SPECTRUM OF MOLECULAR DIAGNOSTIC TESTS

Predisposition/Risk Assessment
- BRCA1/2
- Lynch Syndrome testing

Staging
- Various IHC/FISH

Prognosis
- Oncotype Dx

Predictive
- EGFR
- K-RAS
- BRAF
- HER-2

Monitoring
- PSA
- BCR-ABL

CMTP
Clinical Validity:
- The ability to accurately and reliably predict the clinically defined disorder or phenotype of interest.
- How well does the test result correlate with clinical outcome?

Clinical Utility:
- The evidence of improved measurable clinical outcomes, usefulness and added value to patient management decision-making.
- Does use of the MDx test lead to improved patient health outcomes compared with an alternative?

Actionable test: Tests that produce results that are intended to lead to changes in the clinical management of patients.
THE PROMISE AND PITFALLS OF MDX IN ONCOLOGY

• Widespread recognition that with advances in genomics, MDx tests may have transformational impact on cancer over next several decades.

• Emphasize a molecular, rather than histologic approach to management of various cancers
  • Diagnose and stage cancers
  • Help guide therapy selection and dosing
  • Assess treatment response
  • Aid in detection of residual or recurrent disease

• Inefficient translation and integration into clinical practice
  • Lack of evidence of clinical utility
  • Incomplete/flawed studies of clinical validity
  • Lack of shared evidentiary framework to meet needs of decision-makers
  • Lack of clear and predictable methodological standards for test developers and researchers
EGD FOR MDX TESTS IN ONCOLOGY
PROJECT GOALS

• Use a stakeholder-driven process to develop specific methodological recommendations to address the evidence gaps regarding the clinical validity and clinical utility of actionable MDx tests in oncology.

• Provide clarity regarding stakeholder evidence expectations for clinical and reimbursement policy decision-making, so that there is greater predictability when planning studies.
PROCESS OVERVIEW

1. Conduct Literature Review
2. Define Project Scope
3. Protocol Development for Qualitative Interviews
4. Conduct Key Informant Interviews
5. Institutional Review Board (IRB) Review
6. Identify additional experts (Snowball Sampling)
7. Review interviews to identify key issues and themes
8. Identify Key Methodological issues Related to Clinical Validity & Clinical Utility
9. Draft major issues and recommendations
10. Develop feedback survey for TWG members
11. TWG meetings to develop consensus on issues and draft recommendations
12. MDAG & IOM* workshops to obtain stakeholder input & refine recommendations
13. MDAG & TWG teleconference to refine recommendations and position statements
14. Final EGD: Evaluation of CV and CU Actionable MDx tests in Oncology
<table>
<thead>
<tr>
<th>TWG Member Name</th>
<th>Stakeholder Category</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Linda Bradley</td>
<td>Geneticist/Lab Director</td>
<td>Women &amp; Children's Hospital of Rhode Island</td>
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<tr>
<td>Louis Jacques</td>
<td>Payer</td>
<td>Centers for Medicare &amp; Medicaid Services</td>
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<td>Gary Lyman</td>
<td>Clinician</td>
<td>Duke University</td>
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<td>Howard McLeod</td>
<td>Researcher</td>
<td>UNC Institute PGx &amp; Individualized Therapy</td>
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<tr>
<td>David Nelson</td>
<td>Industry</td>
<td>Epic Sciences, Inc.</td>
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<tr>
<td>Robert McCormack</td>
<td>Industry</td>
<td>Veridex LLC, a Johnson &amp; Johnson company</td>
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<tr>
<td>David Parkinson</td>
<td>Venture Capital</td>
<td>New Enterprise Associates</td>
</tr>
<tr>
<td>Margaret Piper</td>
<td>Payer</td>
<td>Kaiser Permanente (formerly BCBSA TEC)</td>
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<tr>
<td>Richard Simon</td>
<td>Methodologist</td>
<td>National Cancer Institute</td>
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<tr>
<td>Mary Lou Smith</td>
<td>Patients &amp; Consumers</td>
<td>Research Advocacy Network</td>
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# SCOPE OF MDX EGD

<table>
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<tr>
<th>IN</th>
<th>OUT</th>
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<tr>
<td><strong>Type of Test</strong></td>
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<tr>
<td>Actionable</td>
<td>Companion Diagnostics</td>
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<td>High risk</td>
<td>Low/Moderate risk</td>
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<td>New test/existing drug</td>
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<tr>
<td>Stand-alone test</td>
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<td>First generation assays, Next gen assays, Circulating tumor cells</td>
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<td><strong>Target Condition</strong></td>
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<td>Solid Tumors</td>
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<td>Hematologic Malignancies</td>
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<td>Adult patients</td>
<td>Pediatric patients</td>
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<tr>
<td><strong>Recommendations</strong></td>
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<tr>
<td>Clinical Validity</td>
<td>Analytic Validity</td>
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<td>Clinical Utility</td>
<td>Formal Cost-effectiveness analysis</td>
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<td>Implementation barriers</td>
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**Phase 1: Initial Test Performance & Assay Refinement**

Determine test performance of defined assay in targeted population

**Recommendation 1:** Follow standard reporting guidelines to document analytic validity has been established

**Phase 2: Test Validation & Generalizability**

Determine how well test predicts clinically relevant phenotypes in the intended use population

**Recommendation 2:** Study patient population intended for clinical use of test

**Recommendation 3:** Choose appropriate metrics for clinical validation

**Phase 3: Components of Clinical Test Performance & Health Impacts**

Select the components to measure how test affects clinical decision-making (benefits and harms) and related health outcomes

**Recommendation 4:** Anticipate clinical pathways related to test use

**Recommendation 5:** Select outcomes to measure net benefit from the patient perspective

**Phase 4: Comparison with Standard of Care**

Determine the net impact on health outcomes & added value compared to current patient management without MDx testing (clinical utility)

**Recommendation 6:** RCT design selection; OR

**Recommendation 7:** Prospective-retrospective study; OR

**Recommendation 8:** Single-arm study; OR

**Recommendation 9:** Prospective observational study OR

**Recommendation 10:** Modeling techniques (e.g., decision-analytic)
CU studies of MDx tests should include outcome measures that assess both potential benefits and harms of testing *from the patient perspective*, recognizing that these outcomes may occur at different time points and are the result of clinical management decisions guided by test results.

- Should routinely include patient-reported outcome measures that are appropriate and validated for the clinical context.
- May also include important endpoints such as survival and downstream health care resource utilization.
- *Process measures such as changes in physician behavior are typically insufficient to qualify as study endpoints.*
- Studies designed to report intended care plans following an MDx test are insufficient to demonstrate CU.
When the clinical utility of an MDx biomarker is assessed with RCTs:

- RCT should evaluate the effectiveness of the clinical decision (treatment or other clinical pathway) relative to control for both marker-positive and marker-negative patients.
- Enrichment designs excluding patients with a particular marker status should be avoided unless a clear and valid rationale exists for exclusion.
- Marker-based strategies randomizing patients to genomics-guided treatment vs. usual care partially duplicate actions to be taken between the intervention and control arms, reduce statistical power, and therefore are not optimal.
Under limited, specified circumstances, *longitudinal* observational study designs are acceptable options for assessing clinical utility of MDx tests

- Must have compelling rationale for not doing RCT
- Steps to minimize confounding must be documented
- Good research practices followed, including public registration of studies
- Retrospective studies not adequate for CU of MDx tests due to lack of required information in secondary databases.
- Secondary databases may be one source for data collection, but prospective data collection needed to obtain missing data or develop validated approaches to approximate these data elements from the existing secondary data.
Formal decision-analytic modeling techniques can be used to elucidate the relationship between test results, corresponding clinical pathways and downstream patient outcomes.

- Applies to cases where MDx test has established evidence of clinical validity and plausible evidence of clinical utility based on initial scenario modeling.
- Scenario modeling is a simplified approach to decision analysis that typically includes outcomes evaluated under 3 scenarios: base case, best case, worst case.
- Stakeholder input recommended to conduct scenario modeling.
LESSONS LEARNED

• Need clear process for defining the project scope
  • Shared understanding of specific research question(s) to be addressed is critical

• Process needs to be faster (took 3 years)
  • Recommend dedicated CMTP project staff

• Technical expert as lead author
  • Technology and methods evolve, need ability to maintain expertise

• Need feedback from larger, more diverse group of stakeholders
  • Methods symposium conducted with IOM inefficient
  • Need targeted outreach to ensure relevancy, accuracy
LESSONS LEARNED (2)

- CMTP’s expertise
  - Stakeholder engagement – critical to ensure transparency; all perspectives are heard; acceptability of final recommendations
  - EGD process – addressing information needs of decision-makers; ensuring recommendations are actionable

- Evaluation of the process is critical, should be conducted throughout

- Criteria for measuring a “good” process
  - Legitimacy
  - Respect
  - Trust
  - Fairness
  - Accountability
  - Trust
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