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

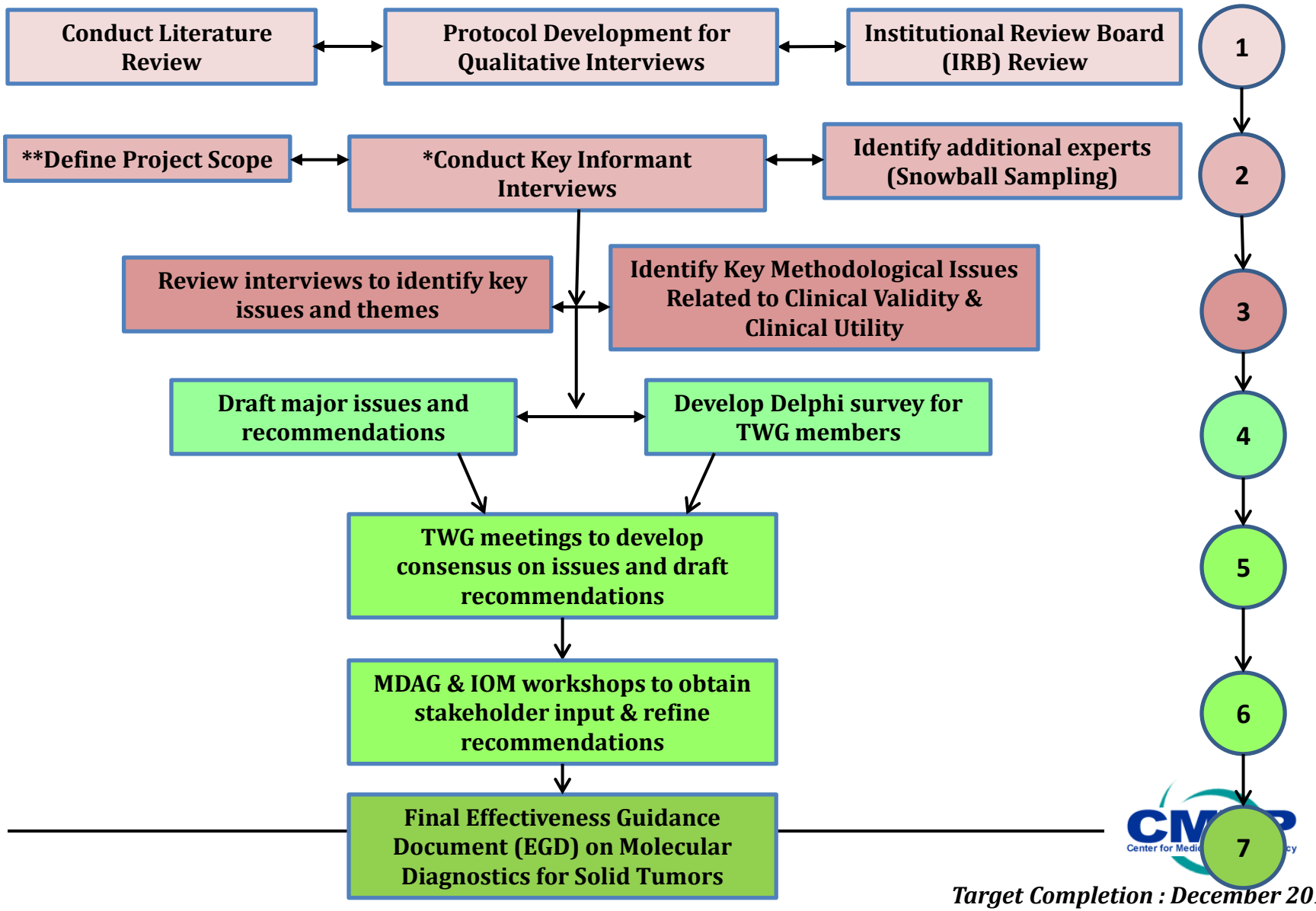
- In defining the evidence "goal line" for MDx, there is a need to find the right balance of:
  - Internal validity
  - External validity / generalizability
  - Feasibility, Cost and Timeliness

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

Project Initiation: July 2010



Target Completion : December 2012

Technical Working Group on Clinical Utility of MDx in Oncology

TWG Member Name	Stakeholder Category	Affiliation
Linda Bradley	Geneticist/Lab Director	Women & Children's Hospital of Rhode Island
Louis Jacques	Payer	Center for Medicare & Medicaid Services
Gary Lyman	Clinician	Duke University
Howard McLeod	Researcher	UNC Institute PGx & Individualized Therapy
David Nelson	Industry	Epic Sciences
David Parkinson	Industry	Nodality
Liz Mansfield	FDA	FDA Representative (ex officio)
Margaret Piper	Payer	Blue Cross Blue Shield Tech Assessment
Richard Simon	Methodologist	National Cancer Institute
Mary Lou Smith	Patients & Consumers	Research Advocacy Network

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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.

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Draft Recommendations – Clinical Utility

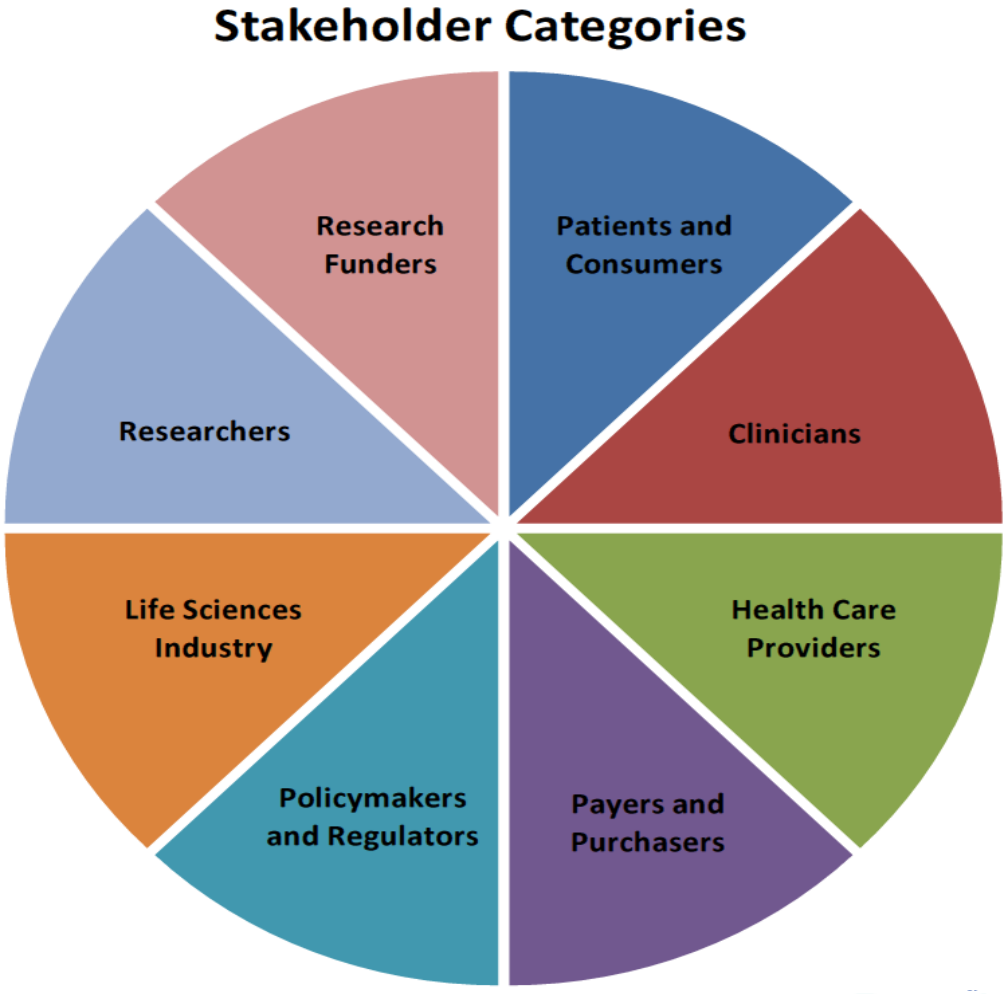
- CU studies should include the assessment of proven outcomes that measure both benefits and harms, recognizing that these outcomes may occur at different time points and are the result of management decisions guided by the test results. For example, measures of benefits and harms could include:
    - 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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