Facilitating Development and Utilization of Genome-Based Diagnostic Technologies

Tumor Biomarkers in Clinical Practice: Problems and Solutions

Daniel F. Hayes, M.D.
Declarations of Conflicts

- I receive research funding from Veridex
- I have two patents pending regarding CTC
- I am a funded clinical and translational investigator
- I chair the ASCO Tumor Marker and I am a member of NCCN Guidelines Committees
- I am a practicing medical oncologist/caregiver
- I pay taxes
- I pay health insurance premiums
- I will probably have cancer in my lifetime
A Question of Values: Is it worth it

Personalized Patient Care: focus the “right therapy on the right patient” -
- Improved cancer outcomes
  - Cure
  - Survival
  - Palliation
- Decrease exposure to toxicity of unneeded or inactive therapy
- Decrease costs
**Tumor BioMarkers**

- A bad tumor biomarker is as harmful as a bad drug!

- Would you use a drug if:
  - You aren’t sure how it is mixed?
  - You aren’t sure what the concentration is?
  - You don’t have clinical data about how the drug might be useful?
  - You don’t have reliable clinical research data to determine how much efficacy it might have?
What’s the Problem?

- Very few cancer biomarker tests that have clinical utility have been introduced into clinical practice over the last 30 years

- Cancer biomarkers that do not have proven clinical utility have been introduced into clinical care
Undervalue of Tumor BioMarkers: A Vicious Cycle

Marker Utility is Poorly Valued
- Lower Ability and Incentive to Conduct Properly Designed Clinical Studies
- Lower Academic Prestige
- Poor Reimbursement
- Weak Regulatory Environment
- Low Funding/Investment for Tumor Marker Research

Reduced Data Certainty
- Higher Scrutiny and Skepticism
- Few Recommendations for Clinical Use

Lower Level of Evidence

Lower Ability and Incentive to Conduct Properly Designed Clinical Studies

Lower Academic Prestige
Summary of Recommendations

- Reform Tumor Biomarker Regulatory Approach
  - Combine into one FDA Oncologic Office
  - Eliminate Laboratory Developed Test rule
  - Approve Tumor Biomarker Assays based on Clinical Utility
- Reimburse Tumor Biomarkers Commensurate with Their Value
Recommendations to Break the Vicious Cycle

A. Reform Regulatory Management of Tumor Biomarkers

1. Combine **ALL** oncologic products into single FDA Oncology Office
   - Drugs
   - Devices, including Tumor Biomarkers

2. Eliminate **Laboratory Developed Test** rule

3. Base FDA approval on:
   - Analytical Validity (already) &
   - **CLINICAL UTILITY**
   - *NOT* Clinical Validity/Manufact Intended Use
Recommendations to Break the Vicious Cycle

B. Base Reimbursement on Commensurate Value of Tumor Biomarker

1. Cost-effective analyses: Carefully assess value to patient and society and 3rd payers:
   - Elimination of expensive and costly treatment for patients who:
     - Do not need the therapy
     - Will not benefit
     - Will suffer toxicity
Barriers to These Recommendations
A. Reform Regulatory Management of Tumor Biomarkers

1. Combine ALL oncologic products into single FDA Oncology Office

PROBLEM: Requires fundamental reorganization of FDA

- Currently, drugs are in Center for Drug Evaluation and Research (CDER)
  - Oncologic Drugs Advisory Board: Standing Board
    - Multi-disciplinary strength, but less analytical
    - “Corporate memory”
  - New Office of Hematology and Oncology Products (OHOP), coupled with co-development “Critical Pathway” is a step forward, but only handles “co-developed” biomarkers

- Devices NOT linked to specific therapeutics are in Center for Devices and Radiological Health (CDRH)
  - Enormous analytical expertise
  - Weaker Oncologic expertise
  - Ad hoc advisory boards
    - Less oncologic expertise
    - No corporate memory
A. Reform Regulatory Management of Tumor Biomarkers

2. Eliminate Laboratory Developed Test rule

PROBLEM: LDT is a commonly used strategy to introduce tests into practice

- Requires only CLIA review
- No review of analytical or clinical validity, let alone clinical utility
- Elimination would remove many commonly used tests
  - Especially in situ tissue-based tests (IHC, IF, etc)
  - Not clear how many of these have analytical validity, and more importantly, clinical utility?

- Corporate and Political push back
  - Draft Guidance is in Office of Management and Budget (OMB)
    - 3rd party labs are opposed
    - Climate of anti-Regulation
A. Reform Regulatory Management of Tumor Biomarkers

3. Base FDA approval on:
   - Analytical Validity (already) &
   - CLINICAL UTILITY

PROBLEM: Current FDA approval is based on Manufacturer’s intended use, which usually does not = clinical utility
   - Will increase time and resources to get FDA approval
   - Will require following one of 3 pathways to get approval
Recommended Pathways to Generate LOE I Data for Clinical Utility

I. Retrospective/Prospective Study with Archived Specimens

   Adequate archived dataset does not exist

II. Prospective Clinical Trial; Marker does NOT direct patient management

   OR

III. Prospective Clinical Trial; Marker directs patient management

Generation of High Level Evidence for Intended Clinical Use of Tumor Biomarker Test

FDA Approval/Clearance

Tech Assessment, Practice Guidelines and Reimbursement Deem Adequate

Clinical Use
**B. Base Reimbursement on Commensurate Value of Tumor Biomarker**

**Problem:** Requires fundamental increase in value of tumor biomarkers

- **Third Party Payers** will need to agree that reimbursement for tumor biomarkers needs to be sufficient to recoup the increased costs of previous recommendations.
- **Cost Effective Analyses** and **Comparative Effectiveness Research** will be needed to demonstrate that the costs of a tumor biomarker with demonstrated clinical utility is far outweighed by the benefits to:
  - Their covered patients
  - Society
  - The Payers themselves, by substantially reducing use of expensive but needless or ineffective cancer therapies
How Do We Overcome These Barriers, and Who are the Stakeholders?
Undervalue of Tumor Biomarkers: A Vicious Cycle

- Marker Utility is Poorly Valued
- Lower Ability and Incentive to Conduct Properly Designed Clinical Studies
- Lower Academic Prestige
- Poor Reimbursement
- Weak Regulatory Environment
- Low Funding/Investment for Tumor Marker Research
- Reduced Data Certainty
- Higher Scrutiny and Skepticism
- Few Recommendations for Clinical Use
- Lower Level of Evidence
- Lower Ability and Incentive to Conduct Properly Designed Clinical Studies
- Lower Academic Prestige
Who are the Stakeholders in the Vicious Cycle?

- **Regulatory Agencies** (FDA, CLIA, Foreign)
- **3rd Party Payers** (CMMS, Private)
- **Pharma/Commercial**
- **Research Funding Entities** (Gov’t, Private)
- **Patients/Advocates**
- **Academic Centers/Investigators**
- **Clinical Guidelines/Tech Assessment Panels** (EGAPP, AHRQ, ASCO, NCCN)
- **Physicians/Other Caregivers**
Highly Valued Tumor BioMarkers: A Virtuous Cycle

Marker Utility is Highly Valued

Strong Ability and Incentive to Conduct Properly Designed Clinical Studies

High Academic Prestige

Commensurate Level of Reimbursement

Strong/Predictable Regulatory Environment

Adequate Funding/Investment for Tumor Marker Research

CMS/BCBS/etc

Adequate Funding/Investment for Tumor Marker Research

FDA

Adequate Funding/Investment for Tumor Marker Research

Gov’t/Private/Industry

High Level of Evidence

Strong Ability and Incentive to Conduct Properly Designed Clinical Studies

Cooper Groups, Cancer Centers, Industry

High Level of Evidence

Tech Assessment/Guidelines Panels

Strong Data Certainty

Transparency Clinical Utility

Many Recommendations for Clinical Use

SOCIETY Caregivers/Advocates

High Level of Evidence

Strong Ability and Incentive to Conduct Properly Designed Clinical Studies
Definitions:
Semantics Regarding Evidence for Tumor Markers

- **Analytical Validity**
  - Does the assay accurately and reproducibly measure what you say?

- **Clinical (Biologic) Validity**
  - Does the assay actually identify a biologic difference ("pos" vs. "neg") that may or may not be clinically useful?

- **Clinical Utility**
  - Do results of the assay lead to a clinical decision that has been shown with high level of evidence to improve outcomes?

*Teutsch S.M., et al.  Genet Med. 11:3-14, 2009*
Current Pathways to Introduce a Tumor Biomarker Test into Clinical Practice

FDA Approval or Clearance (PMA or 510 K)
- CLIA approved Laboratory ✓
- Analytical Validity ✓
- Manufacturer’s Intended Use ✓
- Clinical Utility Not Required

Laboratory Developed Test
- CLIA approved Laboratory ✓
- Analytical Validity Not Necessarily
- Manufacturer’s Intended Use NA
- Clinical Utility Not Required

Many Guidelines Panels (ASCO, NCCN) ignore whether test has FDA Approval or NOT:
- *FDA approval does not = Clinical Utility*
- *Clinical Utility may exist for an LDT*
Acceptance of Tumor Markers: Balance of Carrots and Sticks

- Rapid Clinical Acceptance
  - Patient and clinician desire
  - Financial and academic benefits

- Validated Clinical Utility
  - LOE I studies
  - Financial burden/Low Payoff
What’s the Problem?

- Very few cancer biomarker tests that have clinical utility have been introduced into clinical practice over the last 30 years

- Cancer biomarkers that do not have proven clinical utility have been introduced into clinical care
ASCO Tumor Marker Guidelines Panel

Recommended Markers for Breast Cancer

- ER, PgR
  Select Endocrine Therapy
- HER2
  Select Trastuzumab/Lapitinib
- UPA/PAI -1
  Avoid Chemo if ER+/Node neg
- 21-gene RS
  Avoid Chemo if ER+/Node neg

What’s the Problem?

- Very few cancer biomarker tests that have clinical utility have been introduced into clinical practice over the last 30 years.

- Cancer biomarkers that do not have proven clinical utility have been introduced into clinical care:
  - PSA to screen for prostate cancer
  - CA125 to monitor patients with ovary cancer who are free of disease
How Can We Address the Problem?

• Admit we have a problem
• Speak the same language
• Identify factors that perpetuate the problem
• Target those issues that:
  • Are critical parts of the problem
  • Can be fixed
How Can We Address the Problem?

• Admit we have a problem
• Speak the same language
• Identify factors that perpetuate the problem
• Target those issues that:
  • Are critical parts of the problem
  • Can be fixed
How Can We Address the Problem?

• Admit we have a problem
• Speak the same language
• Identify factors that perpetuate the problem
• Target those issues that:
  • Are critical parts of the problem
  • Can be fixed
Undervalue of Tumor Markers: A Vicious Cycle

Marker Utility is Poorly Valued

- Lower Ability and Incentive to Conduct Properly Designed Clinical Studies
- Lower Academic Prestige
- Poor Reimbursement
- Weak Regulatory Environment
- Low Funding/Investment for Tumor Marker Research
- Reduced Data Certainty
- Higher Scrutiny and Skepticism
- Few Recommendations for Clinical Use
- Lower Level of Evidence

Lower Ability and Incentive to Conduct Properly Designed Clinical Studies

Lower Academic Prestige

Low Funding/Investment for Tumor Marker Research

Reduced Data Certainty

Higher Scrutiny and Skepticism

Few Recommendations for Clinical Use

Lower Level of Evidence

Weak Regulatory Environment
How Can We Address the Problem?

• Speak the same language
• Admit we have a problem
• Identify factors that perpetuate the problem
• Target those issues that:
  • Are critical parts of the problem
  • Can be fixed
Marker Utility is Poorly Valued

- Reduced Data Certainty
- Higher Scrutiny and Skepticism
- Few Recommendations for Clinical Use

Low Funding/Investment for Tumor Marker Research

- Poor Reimbursement
- Weak Regulatory Environment

Lower Academic Prestige

- Lower Ability and Incentive to Conduct Properly Designed Clinical Studies

Lower Level of Evidence
Incorporation of Tumor Marker Into Clinical Care

- What evidence is required from stakeholders?
- How should this evidence be generated?
- What are the barriers to generating this evidence and how can they be overcome?
Incorporation of Tumor Marker Into Clinical Care

- What evidence is required from stakeholders?
- How should this evidence be generated?
- What are the barriers to generating this evidence and how can they be overcome?
## TMUGS: Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Prospective, Marker Primary Objective, Well-powered OR Meta-analysis</td>
</tr>
<tr>
<td>II</td>
<td>Prospective, Marker Secondary Objective</td>
</tr>
<tr>
<td>III</td>
<td>Retrospective, Outcomes, Multivariate Analysis</td>
</tr>
<tr>
<td>IV</td>
<td>Retrospective, Outcomes, Univariate</td>
</tr>
<tr>
<td>V</td>
<td>Retrospective, Correlation with Other Marker, No Outcomes</td>
</tr>
</tbody>
</table>

*Hayes, et al; J Nat Cancer Institute 88:1456, 1996*
### TMUGS: Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Prospective, Marker Primary Objective, Well-powered OR Meta-analysis</td>
</tr>
<tr>
<td>II</td>
<td>Prospective, Marker Secondary Objective</td>
</tr>
<tr>
<td>III</td>
<td>Retrospective, Outcomes, Multivariate Analysis</td>
</tr>
<tr>
<td>IV</td>
<td>Retrospective, Outcomes, Univariate</td>
</tr>
<tr>
<td>V</td>
<td>Retrospective, Correlation with Other Marker, No Outcomes</td>
</tr>
</tbody>
</table>

*Hayes, et al; J Nat Cancer Institute 88:1456, 1996*
<table>
<thead>
<tr>
<th>Level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Prospective, Marker Primary Objective, Well-powered OR Meta-analysis</td>
</tr>
<tr>
<td>II</td>
<td>Prospective, Marker Secondary Objective</td>
</tr>
<tr>
<td>III</td>
<td>Retrospective, Outcomes, Multivariate Analysis</td>
</tr>
<tr>
<td>IV</td>
<td>Retrospective, Outcomes, Univariate</td>
</tr>
<tr>
<td>V</td>
<td>Retrospective, Correlation with Other Marker, No Outcomes</td>
</tr>
</tbody>
</table>

When is a Diagnostic Clinically Useful?

- It is either **prognostic** or **predictive** of cancer outcomes or predicts toxicity
- The **magnitude** of effect is sufficiently large that clinical decisions based on the data result in outcomes that are acceptable
  - Greater chance for benefit
  - Smaller toxicity risk
- The estimate of magnitude of effect is **reliable**
  - Assay is reproducible
  - Clinical trial/marker study design is appropriate
  - Results are validated in subsequent well-designed studies (Levels of Evidence I or II)

Henry N.L., Hayes DF; Oncologist. 11:541-52, 2006
Incorporation of Tumor Marker Into Clinical Care

- What evidence is required from stakeholders?
- How should this evidence be generated?
- What are the barriers to generating this evidence and how can they be overcome?
Strategies to “Test the Test” and Generate LOE I data:

Prospective Clinical Trials: Marker is Primary Objective!


At present, very few such trials are ongoing in N.A.

For example, in breast cancer, there are 3:

<table>
<thead>
<tr>
<th>Trial</th>
<th>Disease</th>
<th>Test</th>
<th>Num pts</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>TailorRx</td>
<td>Adj Breast</td>
<td>21-gene RS</td>
<td>~6500</td>
<td>Fully accrued</td>
</tr>
<tr>
<td>S0500</td>
<td>Met Breast</td>
<td>CellSearch</td>
<td>~120</td>
<td>Ongoing</td>
</tr>
<tr>
<td>S1007</td>
<td>Adj Breast</td>
<td>21-gene RS</td>
<td>~4000</td>
<td>In development</td>
</tr>
</tbody>
</table>
Prospective Clinical Trials: Marker is Primary Objective!


Is a Prospective Trial Always Necessary For Marker Utility?

- NO! But use of archived tissue must be done with rigor
# Use of Archived Tissues To Determine Clinical Utility of Tumor Markers

<table>
<thead>
<tr>
<th>Category</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial Design</strong></td>
<td>Prospective</td>
<td>Prospective using archived samples</td>
<td>Prospective /observational</td>
<td>Retrospective/observational</td>
</tr>
<tr>
<td><strong>Clinical trial</strong></td>
<td>PRCT designed to address tumor marker</td>
<td>Prospective trial not designed to address tumor marker, but design accommodates tumor marker utility. Accommodation of predictive marker requires PRCT</td>
<td>Prospective observational registry, treatment and follow up not dictated</td>
<td>No prospective aspect to study</td>
</tr>
<tr>
<td><strong>Patients and patient data</strong></td>
<td>Prospectively enrolled, treated, and followed in PRCT</td>
<td>Prospectively enrolled, treated, and followed in clinical trial and, especially if a predictive utility is considered, a PRCT addressing the treatment of interest</td>
<td>Prospectively enrolled in registry, but treatment and follow up standard of care</td>
<td>No prospective stipulation of treatment or follow up; patient data collected by retrospective chart review</td>
</tr>
<tr>
<td><strong>Specimen collection, processing, and archival</strong></td>
<td>Specimens collected, processed and assayed for specific marker in real time</td>
<td>Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion.</td>
<td>Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion.</td>
<td>Specimens collected, processed and archived with no prospective SOPs</td>
</tr>
<tr>
<td><strong>Statistical Design and analysis</strong></td>
<td>Study powered to address tumor marker question.</td>
<td>Study powered to address therapeutic question; underpowered to address tumor marker question. Focused analysis plan for marker question developed prior to doing assays</td>
<td>Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study. Focused analysis plan for marker question developed prior to doing assays</td>
<td>Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study. No focused analysis plan for marker question developed prior to doing assays</td>
</tr>
<tr>
<td><strong>Validation</strong></td>
<td>Result unlikely to be play of chance Although preferred, validation not required</td>
<td>Result more likely to be play of chance that A, but less likely than C. Requires one or more validation studies</td>
<td>Result very likely to be play of chance. Requires subsequent validation studies</td>
<td>Result very likely to be play of chance. Requires subsequent validation studies</td>
</tr>
</tbody>
</table>

---

# Revised LOI Scale: Use of Archived Tissues

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Category from Table 1</th>
<th>Validation Studies Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>None required</td>
</tr>
<tr>
<td>I</td>
<td>B</td>
<td>One or more with consistent results</td>
</tr>
<tr>
<td>II</td>
<td>B</td>
<td>None or Inconsistent results</td>
</tr>
<tr>
<td>II</td>
<td>C</td>
<td>2 or more with consistent results</td>
</tr>
<tr>
<td>III</td>
<td>C</td>
<td>None or 1 with consistent results or Inconsistent results</td>
</tr>
<tr>
<td>IV-V</td>
<td>D</td>
<td>NA</td>
</tr>
</tbody>
</table>

Incorporation of Tumor Marker Into Clinical Care

- What evidence is required from stakeholders?
- How should this evidence be generated?
- What are the barriers to generating this evidence and how can they be overcome?