inadequate.
Draft Recommendations – Clinical Utility

• CU studies should include the assessment of proven outcomes that measure both benefits and harms, recognizing that these outcomes may occur at different time points and are the result of management decisions guided by the test results. For example, measures of benefits and harms could include:
  • Avoiding an ineffective therapy
  • Switching more quickly to an effective therapy
  • Avoidance of high cost treatments; shorter treatment duration
  • Helping to choose among seemingly equal treatment options
  • Patient-reported outcomes (e.g., Quality of Life)
  • Survival and (progression-free survival)
CED and Genomic Diagnostics

• CED provides coverage contingent on participation in a clinical study (clinical trial, registry, etc)
  – For diagnostic tests, evidence of impact on health outcomes may not be feasible for initial coverage
  – However, unconditional coverage significantly reduces incentives to confirm health impacts
  – Optimal public health benefits from genomic diagnostics may be achieved through initial coverage at clinical validity, studies of clinical utility under CED
Multiple Legitimate Social Objectives
Requires Dialogue and Collaboration!
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