IOM Genetics Workshop

Evidence Generation for Genomic Diagnostic Test Development

Health Care Provider Perspective

Daniel F. Hayes, M.D.

University of Michigan
Health System

Comprehensive Cancer Center

A Question of Values: Is it worth it

- **Patient care**
  - **Improved cancer outcomes, by focusing the "right therapy on the right patient"- increase chance of:**
    - **Cure**
    - **Survival**
    - **Palliation**
  - **Decrease exposure to toxicity of useless therapy**

Incorporation of Tumor Marker Into Clinical Care

- **What evidence is required from stakeholders?**
- **How is evidence currently being generated?**
- **Are there innovative ways to generate higher quality evidence more efficiently?**
- **What are the barriers to generating this evidence and how can they be overcome?**

Incorporation of Tumor Marker Into Clinical Care

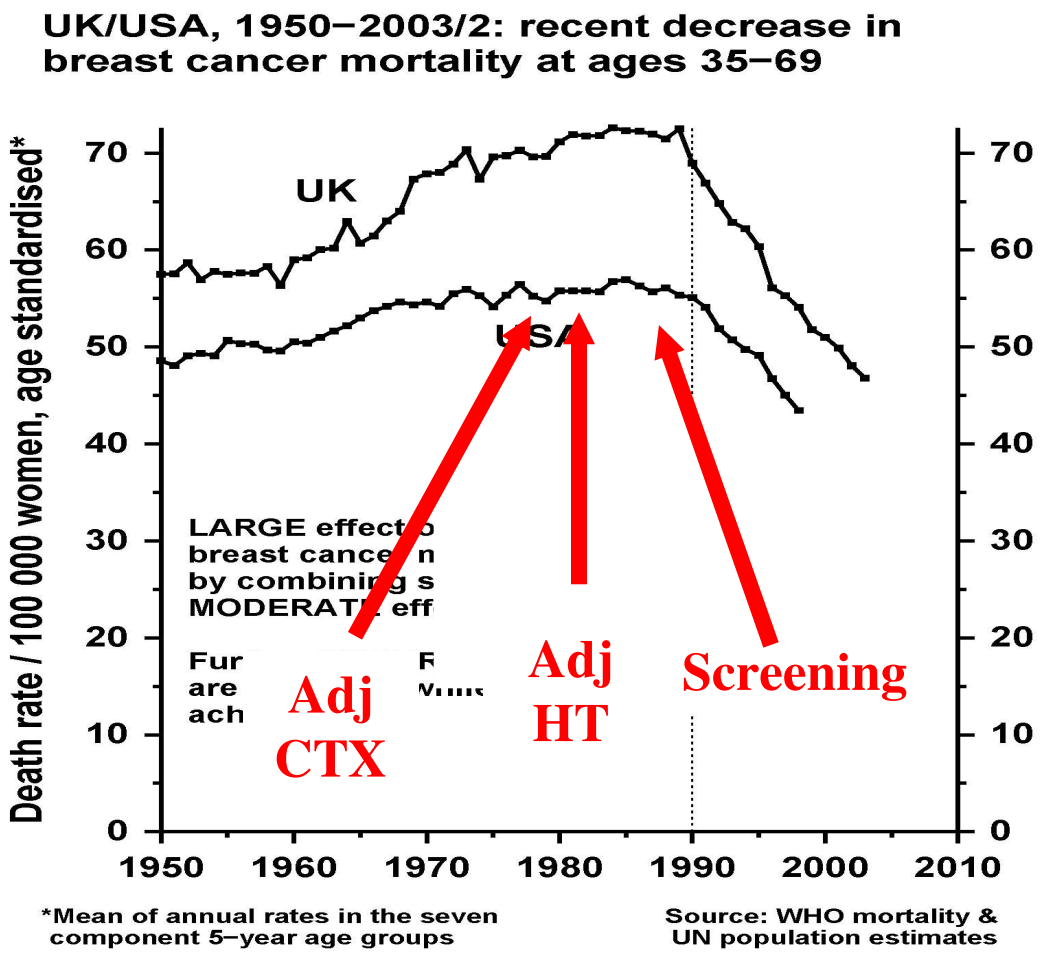
- **What evidence is required from stakeholders?**
- **How is evidence currently being generated?**
- **Are there innovative ways to generate higher quality evidence more efficiently?**
- **What are the barriers to generating this evidence and how can they be overcome?**

Definitions:
Semantics Regarding Evidence for Tumor Markers

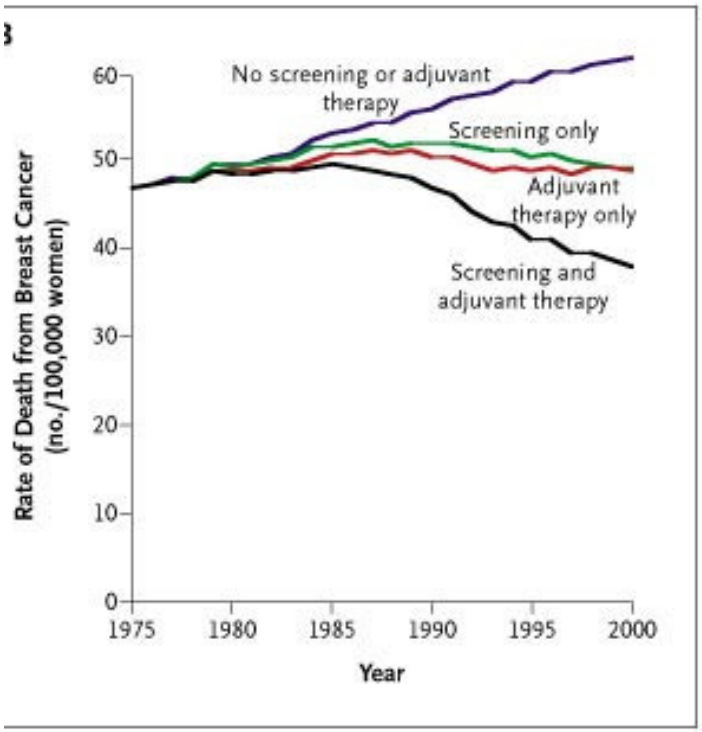
- **Analytical Utility**
  - **Does the assay accurately and reproducibly measure what you say?**
- **Clinical Validity**
  - **Does the assay actually identify a biologic difference ("pos" vs. "neg") that may or may not be clinically useful?**
- **Clinical Utility**
  - **Do results of the assay lead 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

Recent decrease in UK and USA breast cancer mortality at ages 35-69 years



Modified from Peto et al. Lancet 355:1822, 2000



Berry D.A., et al. N Engl J Med. 353:1784-92, 2005

Adjuvant Systemic Therapy

- **Should All Patients Receive All Therapy?**
  - **If pt is willing to accept ANY toxicity for ANY benefit: *then treat her with everything***
  - **If pt is willing to forego SOME benefit to avoid SOME toxicity, OR**
  - **If patient and society are willing to forego SOME benefit to avoid cost: *then select therapy carefully***
- **Depends on:**
  - **Well -defined subgroups that do or do not benefit from therapy**
  - **Patient's, Doctor's, and Society's Perspectives Regarding Risks, Benefits, and Costs of Therapy**

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**
- **Oncotype DX** — **Avoid Chemo if ER+/Node neg**

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

ASCO Tumor Marker Guidelines

- **Why Are the Guidelines So Conservative?**
  - **Recommended only those markers for which results would change clinical decisions**
  - **Evidence-based**
  - **Lack of Level of Evidence I or II studies:**
    - ***A Tumor Marker Utility Grading Scale***

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

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

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

MOST TUMOR MARKER STUDIES

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

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

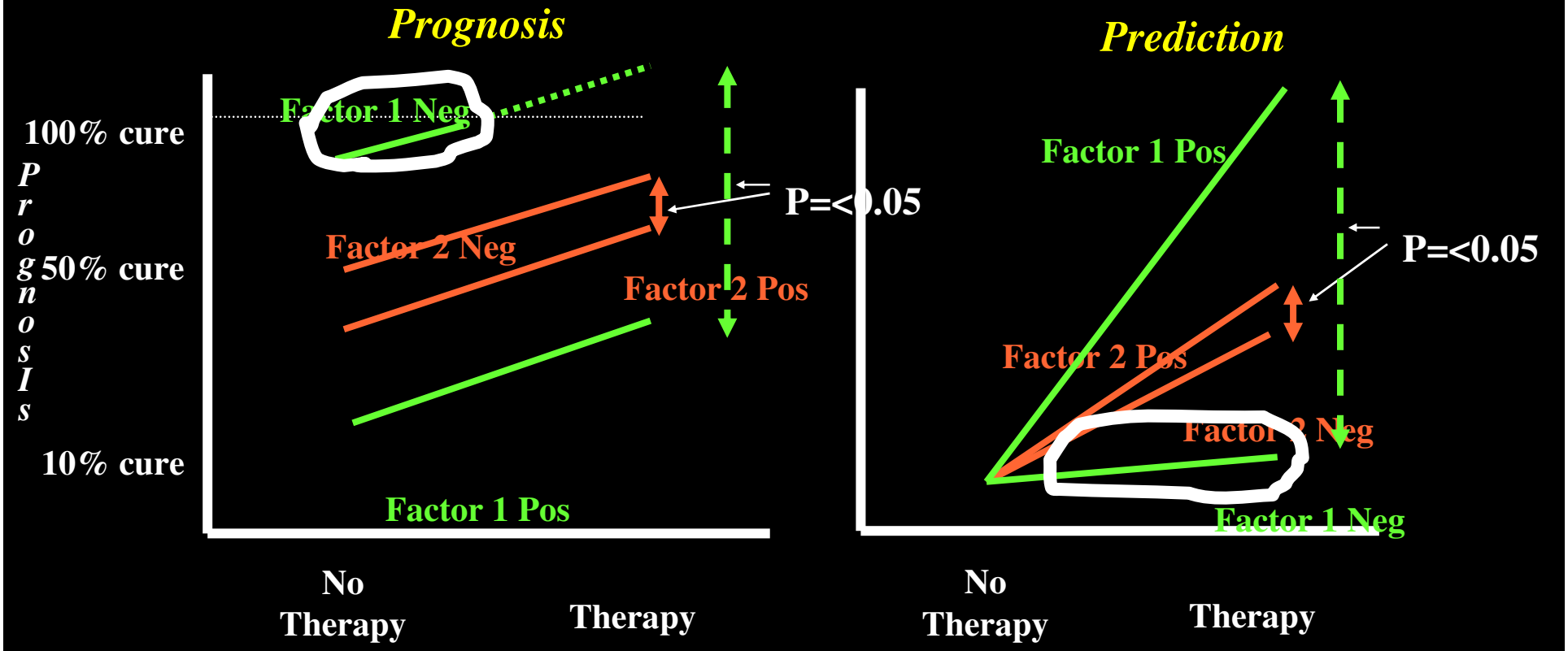
When is a Diagnostic Clinically Useful?

- **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

Value of Cancer Diagnostics:

*Identify Those Patients for Whom Benefits **Do NOT** Outweigh Risks, and Therefore We Can Safely Recommend Withholding that Treatment*

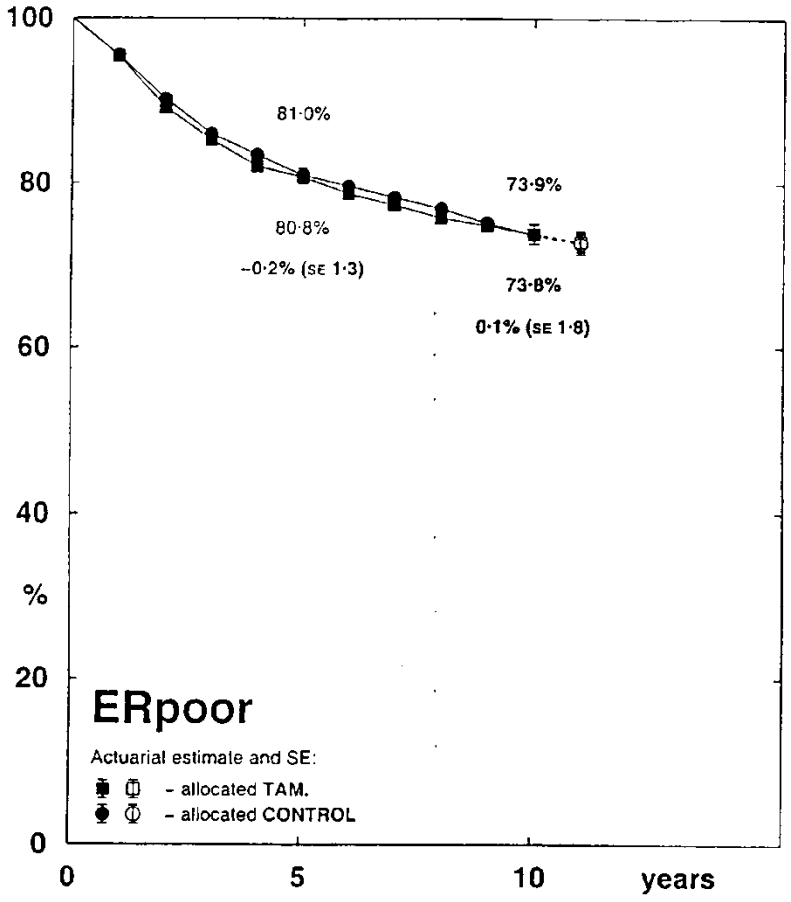


Cancer Diagnostics: Why Use Them?

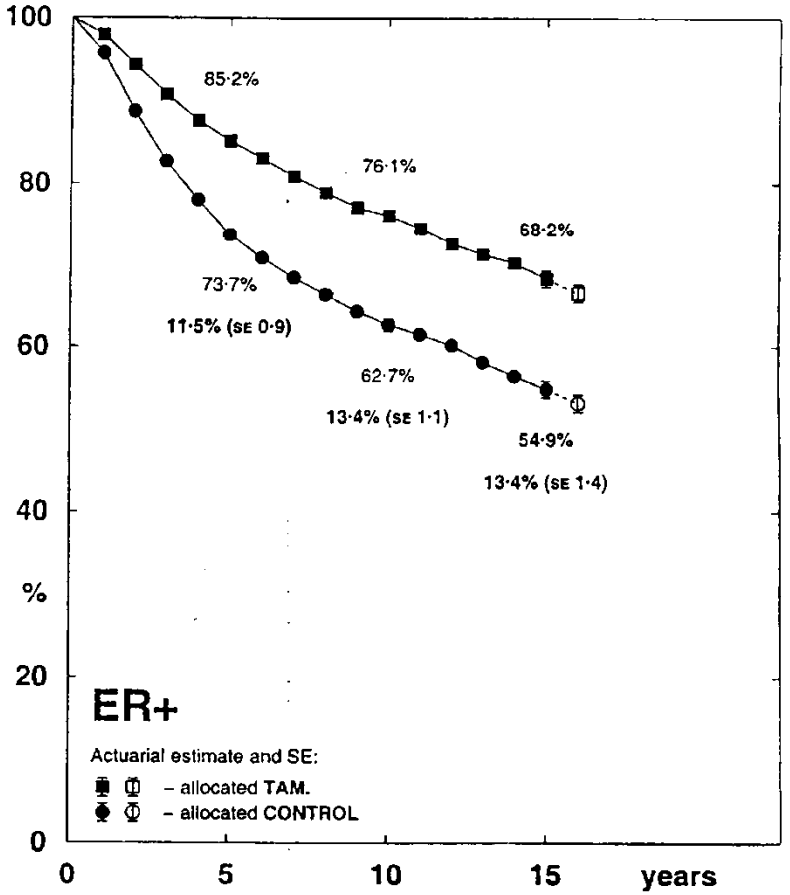
- **Identify patients who would FOREGO or DISCONTINUE therapy to AVOID toxicities.**
  - **All are exposed to cost and toxicity**
    - **Some but not all "positive" patients will benefit**
    - **Few if any "negative" patients will benefit**

Tamoxifen vs. Not
RECURRENCES
Effect of ER

POOR



POSITIVE



Early Breast Cancer Trialists' Collaborative Group. Lancet. 365:1687-717, 2005

Incorporation of Tumor Marker Into Clinical Care

- What evidence is required from stakeholders?
- **How is evidence currently being generated?**
- Are there innovative ways to generate higher quality evidence more efficiently?
- What are the barriers to generating this evidence and how can they be overcome?

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 Status	Test	Num pts	
TailorRx accrued	Adj Breast	21-gene RS	~6500	Fully
S0500	Met Breast Ongoing	CellSearch	~120	

Incorporation of Tumor Marker Into Clinical Care

- **What evidence is required from stakeholders?**
- **How is evidence currently being generated?**
- **Are there innovative ways to generate higher quality evidence more efficiently?**
- **What are the barriers to generating this evidence and how can they be overcome?**

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
  - ***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. 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. 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. 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. No focused analysis plan for marker question developed prior to doing assays
Validation	Result unlikely to be play of chance Although preferred, validation not required	Result more likely to be play of chance that A, but less likely than C. Requires one or more validation studies	Result very likely to be play of chance. Requires subsequent validation studies	Result very likely to be play of chance. Requires subsequent validation

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

Use of Archived Tissues To Determine Clinical Utility of Tumor Markers

Category	A
Trial Design	Prospective
Clinical trial	PRCT designed to address tumor marker
Patients and patient data	Prospectively enrolled, treated, and followed in PRCT
Specimen collection, processing, and archival	Specimens collected, processed and assayed for specific marker in real time
Statistical Design and analysis	Study powered to address tumor marker question.
Validation	Result unlikely to be play of chance Although preferred, validation not required

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

Use of Archived Tissues To Determine Clinical Utility of Tumor Markers

Category	B
Trial Design	Prospective using archived samples
Clinical trial	Prospective trial not designed to address tumor marker, but design accommodates tumor marker utility. Accommodation of predictive marker requires PRCT
Patients and patient data	Prospectively enrolled, treated, and followed in clinical trial and, especially if a predictive utility is considered, a PRCT addressing the treatment of interest
Specimen collection, processing, and archival	Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion.
Statistical Design and analysis	Study powered to address therapeutic question; underpowered to address tumor marker question. Focused analysis plan for marker question developed prior to doing assays
Validation	Result more likely to be play of chance that A, but less likely than C. Requires one or more validation studies

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

Use of Archived Tissues To Determine Clinical Utility of Tumor Markers

Category	C
Trial Design	Prospective /observational
Clinical trial	Prospective observational registry, treatment and follow up not dictated
Patients and patient data	Prospectively enrolled in registry, but treatment and follow up standard of care
Specimen collection, processing, and archival	Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion.
Statistical Design and analysis	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
Validation	Result very likely to be play of chance. Requires subsequent validation studies

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

Use of Archived Tissues To Determine Clinical Utility of Tumor Markers

Category	D
Trial Design	Retrospective/observational
Clinical trial	No prospective aspect to study
Patients and patient data	No prospective stipulation of treatment or follow up; patient data collected by retrospective chart review
Specimen collection, processing, and archival	Specimens collected, processed and archived with no prospective SOPs
Statistical Design and analysis	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
Validation	Result very likely to be play of chance. 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 or Inconsistent results
II	C	2 or more with consistent results
III	C	None or 1 with consistent results or Inconsistent results
IV-V	D	NA

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

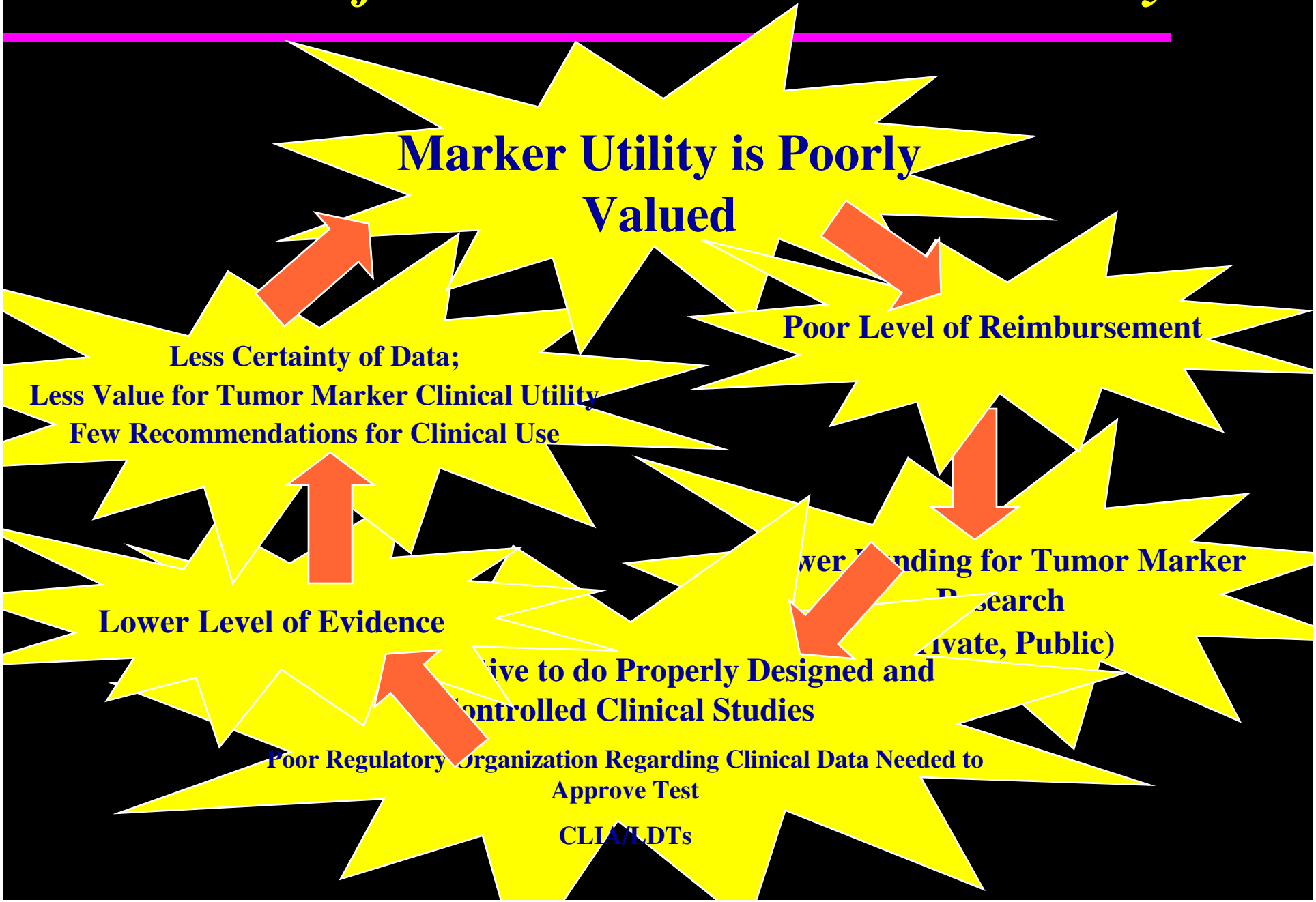
Incorporation of Tumor Marker Into Clinical Care

- **What evidence is required from stakeholders?**
- **How is evidence currently being generated?**
- **Are there innovative ways to generate higher quality evidence more efficiently?**
- **What are the barriers to generating this evidence and how can they be overcome?**

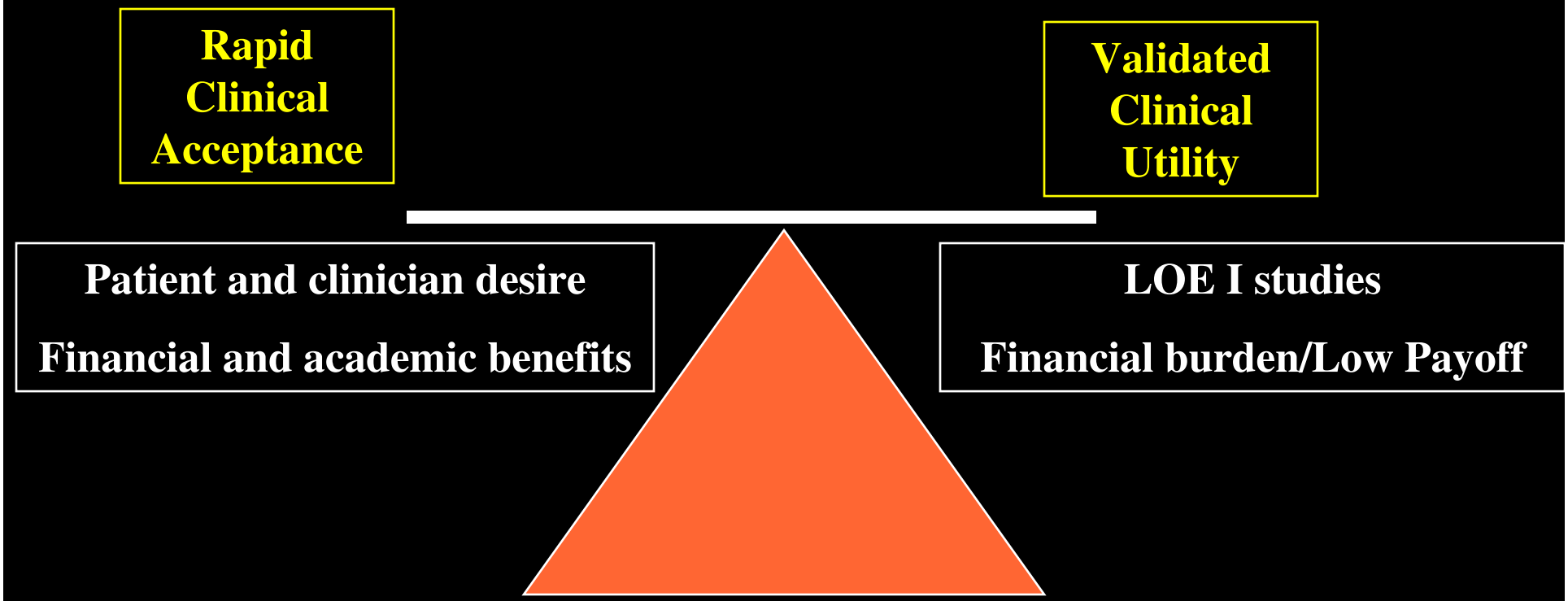
Undervalue of Tumor Markers: Multi-factoral

- **Tumor Marker Research is not perceived to be as exciting or important as new therapeutics, especially the clinical component**
  - **Less Academic credit**
    - **Breast Cancer Steering Committee Review of New Concept:**
      - **"of course, the secondary randomization to "new drug" is the exciting part"**
  - **Less Funding**
    - **Cancer Center Support Grants:**
      - **"lack of investigator initiated THERAPEUTIC Trials is significant weakness"**
  - **Less Rigor**
  - **Less evidence required for clinical use**
    - **FDA**
    - **Guidelines Panels**
  - **Less QC/QA/Proficiency testing (test dependent)**
  - **Less reimbursement**

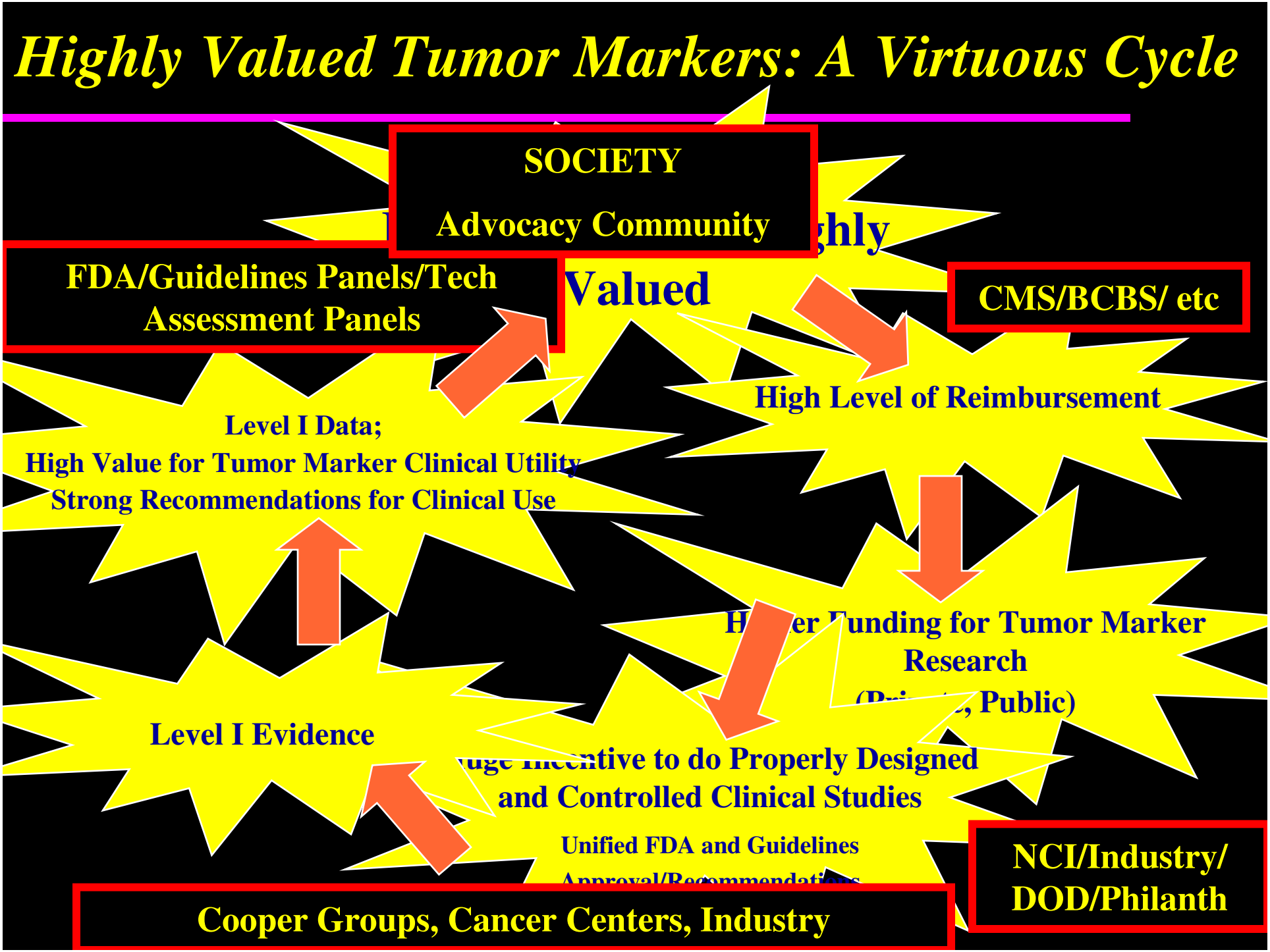
Undervalue of Tumor Markers: A Vicious Cycle



Acceptance of Tumor Markers: Balance of Carrots and Sticks



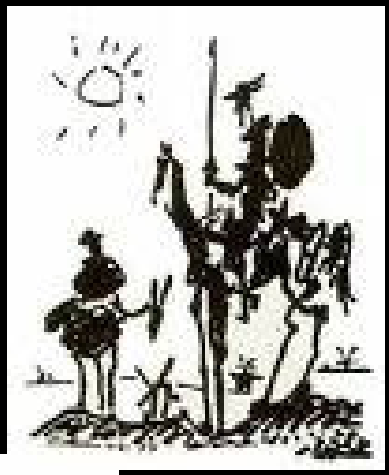
Highly Valued Tumor Markers: A Virtuous Cycle



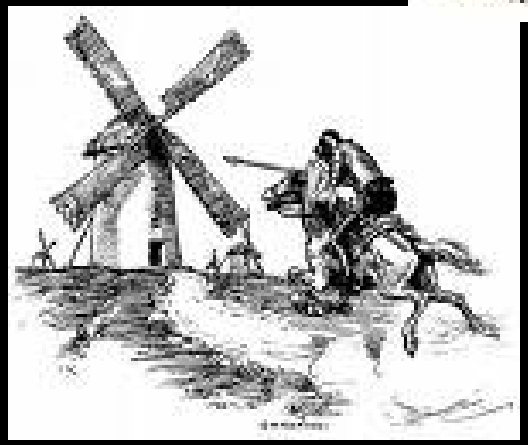
Increase Value of Tumor Markers: Proposals

- **Recom'ns for clinical tumor marker use be evidence-based for clinical utility**
- **Increase reimbursement for tumor markers IF clinical utility**
- **Increase funding for tumor marker research = to that for therapeutics.**
- **Reform regulatory review of tumor markers.**
  - **Organize "Oncologic Product Line" including ODAC and OIVD**
  - **FDA criteria should require analytical validity and clinical utility**
  - **Eliminate laboratory developed test discretion**
  - **Require new drug registration trials have biospecimen bank**
- **Enhance academic credit for tumor marker studies**
- **Increase rigor of tumor marker publications (several publications-REMARK, etc) = Therapeutic Trials**

Thanks to Many Colleagues



- ASCO TM Guidelines Committee
- Richard Schilsky; U. Chicago
- Doug Blayney; U. Michigan
- Steve Gutman; Formerly FDA, now U. Central Florida
- Finley Austin; Roche Diagnostics
- Craig Henderson; U.C.S.F.
- Richard Simon; NCI
- Steve Shak; GHI
- Gerry Doyle; Immunicon/Veridex



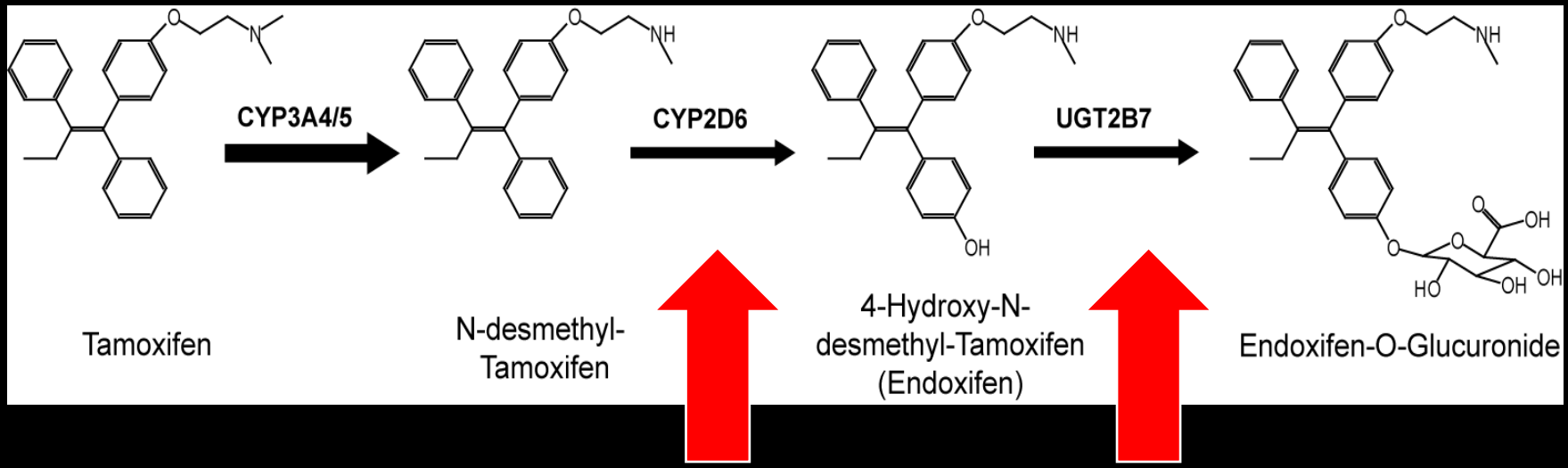
- Robert McCormack; Veridex
- Ted Lawrence, Gary Lyman, Cindy Stephens, Mark Somerfield; ASCO
- Jeff Allen; FOCR
- COBRA: David Flockhart, Vered Stearns, James Rae, others

Tamoxifen and 2D6: Case Study

- **Theoretical Background:**
  - **Tamoxifen may be a pro-drug**
  - **Parent is weak SERM**
  - **Tamoxifen is metabolized to two active moieties:**
    - **4-hydroxy tamoxifen**
    - **4-hydroxy N-desmethyl tamoxifen (Endoxifen)**

Tamoxifen is Activated and Inactivated by Polymorphic Enzymes

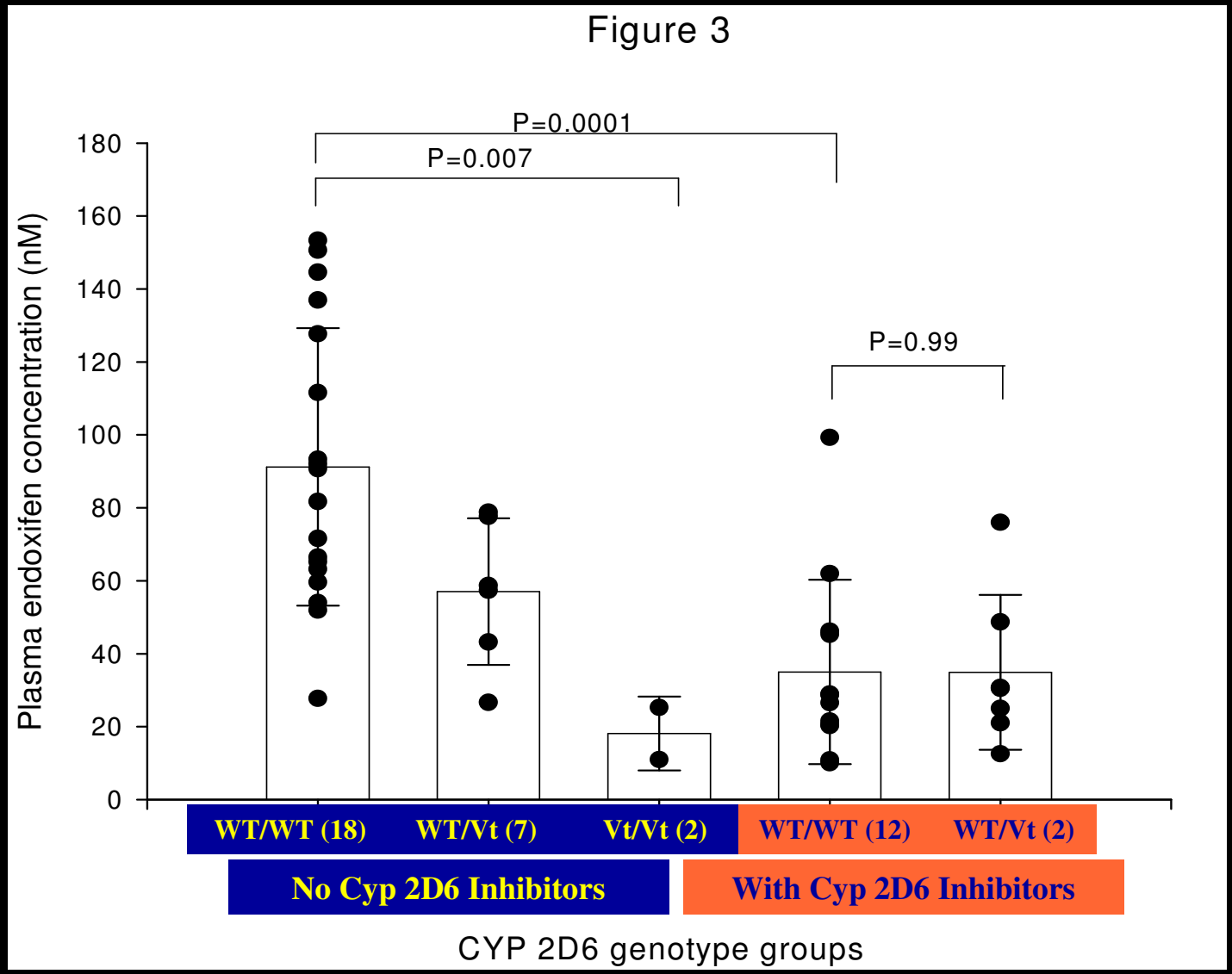
Weak anti-E2 **Weak anti-E2** **Potent anti-E2** **Inactive**



Known Genetic Variants

Rae, J.M.

CYP2D6 variant genotype and CYP2D6 inhibitors lower Endoxifen Concentrations

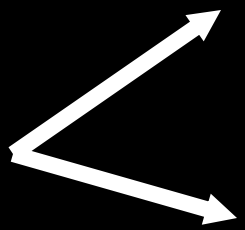


Jin et al; JNCI 97:30, '05

North Central Cancer Treatment Group Adjuvant Breast Cancer Trial

ER +

Newly diagnosed Breast cancer



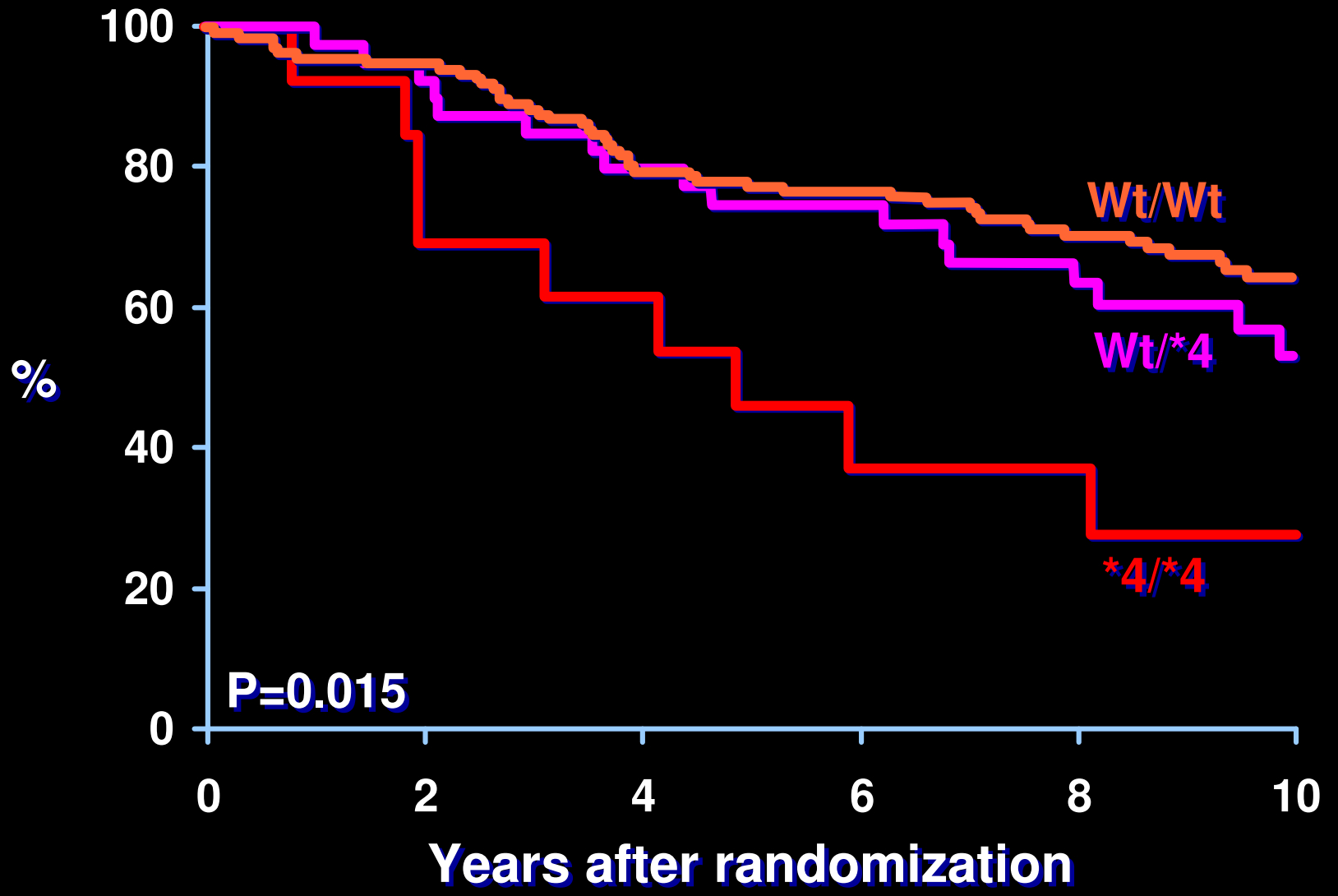
5 years tamoxifen

5 years tamoxifen + 1year fluoxymesterone

OVERALL: *no difference in DFS or OS for addition of fluoxymestrone to tamoxifen*

Ingle JN, et al. Cancer 67:886-891, 1991

*Disease-Free Survival (CYP2D6 *4)*



Goetz, MP, et al. J Clin Oncol. 23:9312, 2005

Category	A	B
Trial Design	Prospective	Prospective using archived samples
Clinical trial	PRCT designed to address tumor marker	Prospective trial not designed to address tumor marker, but design accommodates tumor marker utility. Accommodation of predictive marker requires PRCT
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
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.
Statistical Design and analysis	Study powered to address tumor marker question.	Study powered to address therapeutic question; underpowered to address tumor marker question. Focused analysis plan for marker question developed prior to doing assays
Validation	Result unlikely to be play of chance Although preferred, validation not required	Result more likely to be play of chance that A, but less likely than C. Requires one or more validation studies

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 or Inconsistent results
II	C	2 or more with consistent results
III	C	None or 1 with consistent results or Inconsistent results
IV-V	D	NA

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

CYP2D6 pharmacogenomics: Discordant Results

Swedish study-postoperative radiotherapy vs. adjuvant chemo, w/ (n=112) or w/o (n=114) 40 mg tamoxifen for 2yrs

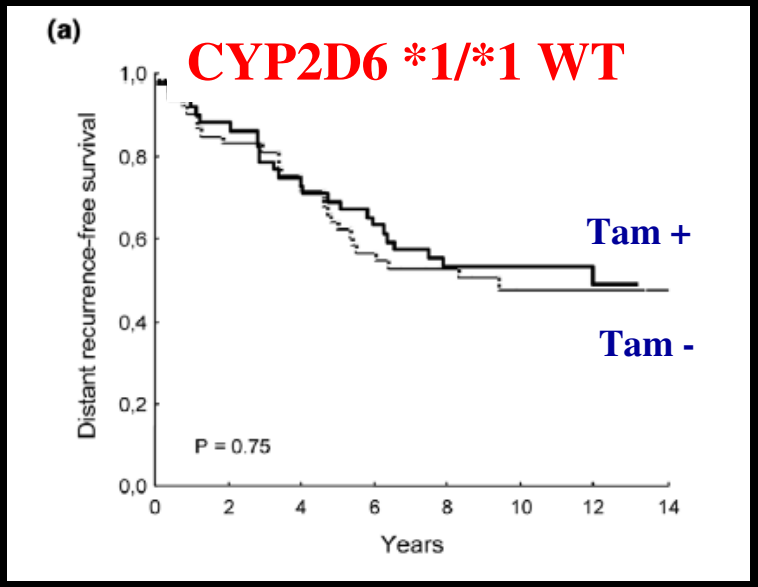
Available online http://breast-cancer-research.com/content/7/3/R284

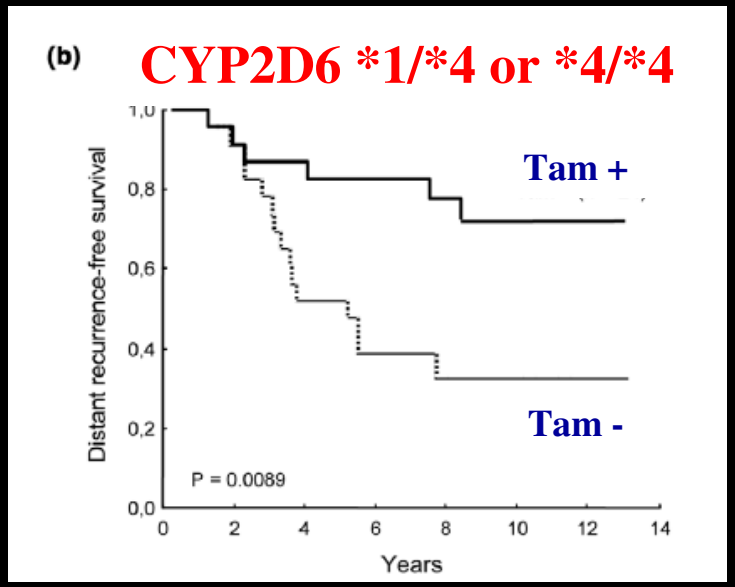
Research article

Open Access

Genotype of metabolic enzymes and the benefit of tamoxifen in postmenopausal breast cancer patients

Pia Wegman[1], Linda Vainikka[1], Olle Stål[2], Bo Nordenskjöld[2], Lambert Skoog[3], Lars-Erik Rutqvist[4] and Sten Wingren[1]





Just the opposite of expected!!

CYP2D6 and Tamoxifen

- ***Since original Goetz paper at least 15 separate studies suggesting that for women taking tamoxifen for prevention or treatment of breast cancer:***
  - **That CYP2D6 var/var OR inhibitors = WORSE outcome**
  - **That CYP2D6 has NOTHING to do with outcome**
  - **That CYP2D6 = BETTER outcome**

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 or Inconsistent results
II	C	2 or more with consistent results
III	C	None or 1 with consistent results or Inconsistent results
IV-V	D	NA

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

Tamoxifen PKG

- **Definitive Validation Studies and New Directions**
  - **Int Tam Pharm Coal** *(SABCS 2009: No interaction)*
  - **ATAC** SABCS 2010
  - **BIG98** SABCS 2010
  - **NSABP P1 and P2** SABCS 2010
  - **UK Prev'n tam vs plac** Completed
  - **Baylor (pop'n based)** SABCS 2010
  - **IES** Work in Progress
  - **E3108** Prosp trial/metastatic ER Pos
    - **Metabolism**
    - **Distribution**
    - **ER pathway/co-activators/repressors**

Total >9,000 patients

Tumor Marker eVALUation

- **What is the problem?**

  There appears to be an Inconsistent/Unclear path to clinical acceptance:

  - **FDA criteria for clearance/approval may not consider specific clnical utility-**
    - **FDA clearance does not mean an assay should be used clinically**
  - **Laboratory Developed Tests (LBT): Home Brew "rule"-**
    - **An assay can be marketed without FDA clearance**
  - **Disagreement about what outcomes need to be improved, and how to measure them-**
    - **There is a disconnect among Guidelines Panels and between them and FDA**
  - **Low reimbursement-**
    - **Entrepreneurs cannot afford to develop new markers if cost of doing so is substantially increased**

Increase Value of Tumor Markers: Proposals

- **Increase research $$ for clinical trials directed towards markers**
  - **Clinical trials in which marker is primary objective of study**
  - **Clinical trials in which marker is secondary endpoint**
    - **Co-development; *or at the least-***
    - **Collection and storage of specimens in association with PRCTs**
- **Consolidate all Oncology Regulatory activities within FDA**
  - **Create an "ODAC"-like committee for tumor markers**
- **Maintain CLIA as mediator of QA/QC; but eliminate "home brew" designation**
  - **All LDTs? Selected assays? New assays?**
- **Have FDA stipulate that no registry trial be accepted without prospective plan for specimen bank:**
  - **Prospective co-development plan; *or at the least-***
  - **Collection/storage**
  - **Transparent system to access specimens**
    - **Independent peer review**
    - **Adequate IP protection**
- **Increase rigor of tumor marker approval to meet all criteria needed for clinical adoption of a tumor marker**
  - **Several Publications**
- **Increase reimbursement commensurate with increased rigor in approval process (as for therapeutics)**
- **Fundamentally change method of care-giver reimbursement, so that doctors get paid for doing the right thing, and not for recommending their "gimmick"**