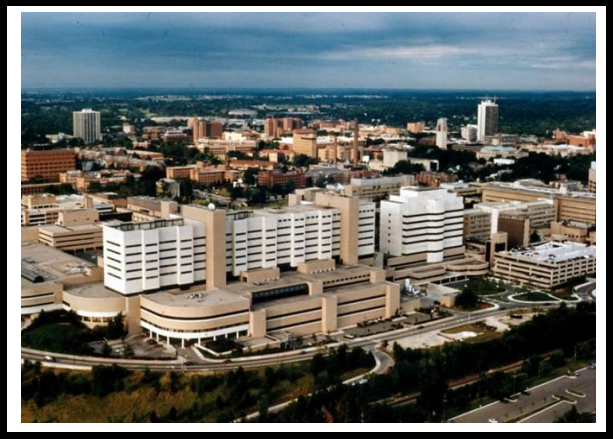
*Facilitating Development and Utilization of Genome-Based Diagnostic Technologies*

# Tumor Biomarkers in Clinical Practice:

## *Problems and Solutions*

**Daniel F. Hayes, M.D.**



University of Michigan
Health System

Comprehensive Cancer Center

# *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*

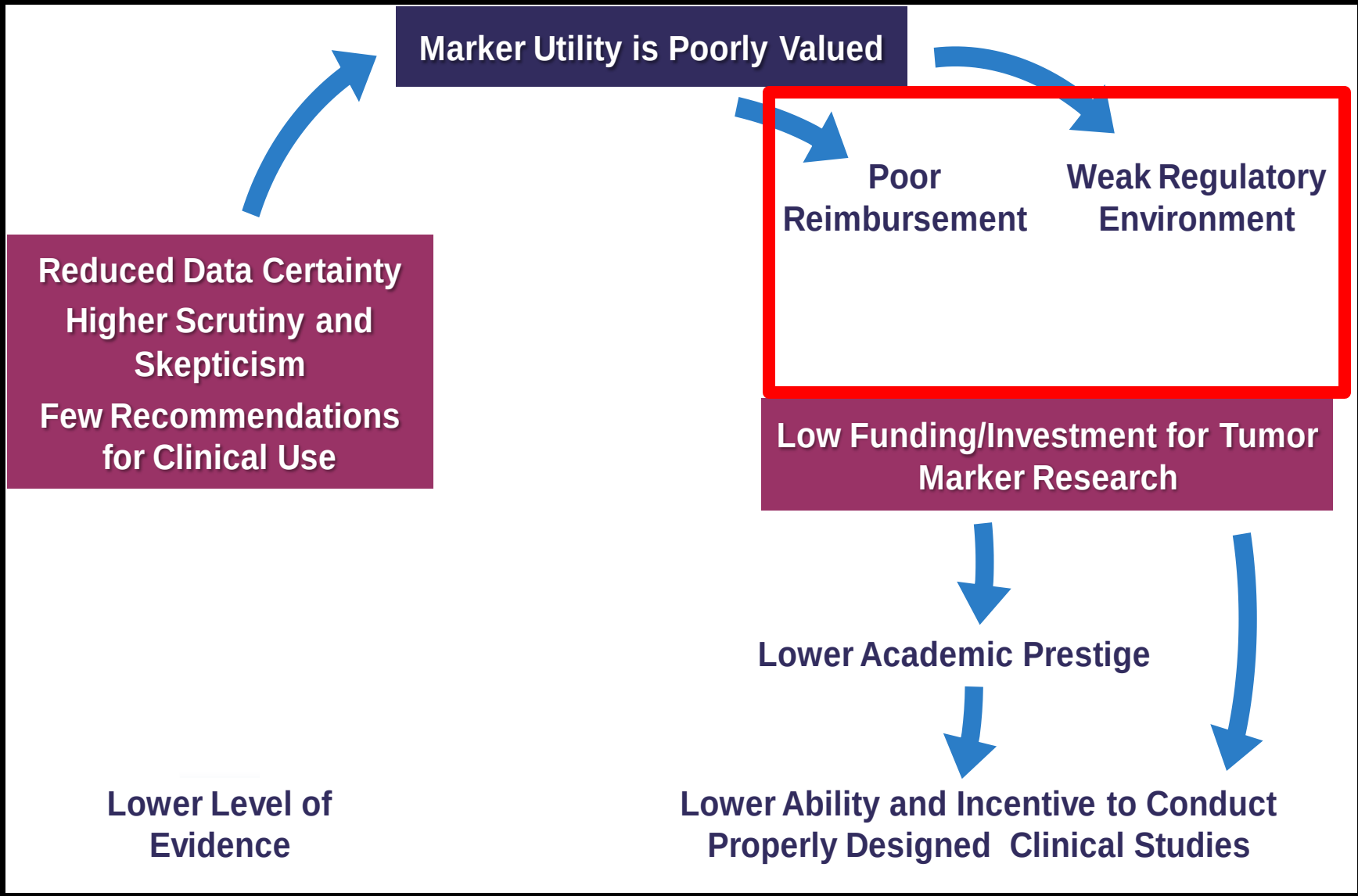
- **A bad tumor biomarker is as harmful as a bad drug!**
- **Would you use a drug if:**
  - **You aren't sure how it is mixed?**
  - **You aren't sure what the concentration is?**
  - **You don't have clinical data about how the drug might be useful?**
  - **You don't have reliable clinical research 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*



# *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*

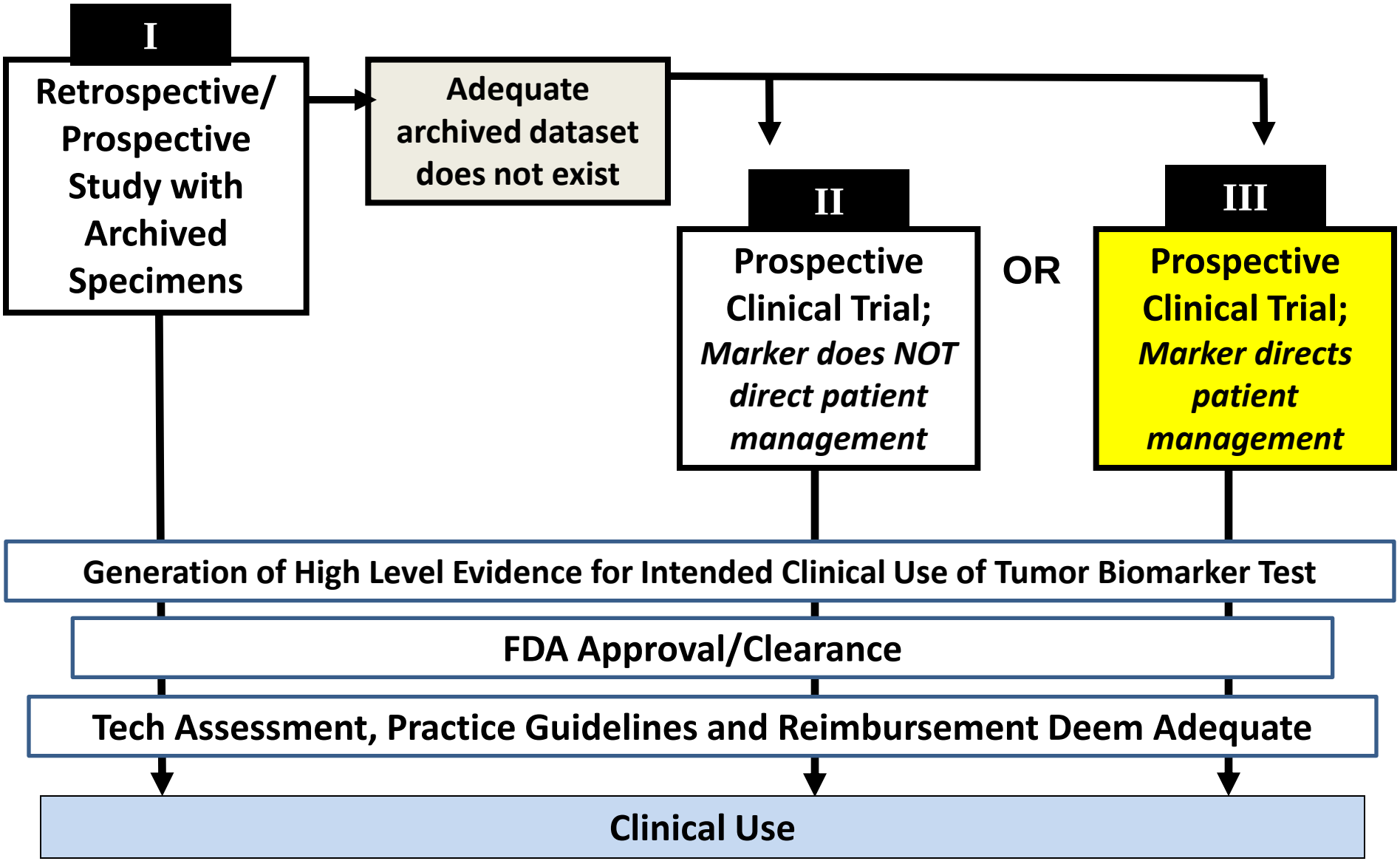
**3. Base FDA approval on:**

- **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*



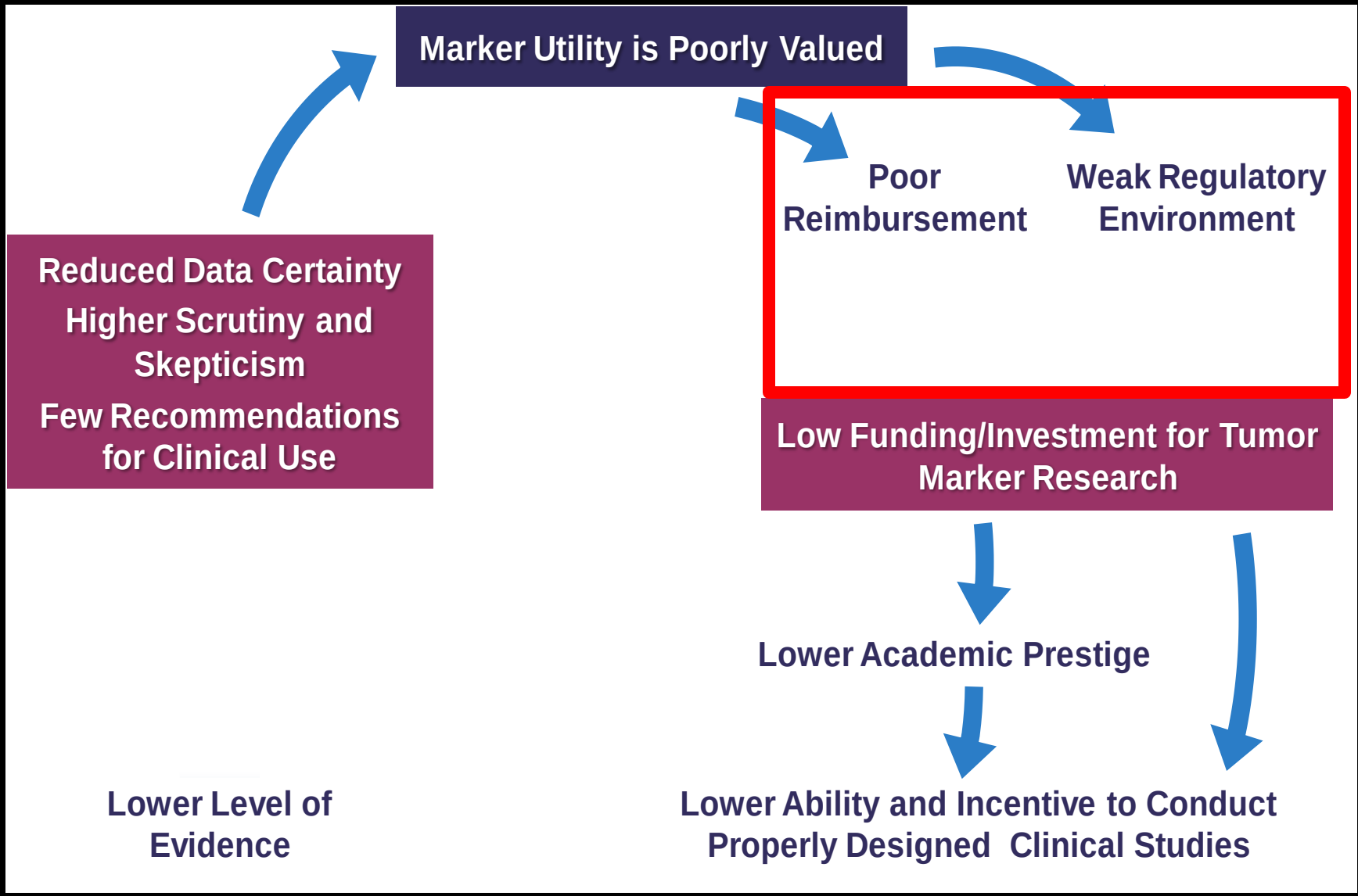
# *B. Base Reimbursement on Commensurate Value of Tumor Biomarker*

**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*



# *Who are the Stakeholders in the Vicious Cycle?*

**Regulatory Agencies (FDA, CLIA, Foreign)**

**3rd Party Payers (CMMS, Private)**

**Pharma/Commercial**

**Physicians/Other Caregivers**

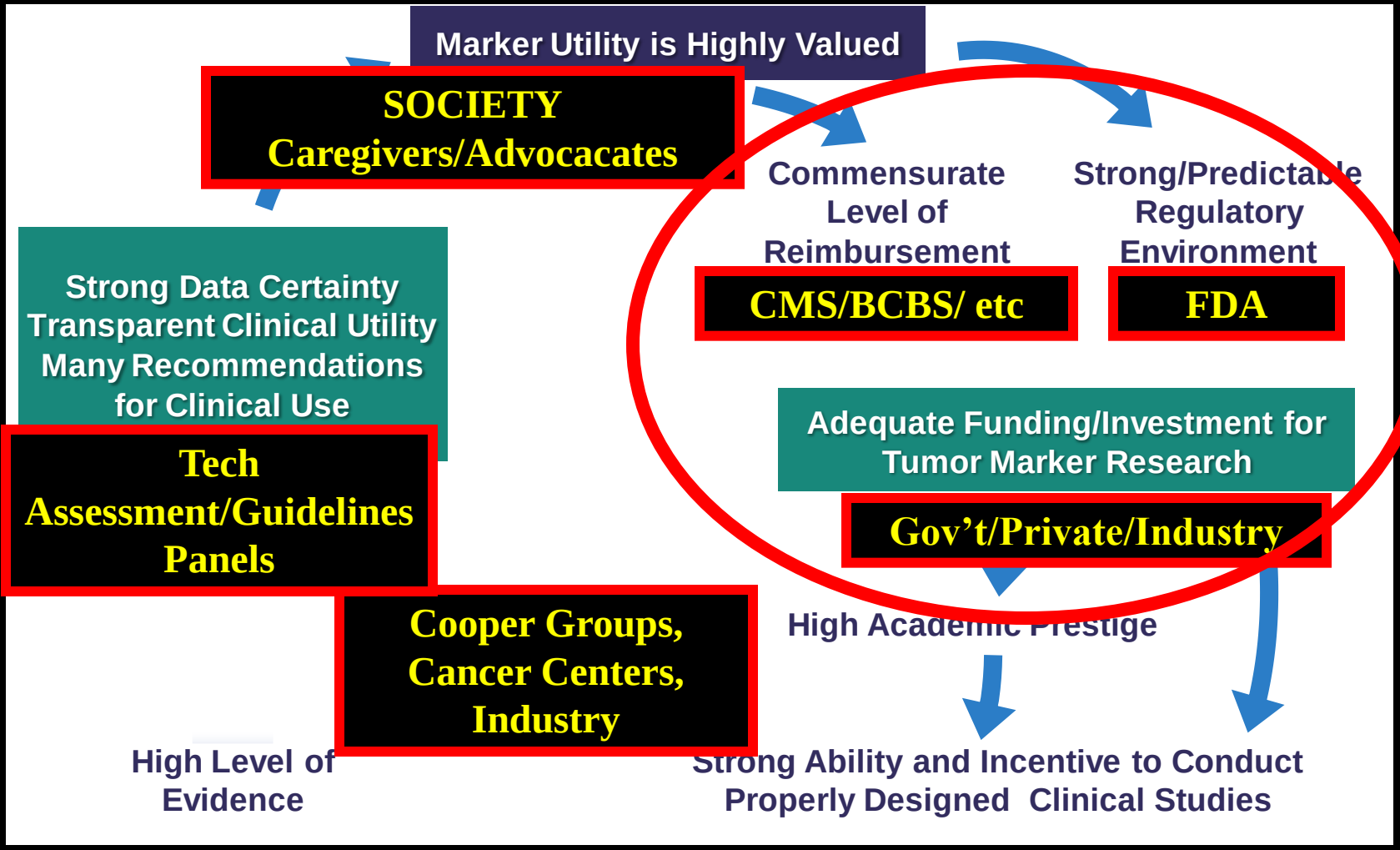
**Patients/Advocates**

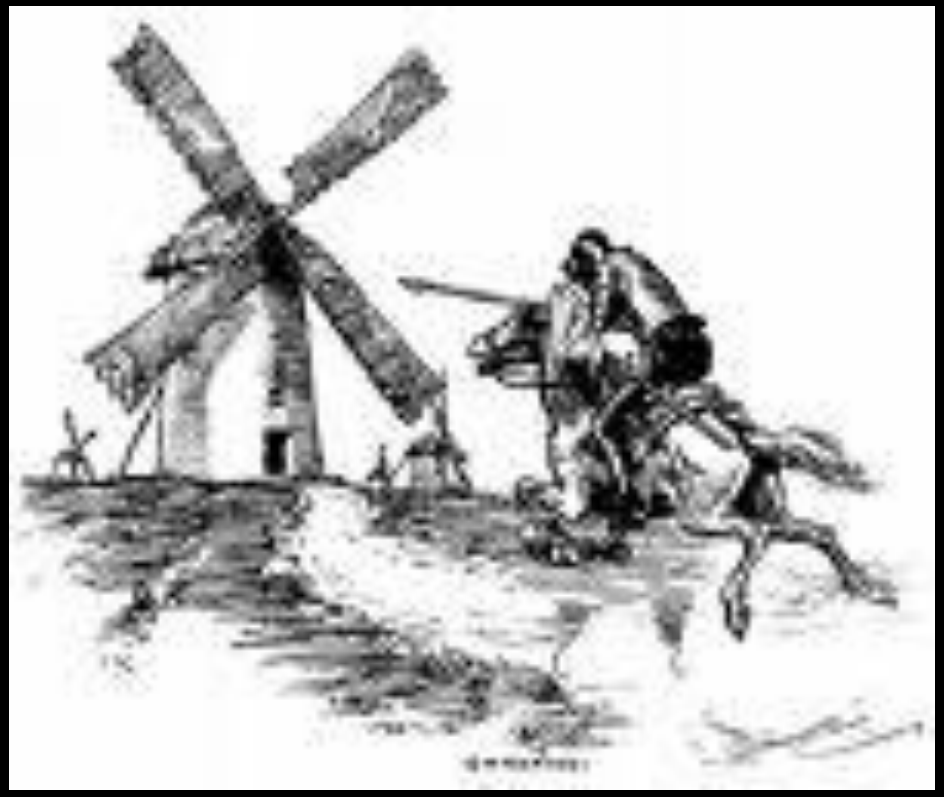
**Clinical Guidelines/Tech Assessment Panels (EGAPP, AHRQ, ASCO, NCCN)**

**Academic Centers/Investigators**

**Research Funding Entities (Gov't, Private)**

# *Highly Valued Tumor BioMarkers: A Virtuous Cycle*





# *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 |

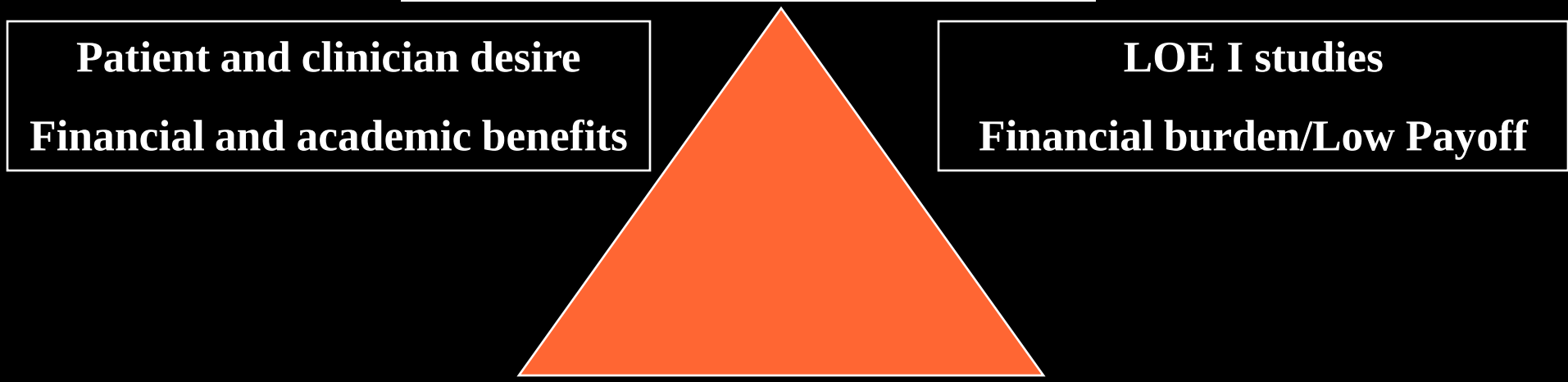
**Many Guidelines Panels (ASCO, NCCN) ignore whether test has FDA Approval or NOT:**

- ***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**

**Validated Clinical Utility**



**Patient and clinician desire**

**Financial and academic benefits**

**LOE I studies**

**Financial burden/Low Payoff**

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# *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**

***Harris L., et al. J Clin Oncol. 2007***

# *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**

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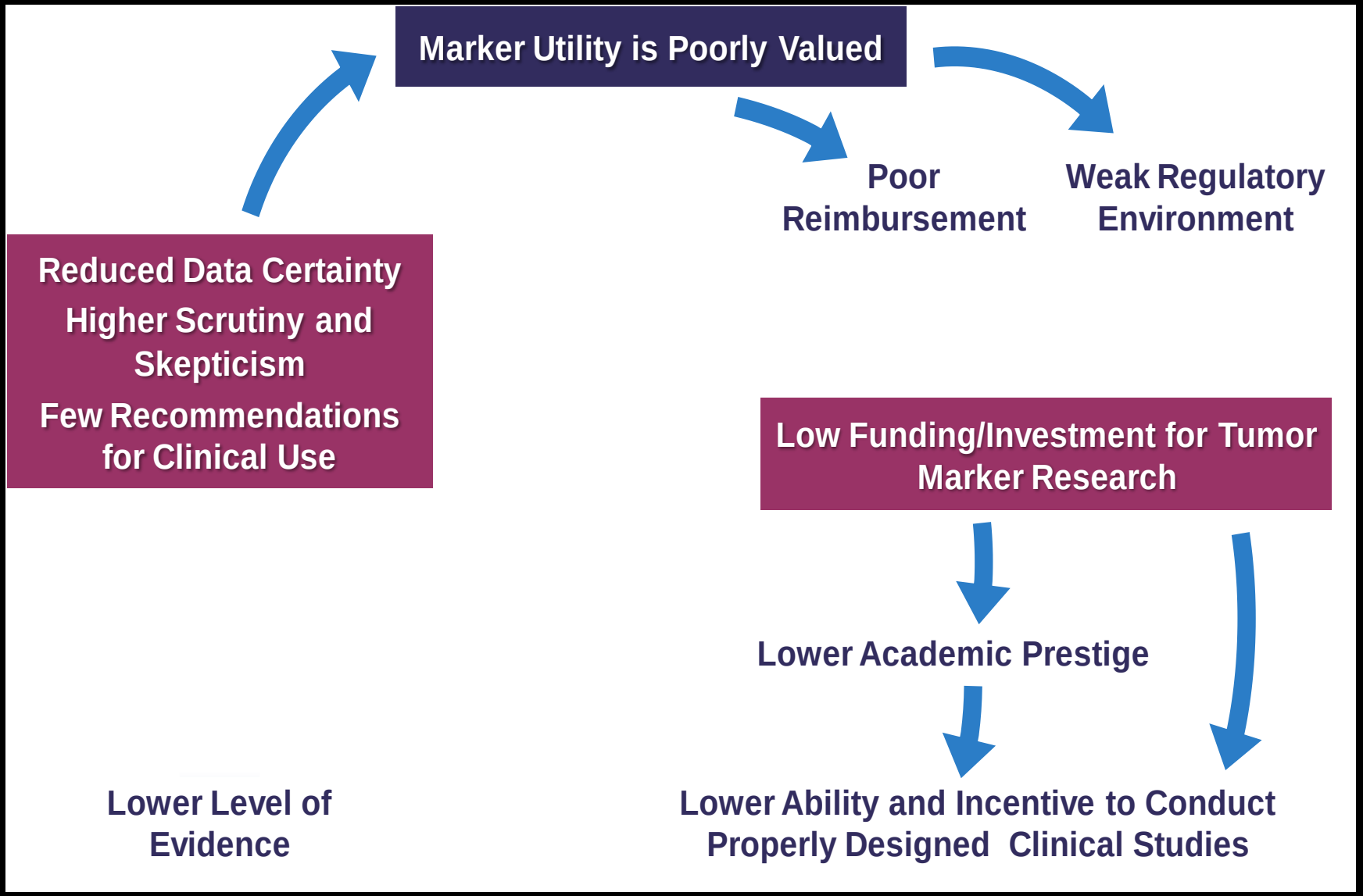

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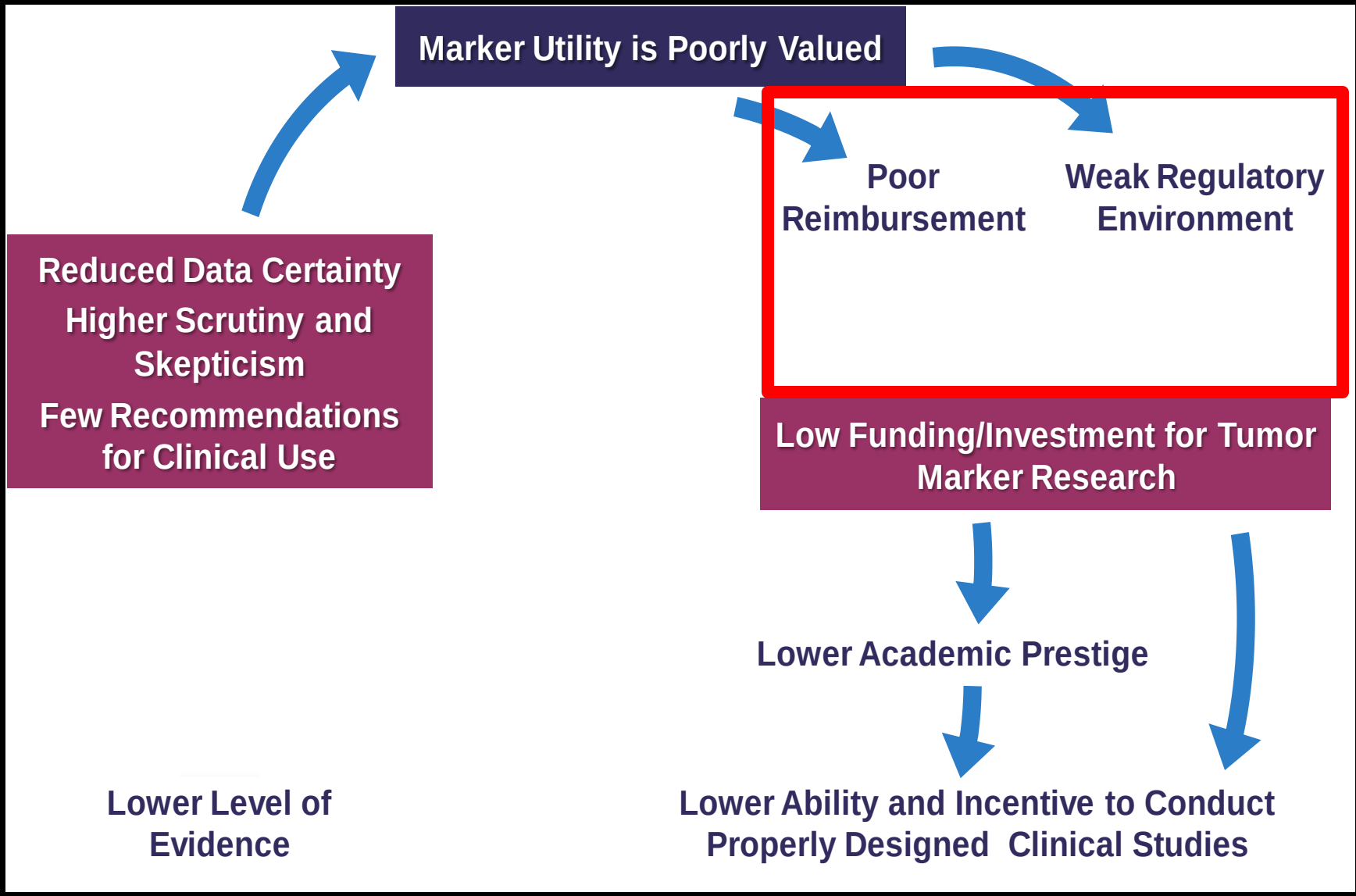

# *Incorporation of Tumor Marker Into Clinical Care*

- **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?**

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# *TMUGS: Levels of Evidence*

| Level | Definition |
|---|---|
| I | Prospective, Marker Primary Objective, Well-powered OR Meta-analysis |
| II | Prospective, Marker Secondary Objective |
| III | Retrospective, Outcomes, Multivariate Analysis |
| IV | Retrospective, Outcomes, Univariate |
| V | Retrospective, Correlation with Other Marker, No Outcomes |

*Hayes, et al; J Nat Cancer Institute 88:1456, 1996*

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**MOST TUMOR MARKER STUDIES**

*Hayes, et al; J Nat Cancer Institute 88:1456, 1996*

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# *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***

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# *Tumor Markers: Determination of Clinical Utility*

- **Strategies to "Test the Test" and Generate LOE I data:**
  - ***Prospective Clinical Trials: Marker is Primary Objective!***
    - *Sargent D.J., et al. J Clin Oncol. 23:2020-7, 2005*
    - *Freidlin B., et al. J Natl Cancer Inst. 102:152-60,* 2010
- **At present, very few such trials are ongoing in N.A.**
  - ***For example, in breast cancer, there are 3:***

| Trial | Disease | Test | Num pts | Status |
|---|---|---|---|---|
| TailorRx | Adj Breast | 21-gene RS | ~6500 | Fully accrued |
| S0500 | Met Breast | CellSearch | ~120 | Ongoing |
| S1007 | Adj Breast | 21-gene RS | ~4000 | In development |

# *Tumor Markers: Determination of Clinical Utility*

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    - *Sargent D.J., et al. J Clin Oncol. 23:2020-7, 2005*
    - *Freidlin B., et al. J Natl Cancer Inst. 102:152-60,* 2010
  - ***Is a Prospective Trial Always Necessary For Marker Utility?***
    - ***NO!*** ***But use of archived tissue must be done with rigor***
      - ***Simon R.M., Paik S, Hayes DF. JNCI 101:1446-52, 2009***

# *Use of Archived Tissues To Determine Clinical Utility of Tumor Markers*

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

*Simon R.M., Paik S, Hayes DF. J Natl Cancer Inst. 101:1446-52, 2009*

# *Revised LOI Scale: Use of Archived Tissues*

| Level of Evidence | Category from Table 1 | Validation Studies Available |
|---|---|---|
| I | A | None required |
| I | B | One or more with consistent results |
| II | B | None<br>or<br>Inconsistent results |
| II | C | 2 or more with consistent results |
| III | C | None<br>or<br>1 with consistent results<br>or<br>Inconsistent results |
| IV-V | D | NA |

*Simon R.M., Paik S, Hayes DF. J Natl Cancer Inst. 101:1446-52, 2009*

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