

National Cancer Policy Forum Workshop

Personalized Medicine: Reimbursement Hurdles

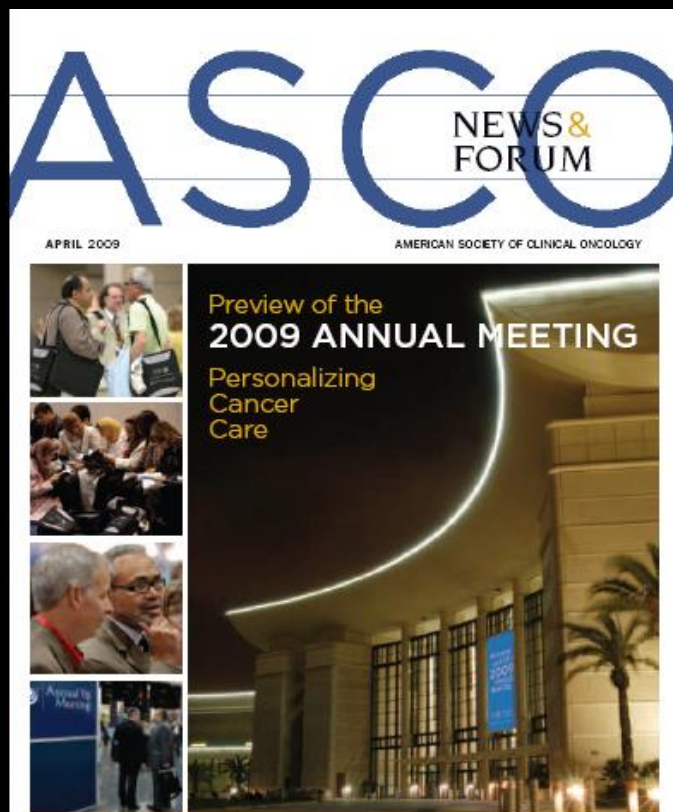
*My Perspective:
A Question of Values*

Daniel F. Hayes, M.D.



Disclosures

- λ **Dr. Hayes receives research funding from the following companies:**
 - λ **Astra-Zeneca**
 - λ **Novartis**
 - λ **Pfizer**
 - λ **Veridex**
- λ **Dr. Hayes and family have no PERSONAL disclosures**
 - λ **Honoraria**
 - λ **Stock, paid advisory boards, or other financial disclosures**



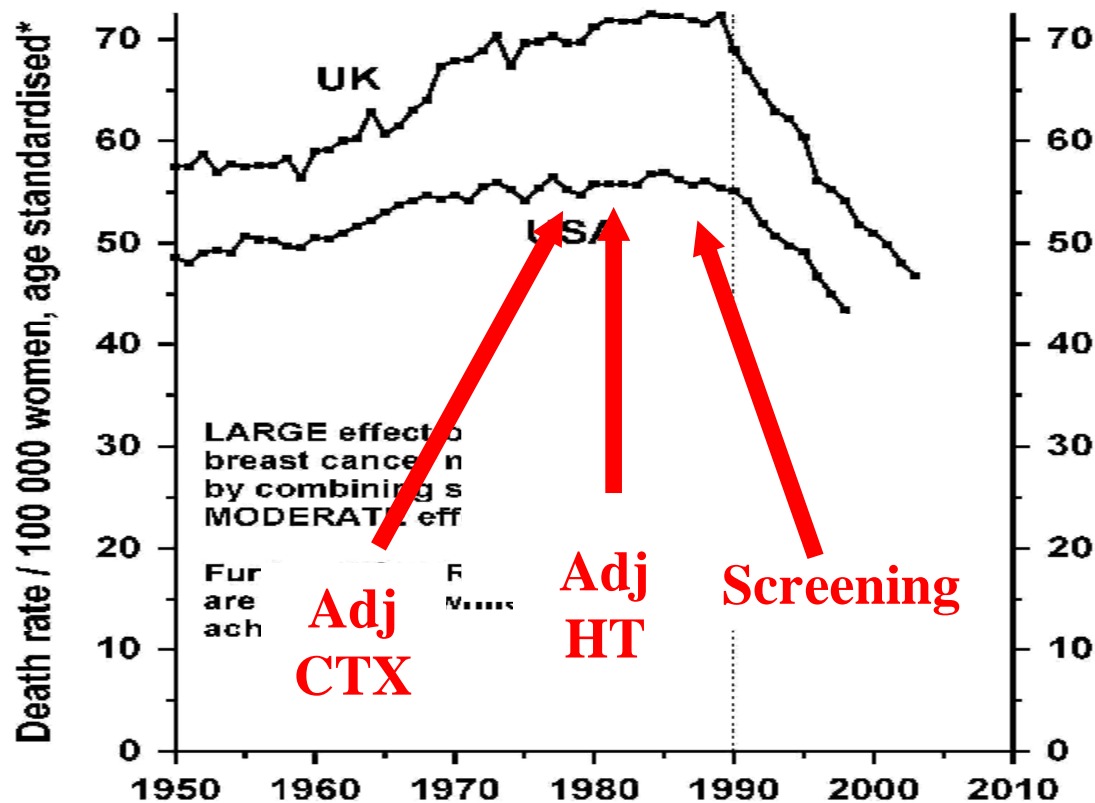
The theme of the 2009 Annual Meeting, chosen by **2008-2009 ASCO President Richard L. Schilsky, MD**, is:

“Personalizing Cancer Care.”

“Each patient with cancer is different—biologically, clinically, economically, and socially—and a one-size-fits-all approach to treating cancer is not optimal,” Dr. Schilsky said. “As oncologists, our focus has always been, and must remain, treating the patient, not the disease. We must each acquire the skills and make the commitment to do so in the optimal way.”

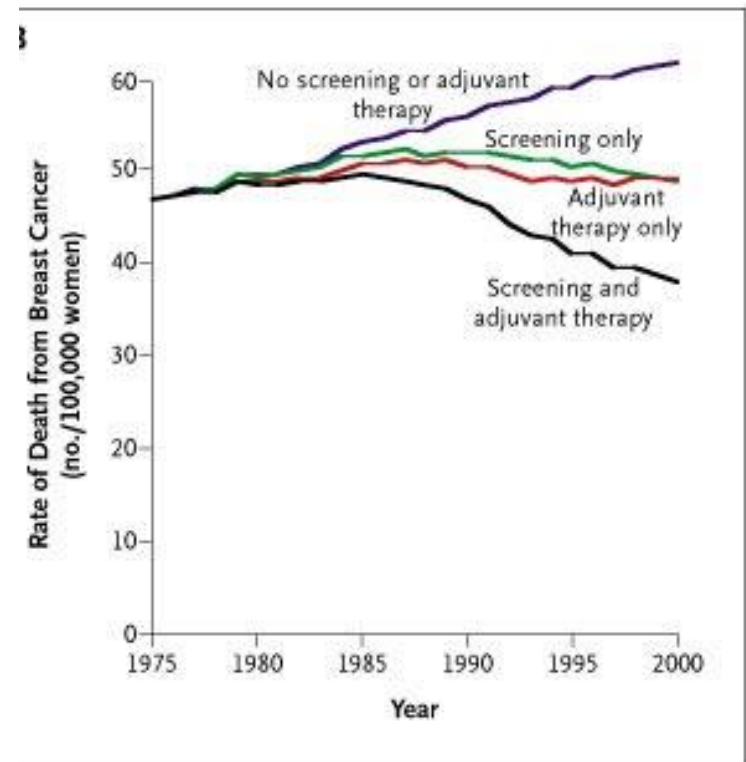
Recent decrease in UK and USA breast cancer mortality at ages 35-69 years

UK/USA, 1950-2003/2: recent decrease in breast cancer mortality at ages 35-69



*Mean of annual rates in the seven component 5-year age groups

Source: WHO mortality & UN population estimates



Adjuvant Systemic Therapy

λ Should All Patients Receive All Therapy?

λ If pt is willing to accept ANY toxicity for ANY benefit: *then treat her with everything*

λ If pt is willing to forego SOME benefit to avoid SOME toxicity, OR

λ If patient and society are willing to forego SOME benefit to avoid cost: *then select therapy carefully*

λ Depends on:

λ Well -defined subgroups that do or do not benefit from therapy

λ 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

- λ **ER, PgR** **Select Endocrine Therapy**
- λ **HER2** **Select Trastuzumab/Lapatinib**
- λ **UPA/PAI -1** **Avoid Chemo if ER+/Node neg**
- λ **Oncotype DX** **Avoid Chemo if ER+/Node neg**

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

ASCO Tumor Marker Guidelines

λ Why Are the Guidelines So Conservative?

λ Recommended only those markers for which results would change clinical decisions

λ Evidence-based

λ Lack of Level of Evidence I or II studies:

λ *A Tumor Marker Utility Grading Scale*

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

TMUGS: Levels of Evidence

<u>Level</u>	<u>Definition</u>
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

MOST TUMOR MARKER STUDIES

II Prospective, Marker Secondary Objective

III Retrospective, Outcomes, Multivariate Analysis

IV Retrospective, Outcomes, Univariate

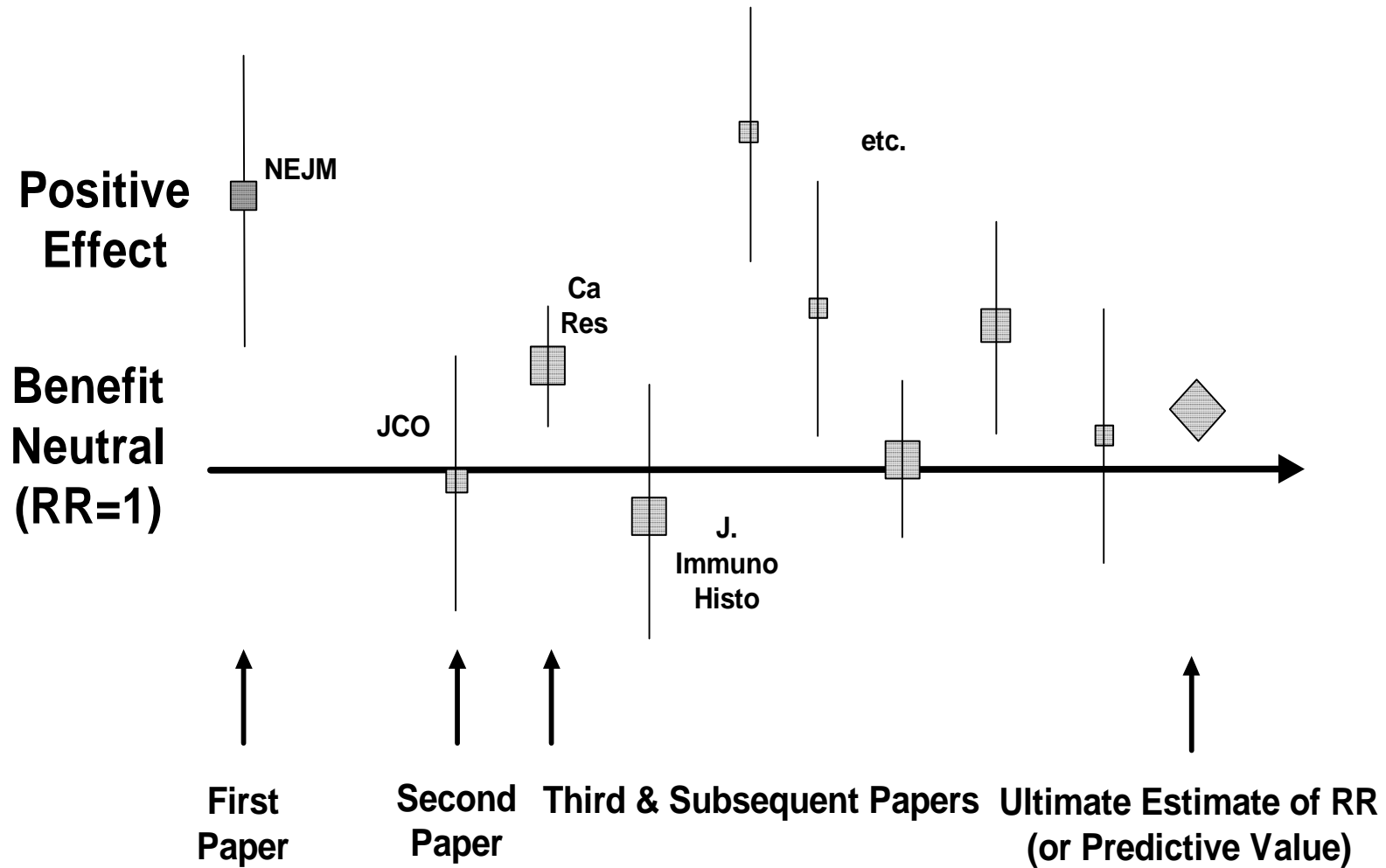
V Retrospective, Correlation with Other Marker, No Outcomes

TMUGS: Levels of Evidence

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

LIFE CYCLE OF A TUMOR MARKER



Tumor Markers

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

Undervalue of Tumor Markers: Multi-factoral

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

Undervalue of Tumor Markers: A Vicious Cycle

Marker Utility is Poorly Valued

Poor Level of Reimbursement

**Less Certainty of Data;
Less Value for Tumor Marker Clinical Utility
Few Recommendations for Clinical Use**

**Lower Funding for Tumor Marker Research
(Private, Public)**

Lower Level of Evidence

**Incentive to do Properly Designed and
Controlled Clinical Studies**

**Poor Regulatory Organization Regarding Clinical Data Needed to
Approve Test**

CLIA/Home Brew Rule

Tumor Marker eVALUation

λ What is the problem?

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

λ FDA criteria for clearance/approval may not consider specific clinical utility-

λ FDA clearance does not mean an assay should be used clinically

λ Home Brew rule-

λ An assay can be marketed without FDA clearance

λ Disagreement about what outcomes need to be improved, and how to measure them-

λ There is a disconnect among Guidelines Panels and between them and FDA

λ Low reimbursement-

λ Entrepreneurs cannot afford to develop new markers if cost of doing so is substantially increased

Values in Cancer Care: Comparison of Therapeutics vs. Diagnostics

λ **Therapeutics**

λ **Cost to Get Clinical Approval:**

\$500M-\$1B

λ **Payoff for Widely Used (“Blockbuster”) Drug:**

\$1B-\$2B/year

λ **Diagnostics**

λ **Current Cost to Get Clinical Approval:**

\$50M-\$200M

λ **Payoff for Approved and Useful Marker:**

\$20-\$50M/year

*If we increase the rigor required to introduce a new diagnostic to that required to introduce a new drug, current reimbursement systems will **smother** innovation*

A Question of Values: Is it worth it

λ Patient care

λ Dollars

A Question of Values: Is it worth it

λ Patient care

λ Improved cancer outcomes, by focusing the “right therapy on the right patient”-increase chance of:

λ Cure

λ Survival

λ Palliation

λ Decrease exposure to toxicity of useless therapy

Definitions

λ **Analytical Utility**

λ Does the assay accurately and reproducibly measure what you say?

λ **Clinical Validity**

λ Does the assay actually identify a biologic difference (“pos” vs. “neg”) that may or may not be clinically useful?

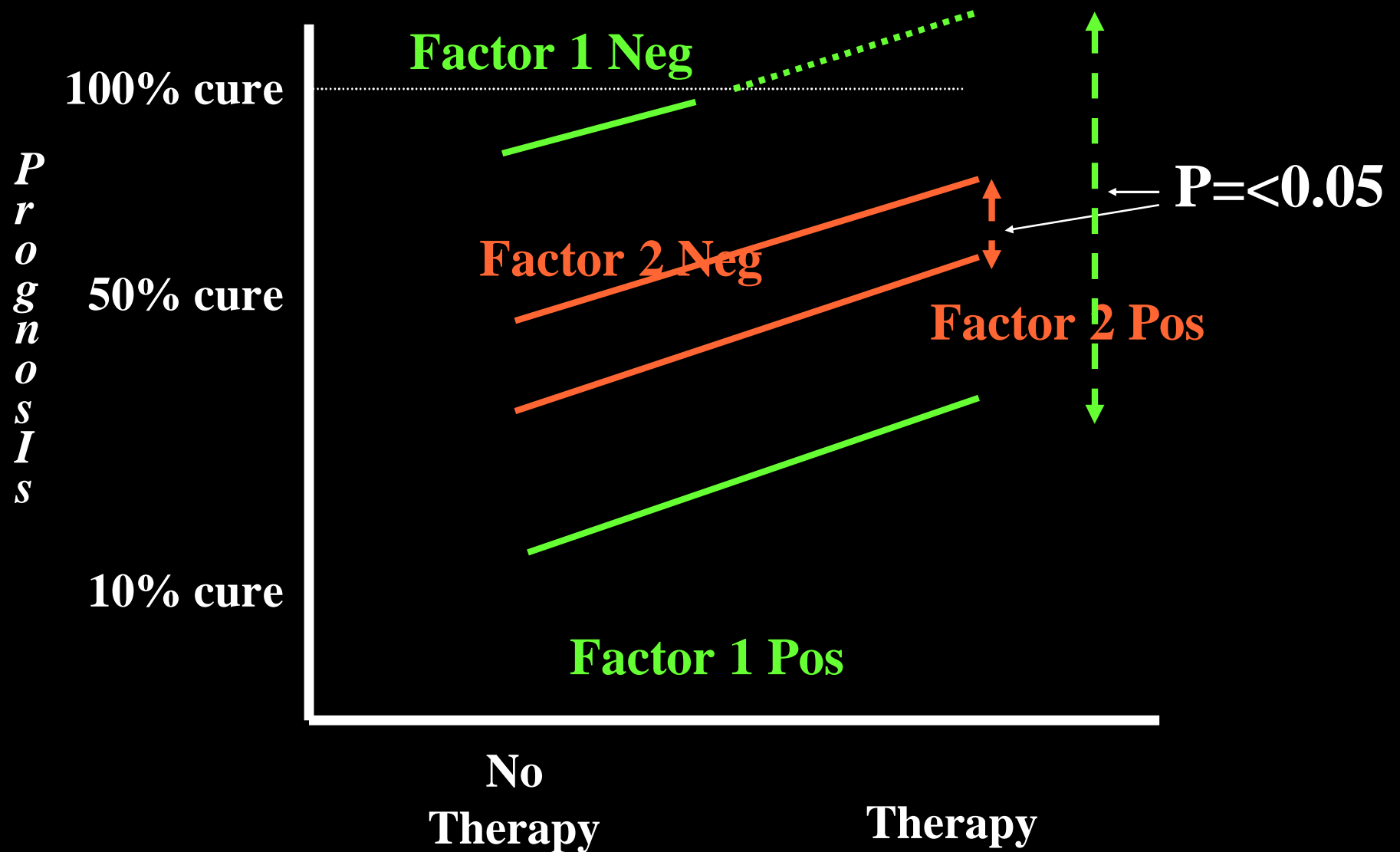
λ **Clinical Utility**

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

When is a Diagnostic Clinically Useful?

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

PURE PROGNOSTIC FACTOR (Unfavorable)



Oncotype DX 21 Gene Recurrence Score

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION

Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN

ER
PR
Bcl2
SCUBE2

$$\begin{aligned} \text{RS} = & + 0.47 \times \text{HER2 Group Score} \\ & - 0.34 \times \text{ER Group Score} \\ & + 1.04 \times \text{Proliferation Group Score} \\ & + 0.10 \times \text{Invasion Group Score} \\ & + 0.05 \times \text{CD68} \\ & - 0.08 \times \text{GSTM1} \\ & - 0.07 \times \text{BAG1} \end{aligned}$$

GSTM1

BAG1

INVASION

Stromolysin 3
Cathepsin L2

CD68

REFERENCE

Beta-actin
GAPDH
RPLPO
GUS
TFRC

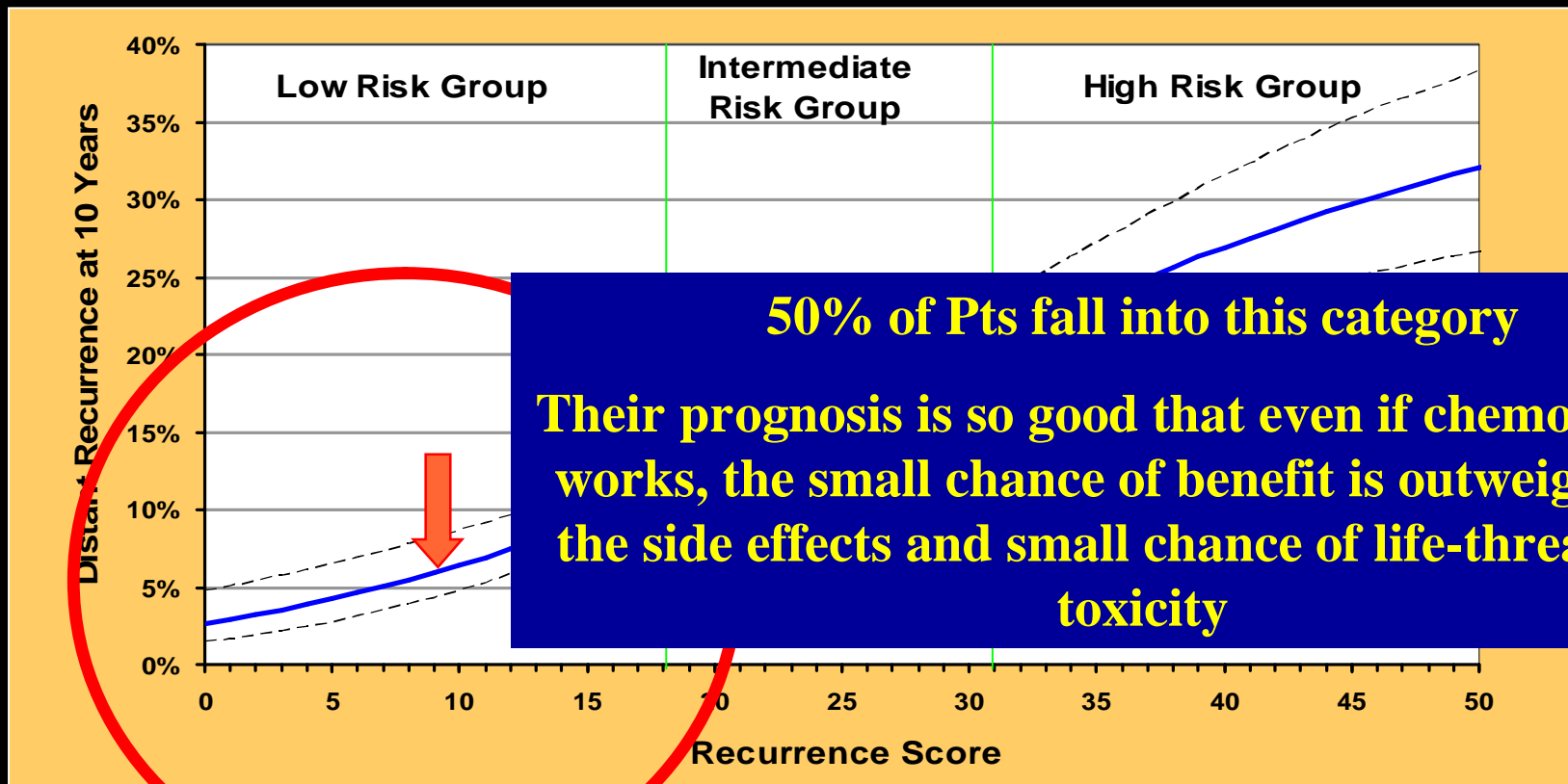
HER2
GRB7
HER2

Category	RS (0 – 100)
Low risk	RS < 18
Int risk	RS ≥ 18 and < 31
High risk	RS ≥ 31

Paik et al, NEJM 35:2817, '04

21 Gene Recurrence Score Predicts Very Favorable Prognosis

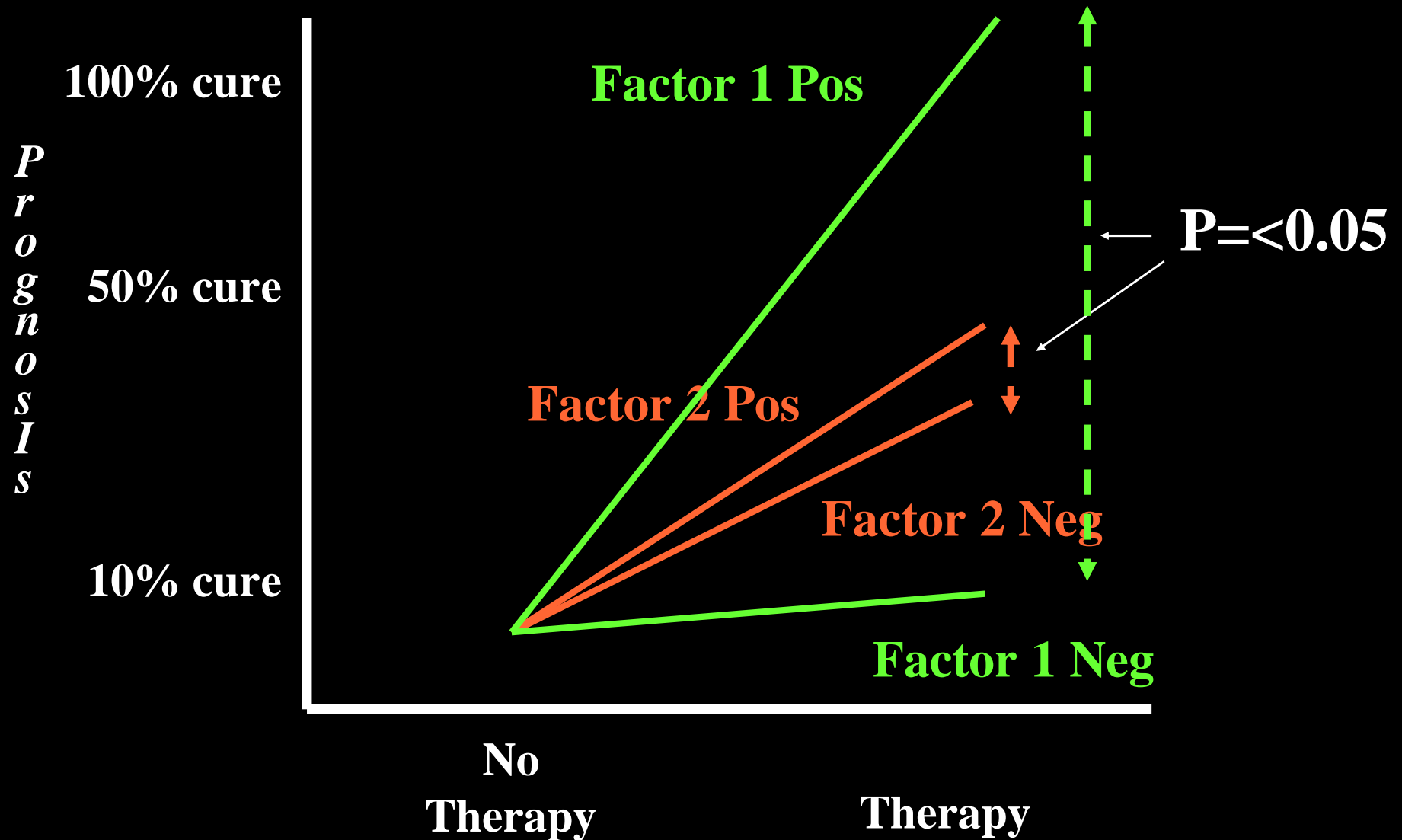
Node Negative, ER Positive Breast Cancer Patients Treated with Hormone Therapy Alone



Paik et al, NEJM 35:2817, '04

PURE PREDICTIVE FACTOR

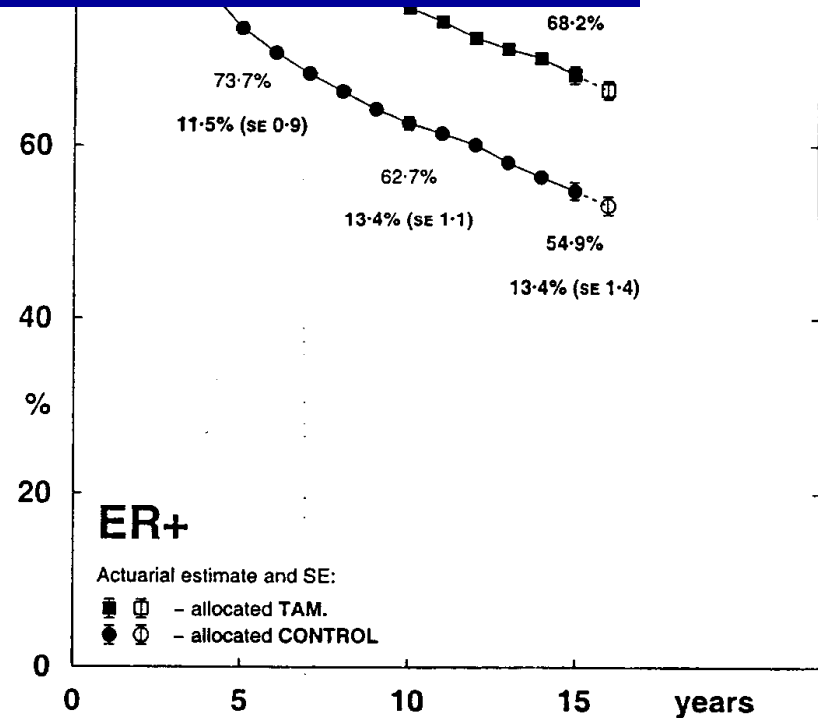
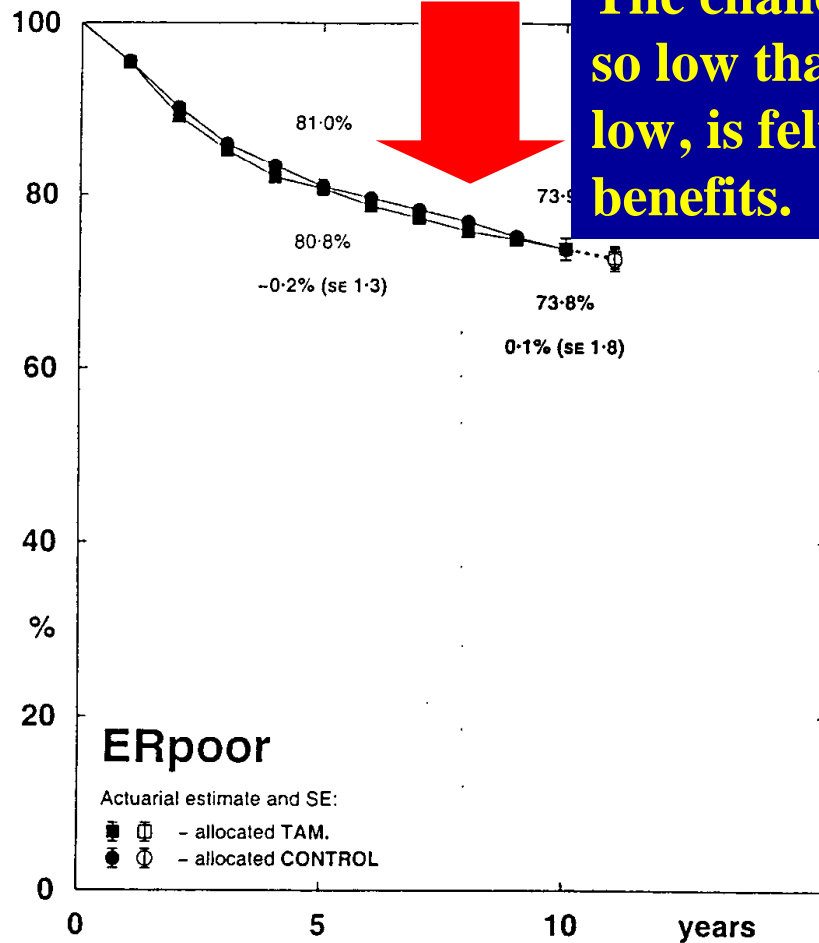
(For Sensitivity to Therapy)



Tamoxifen vs. Not RECURRENCES Effect of ER

NEGATIVE

40% of Pts fall into this category
The chances of benefit from tamoxifen are so low that its potential toxicity, although low, is felt to outweigh its potential benefits.



Cancer Diagnostics: Why Use Them?

λ **Identify patients who would FOREGO or DISCONTINUE therapy to AVOID toxicities.**

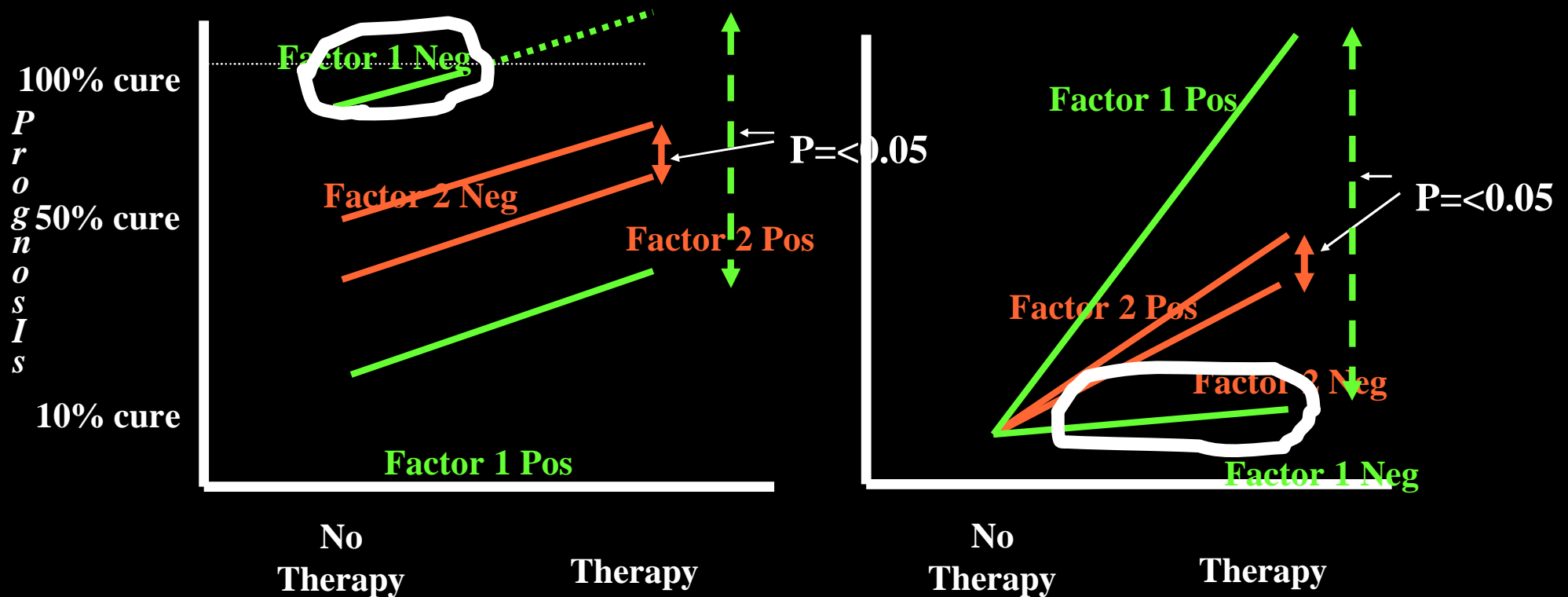
λ **All are exposed to cost and toxicity**

λ **Some but not all “positive” patients will benefit**

λ **Few if any “negative” patients will benefit**

Value of Cancer Diagnostics:

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



A Question of Values: Is it worth it

λ **Dollars**

λ **Example:**

λ **Breast Cancer Adjuvant Therapy**

Value of Cancer Diagnostics: Adjuvant Breast Cancer

- λ **Approximately 90,000 American women received adjuvant chemotherapy using guidelines from 2005**
 - λ Node Neg: 60,000 (about 2/3 of all diagnosed)
 - λ Node Pos: 30,000 (~100% of those diagnosed)
- λ **Approximately 60% of these women are ER Positive = 54,000**
 - λ Node Neg = 36,000
 - λ Node Pos = 18,000
- λ **21 gene LOW Recurrence Score (OncotypeDX™) identifies NODE NEGATIVE, ER POSITIVE patients for whom Chemotherapy unlikely to be of benefit: ~ 25,000**
 - λ ~50% of node neg (=18,000) Paik S., et al. *N Engl J Med.* 351:2817-26, 2004
 - λ ~ 35% of node pos (=7,000) Albain K., et al. *Breast Cancer Research and Treatment.* 106 (suppl 1) 2007
- λ **Standard course of adjuvant chemotherapy at University of Michigan ~ \$50k**
 - λ X 90,000 ~\$3 Billion/year nationwide
 - λ ~25,000 have LOW recurrence score = Save \$1.25 Billion dollars annually if do not RX
- λ **21 gene Recurrence Score ~ \$3500/test**
 - λ Profile 54,000 women annually ~\$189 Million
- λ **Net Savings:**
 - λ Save \$1.25B – at the cost of \$189M= **Net Savings of \$1.06B/Year**

Acceptance of Tumor Markers: Balance of Carrots and Sticks

**Rapid
Clinical
Acceptance**

**Validated
Clinical
Utility**

**Patient and clinician desire
Financial and academic benefits**

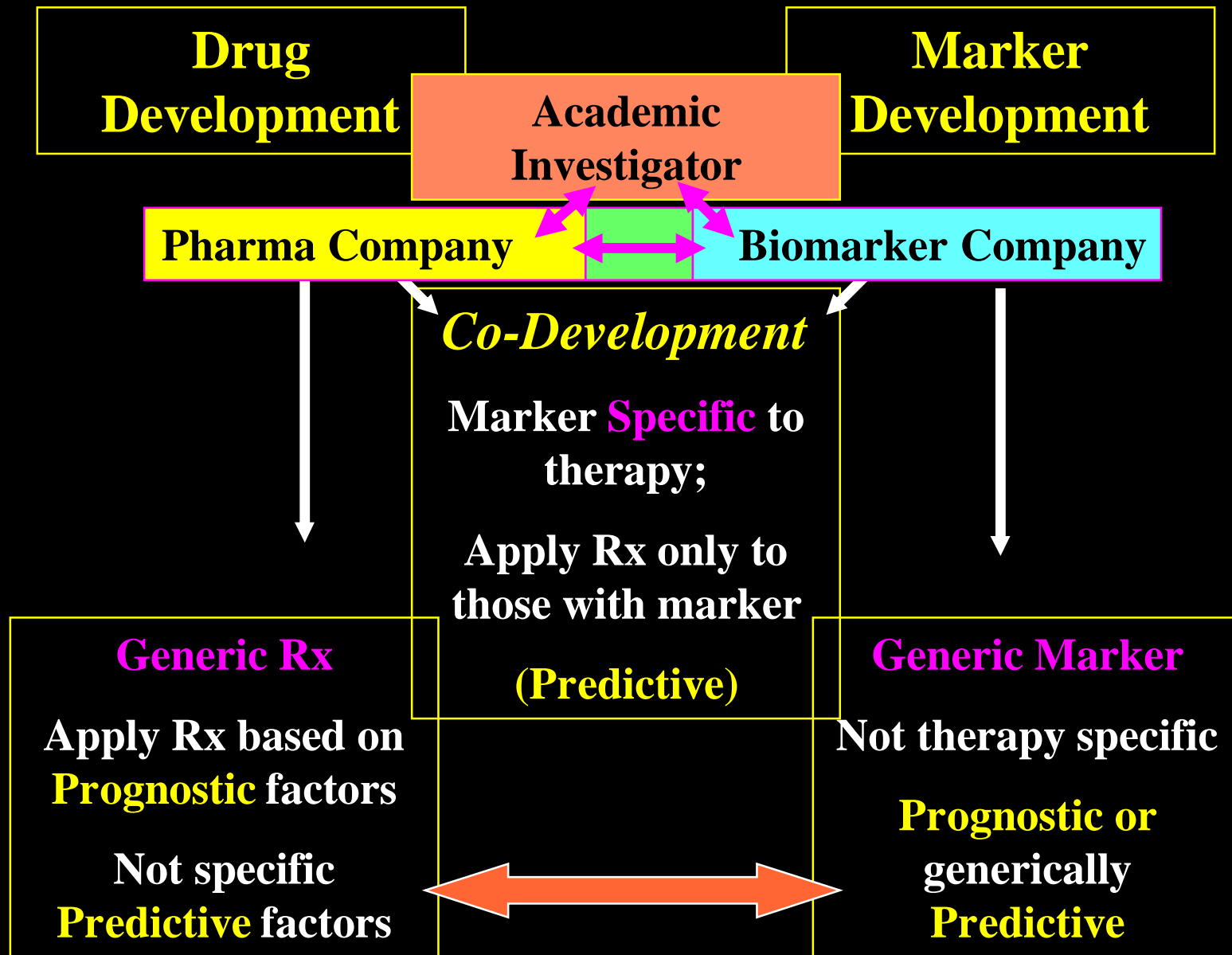
**LOE I studies
Financial burden/Low Payoff**



Highly Valued Tumor Markers: A Virtuous Cycle



Tumor Marker Development: Not JUST Co-Development



Tumor Markers: Carrots and Sticks

λ Research

λ **Funding:** NCI Cancer Biomarkers Study Section (CBSS)

www.cms.csr.nih.gov

λ **Publication:** Recommended Guidelines

λ *Mcshane et al, REporting Recommendations for Tumor MARker Prognostic Studies (REMARK)*

λ *Bossuyt et al, Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD Initiative*

λ **Specimen Sources** Breast Cancer Tissue Resource

Breast Cancer Inter-group Correlative
Sciences Committee

www.ctep.nih.gov/resources/tbci/correlative_studies.html

Tumor Markers: Carrots and Sticks

λ Clinical Use

λ Guidelines

Evidence-based Guidelines Panels

ASCO, NCCN, CAP, NACB

www.asco.org

www.nccn.org

λ Regulatory/Reimbursement

λ CMMS/Blue Cross/other 3rd Party Payer Tech Assessments

λ AACR/NCI/FDA initiative

λ Center for Medical Technology Policy

λ Improved and Clear-cut FDA Rules

λ Center for Devices and Radiologic Health

λ www.fda.gov/cdrh/guidance.html

Increase Value of Tumor Markers: Proposals

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

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; FOCCR**

