The Competitive Dynamics of Personalized and Precision Medicine: Insights from Game Theory

Prof. Ernst R. Berndt, Ph.D., and
Mark R. Trusheim, M.S.
Massachusetts Institute of Technology and
National Bureau of Economic Research

NBER Pre-Conference on Economic Dimensions of Personalized and Precision Medicine

Italian Academy for Advanced Studies in America
Columbia University

September 21-22, 2016

Acknowledgements

- **Research support from the MIT Center for Biomedical Innovation, its biopharmaceutical industry sponsors, IMS Health, Inc., and the National Institutes of Health is gratefully acknowledged. Any opinions and views expressed here are mine, and are not necessarily those of the sponsors.**

- **This presentation is based in part on:**
  - **Trusheim MR, Berndt ER and Douglas FL, "Stratified Medicine: Strategic and Economic Implications of Combining Drugs and Clinical Biomarkers", *Nature Reviews: Drug Discovery*, 6(4):287-293, November 2007**
  - **Trusheim MR and Berndt ER, "An Overview of the Stratified Economics of Stratified Medicine", Cambridge, MA: National Bureau of Economic Research, Working Paper No. 21233, June 2015. Revised and published as:**
  - **Trusheim MR and Berndt ER, "The Clinical Benefits, Ethics and Economics of Stratified Medicine and Companion Diagnostics", *Drug Discovery Today*, 20(12):1439-1450, December 2015.**

Agenda

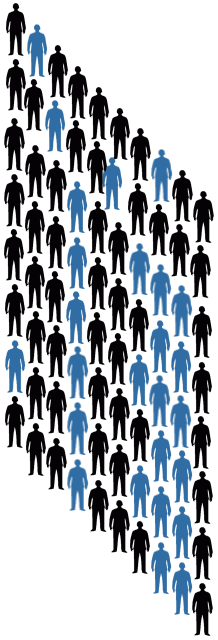
- **Defining Precision Medicine**
- **Fundamental Economics of Precision Medicine**
- **Precision Medicine Under Dynamic Competition**

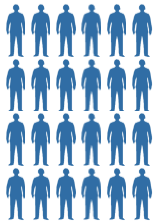
What Are Precision Medicines?
AKA: Stratified, Tailored, Targeted, or Personalized

- **Matching therapies to patient sub-populations aided by clinical biomarkers – also called personalized, targeted, tailored, or precision medicine. My use of stratified is drawn from statistical, not geological concepts**
- **Objective: Exploit potential differential patient responses – enhance probability of achieving efficacy or avoiding ill (adverse reactions)**
- **Clinical Biomarkers -- beyond genotyping, including, e.g.,**
  - **Molecular (gene expression, proteomic, biochemical)**
  - **Imaging**
  - **Clinical observation**
  - **Patient self-reporting**
- **Clinical Biomarker: Any information that provides a reliable, predictive correlation to differential patient responses**

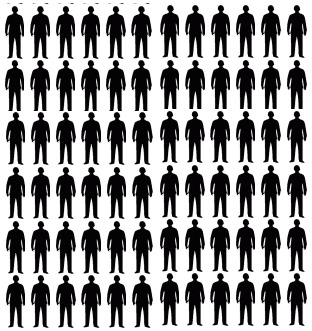
Classic Personalized Medicine: Use a Molecular Diagnostic to Select Responders

- **Targeted prescribing to those possessing proper profile**





Higher response rate,
But also higher price?

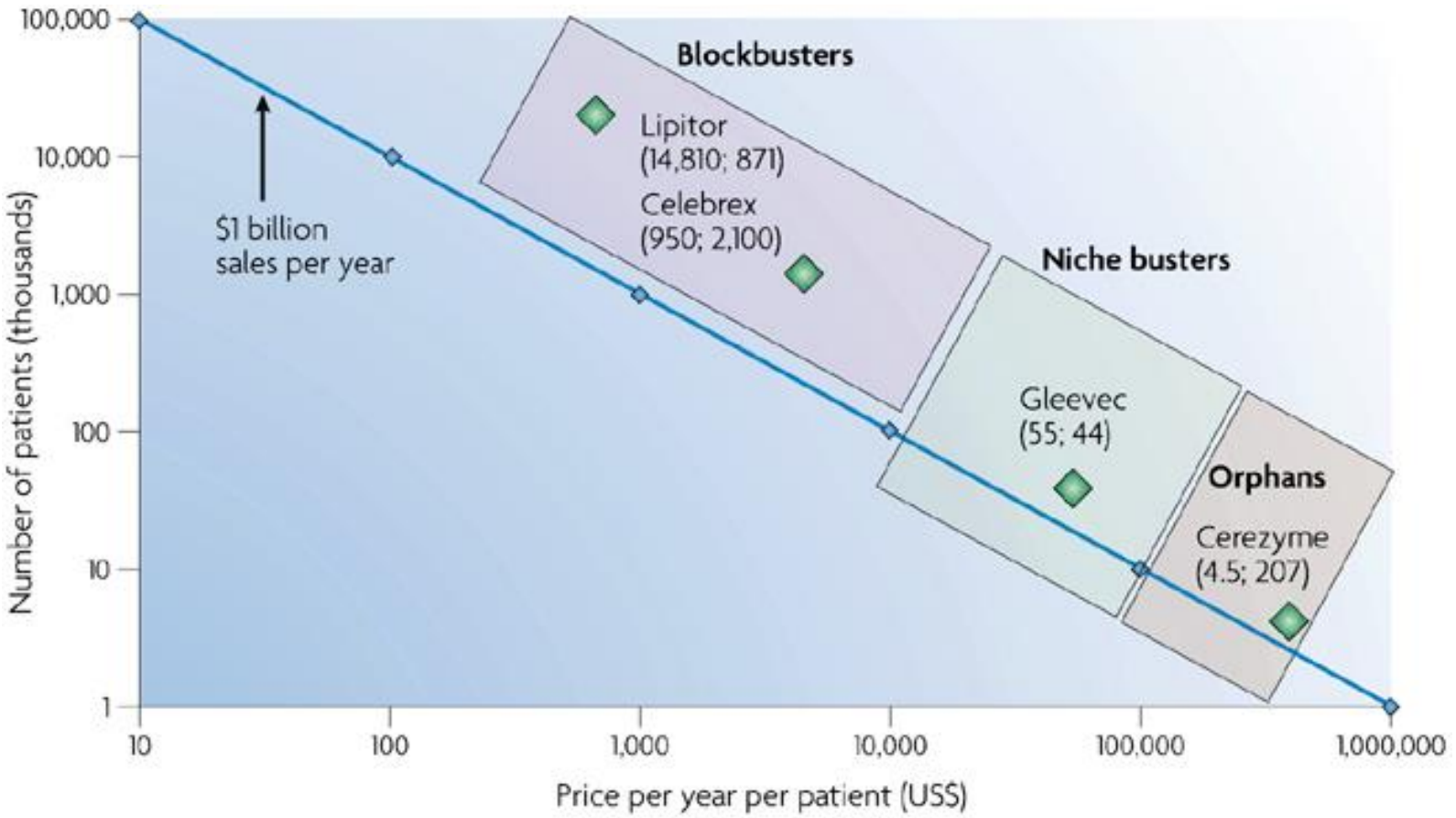


Avoid adverse events
and save critical time

Necessary and Sufficient Conditions for Commercial Feasibility of a Stratified Medicine

- **Differential population treatment response is necessary but not sufficient for a stratified medicine to emerge**
- **A diagnostic clinical biomarker must exist that predicts differential response among sub-populations taking the medicine**
- **But what is therefore also needed is a sustainable, meaningful differential benefit that exceeds the cost of administering the diagnostic clinical biomarker**

Economic Considerations: Large Revenues Are Possible even with Small Populations

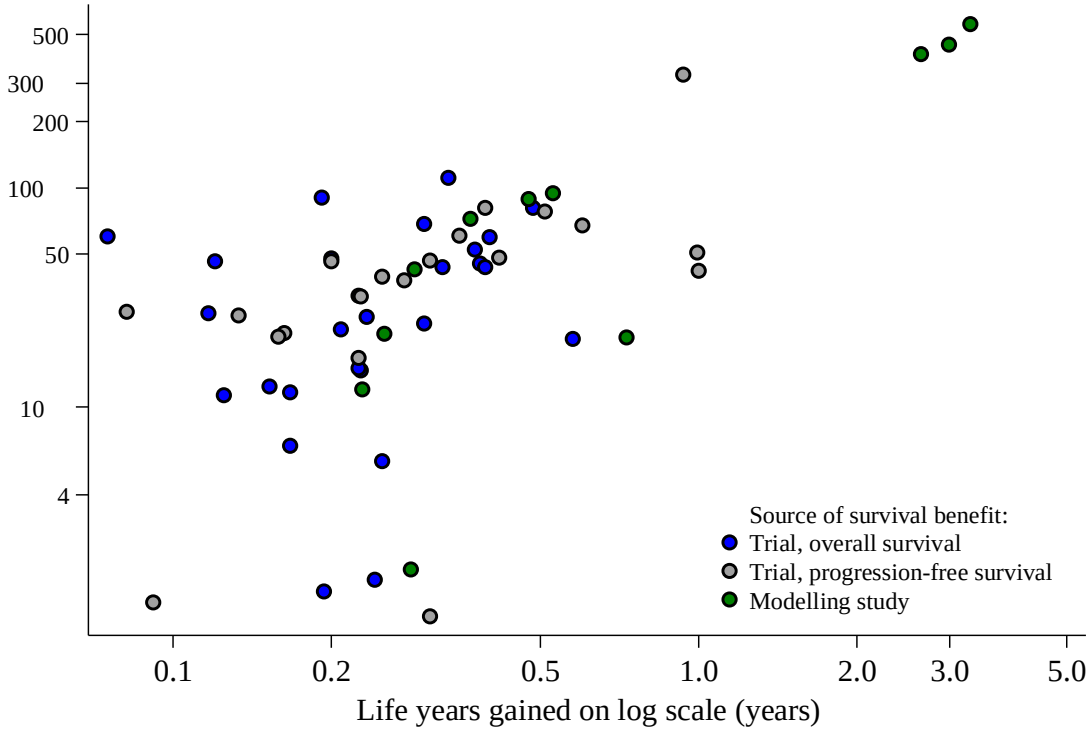


(thousands of patients, average yearly price in $thousands)

Nature Reviews | Drug Discovery

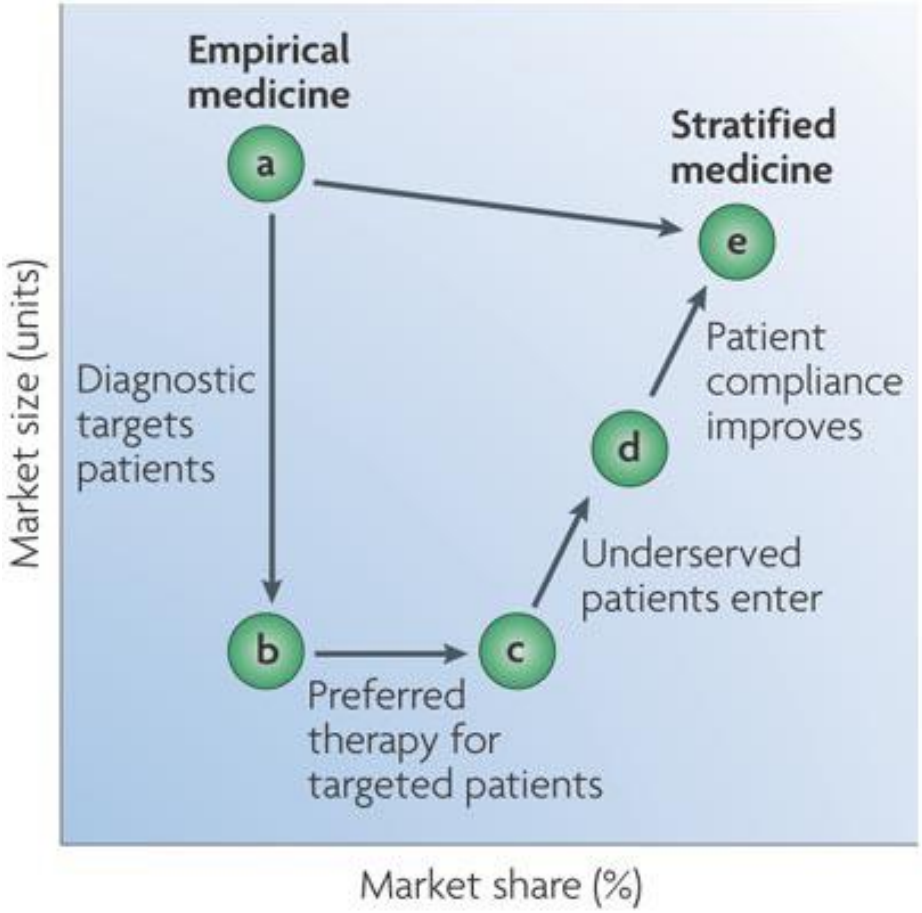
Episode Treatment Prices for Anticancer Drugs Launched 1996-2014

Figure 1: Price versus life years gained



Source: Howard DH, Bach PB, Berndt ER and Conti RM, "Pricing in the Market for Anticancer Drugs", *Journal of Economic Perspectives*, 29(1):139-152, Winter 2015.

The Logic of the Path to a New Equilibrium



Indirect Evidence That Fragmentation May Impact R&D: Rarer Cancers have Fewer Therapeutics

Figure 4: Cancer organ of origin incidence with approved therapeutics for each

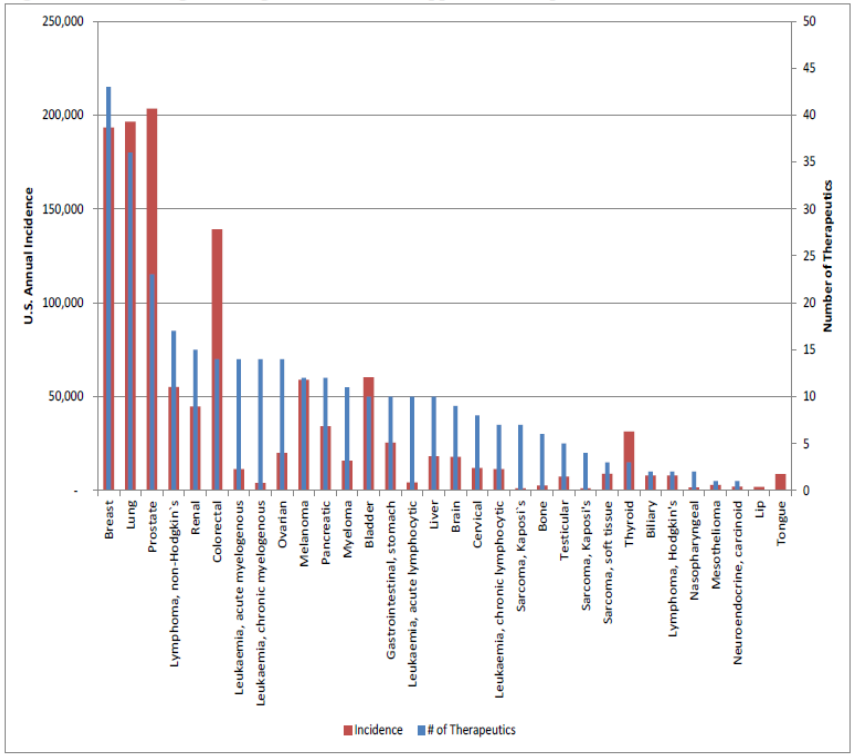
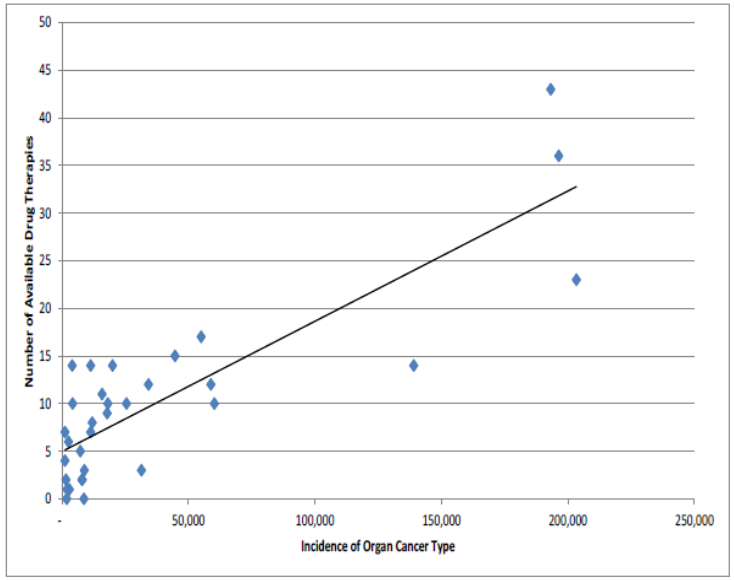
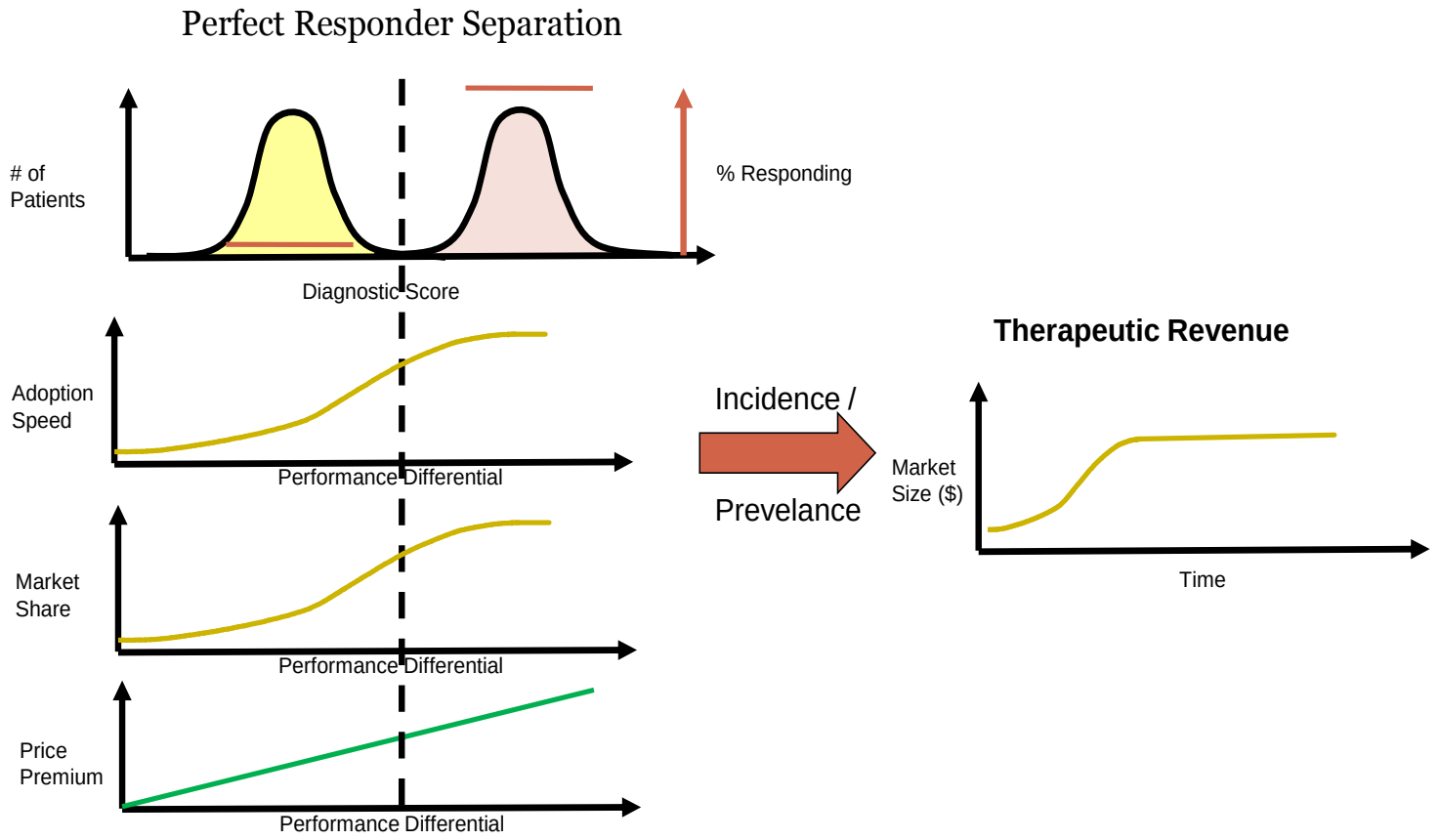


Figure 5: Bivariate regression of segment patient incidence and available drug therapies



Trusheim MR, Berndt ER, Health Management, Policy and Innovation 2012

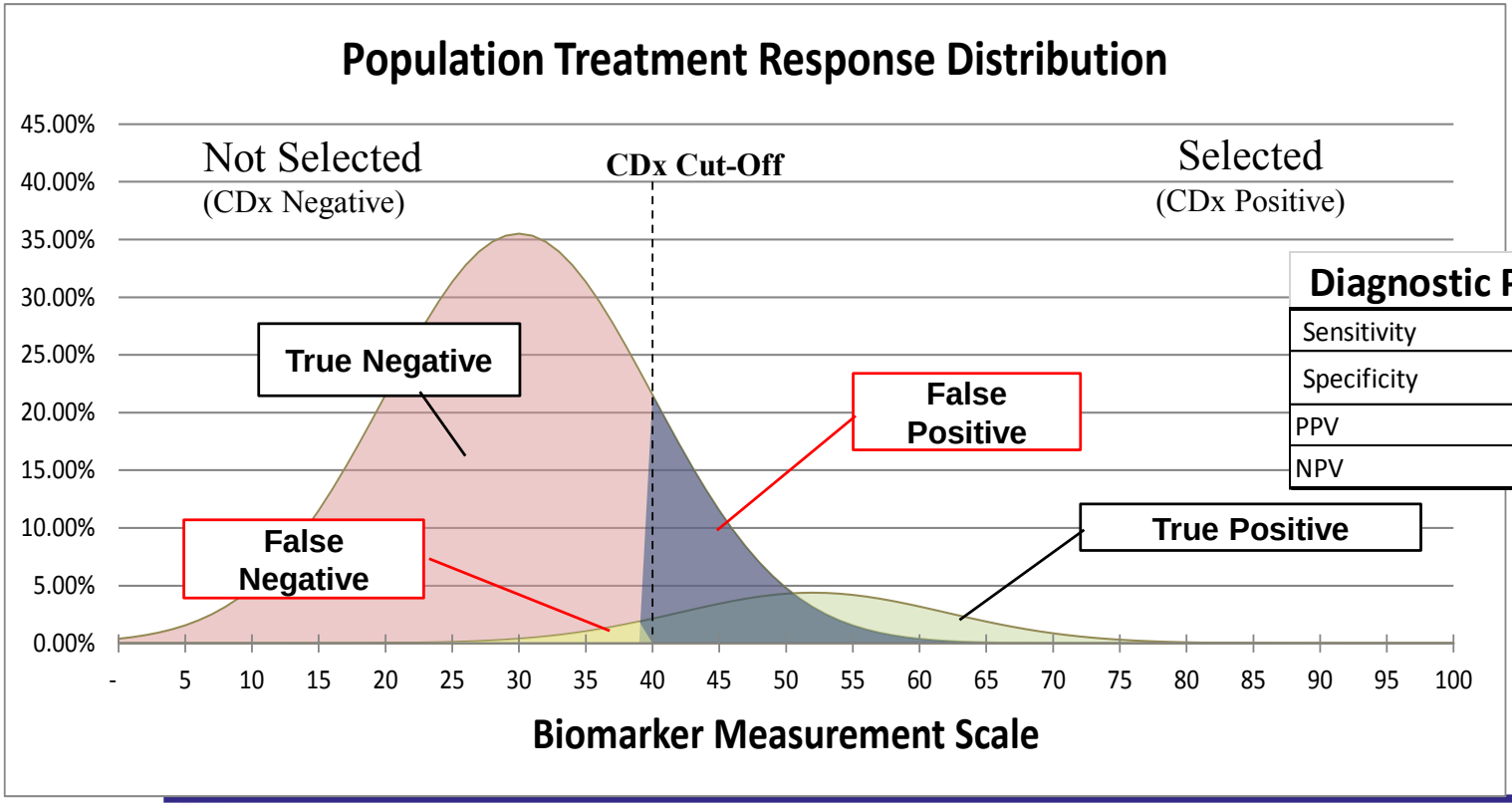
A Precision Medicine with an Ideal Companion Diagnostic



An ideal companion diagnostic perfectly separates therapeutic responders from non-responders resulting in a positive clinical performance differential compared to an all-comers approach, which in turn could lead to faster clinical adoption, greater market share and a price premium.

But No Companion Diagnostic (CDx) is Perfect: Herceptin Created High Value with Imperfect CDx

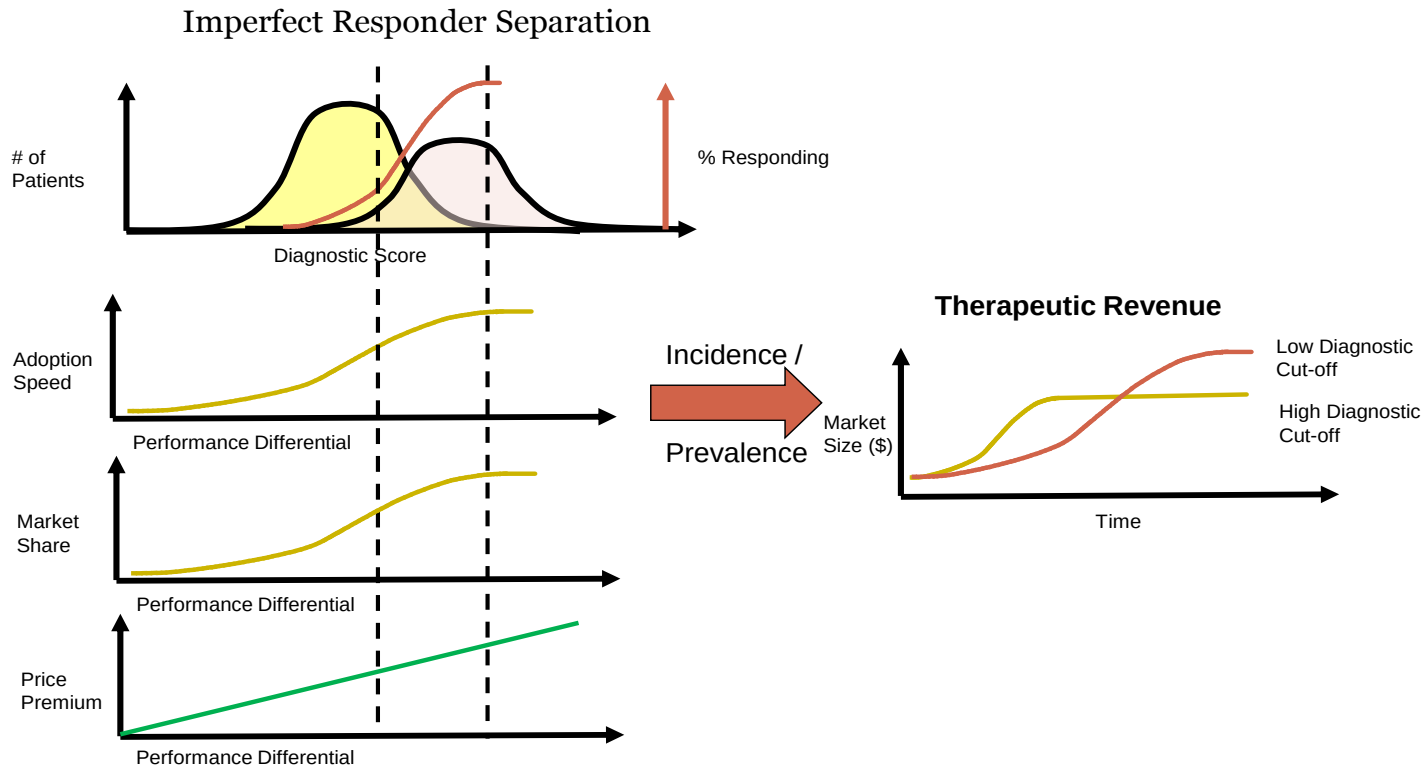
- **Diagnostics always have some errors. CDx does not completely separate drug responders from non-responders**
- **For example, for Herceptin in oncology, the HER2 test selects about 33% of patients, but of those only about a third (10-15% of the 33%) respond to treatment (FDA Label, CHF 6.3B in 2014-Roche)**



Diagnostic Performance

Sensitivity	89%
Specificity	83%
PPV	39%
NPV	98%

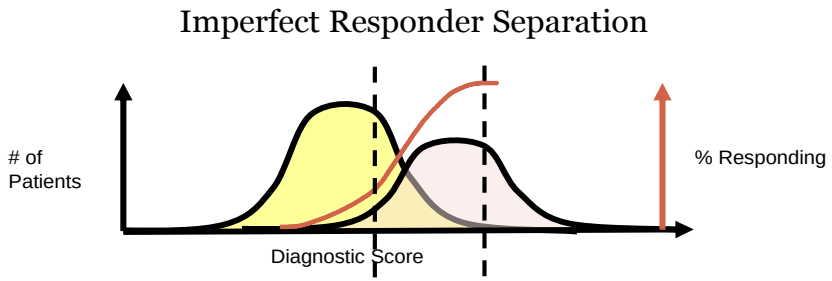
A "Precision" Medicine with an Imprecise Companion Diagnostic



A realistic companion diagnostic imperfectly separates responders from responders, presenting a range of possible cut-off values. The resulting range of potential performance differentials leads to similarly varying revenue results depending on the resulting changes to adoption speed, market share and price as well as the prevalence of therapeutic responders.

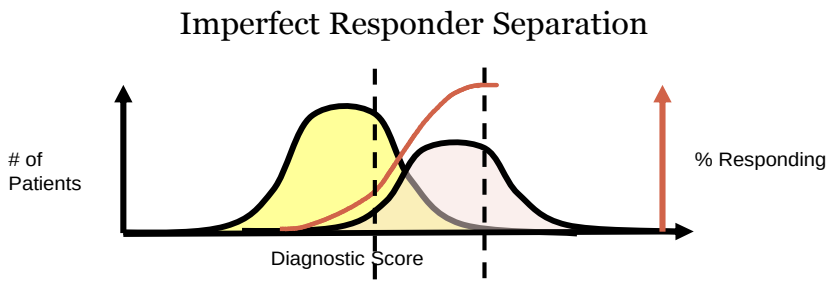
Implications of *High* Cut-off Choice

- Excludes nearly all non-responding patient scores,
  - Nearly all the selected and then treated patients will respond.
  - Few non-responding patients will incur side effects treatment time opportunity cost of pursuing an ineffective treatment
- Technical: Choice yields high specificity – few false poisitives
- Ethical issue: Denies treatment to false negative patients (“off-label”, unreimbursed)
  - For a severe condition with few treatment options, this may be unacceptable.
  - For a condition with many and similarly efficacious treatment options available, or perhaps a condition with low morbidity and mortality, this may be quite acceptable.
- Innovator: Risks low revenues due to small potential patient & perhaps price limits



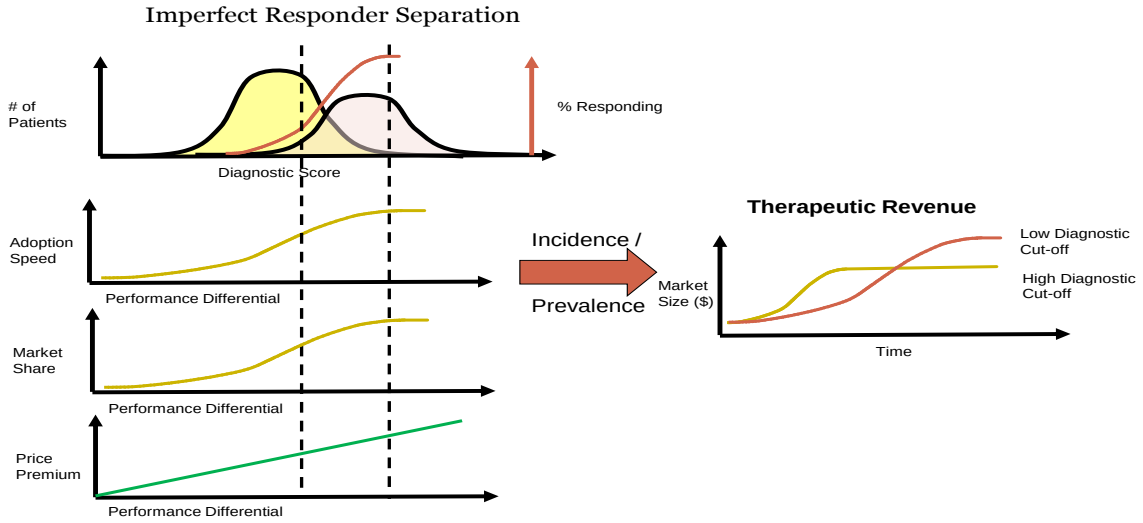
Implications of *Low* Cut-off Choice

- Includes nearly all patients who ***will*** respond
  - Few patients who might benefit are denied treatment
  - Increases non-responding, test positive, patients
- Technical: Choice yields high sensitivity
- Ethical Issue: Knowingly exposes more non-responding patients to side effects and delays in seeking other treatments.
  - For a therapeutic with significant, irreversible side effects this may be unacceptable
  - For a therapeutic with few side effects or for a condition with few treatment alternatives, this may be entirely appropriate.
- Innovator: Lower efficacy may lower price, adoption speed and share of selected. Make it up on volume?



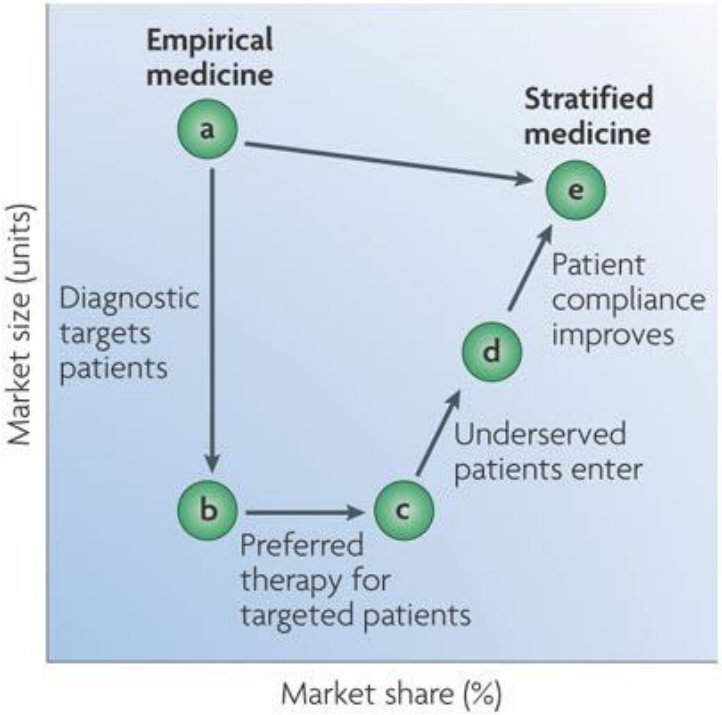
Summary: No Universally Preferred High or Low Cut-off Value for Companion Diagnostic

- Each candidate therapeutic faces unique
  - Unmet medical need
  - Therapeutic performance
  - Companion diagnostic performance
  - Market dynamics
- General rules of thumb for preferring high or low cut-offs not obvious either clinically, ethically or financially



Possible Behavioral Change Impacts from Availability of Precision Medicine

- c→d: Patients may be encouraged to seek, or providers recommend, treatment if a test exists to recommend a particular therapy. This expands the absolute number of patients (market size) and share.
  - Recent experience with hepatitis C and hypercholesterolemia medicines
  - 'Backlog' of patients waiting for treatment
- d→e: CDx may improve patient adherence.
  - Monitoring: Examples include AIDs patients after viral load test introduced – improved HAART drug adherence; and more recently, LDL testing in homozygous familial hypercholesterol-emia patients.
  - Conviction effect: CDx might reduce search for better treatment and tolerance for treatment inconvenience or side effects

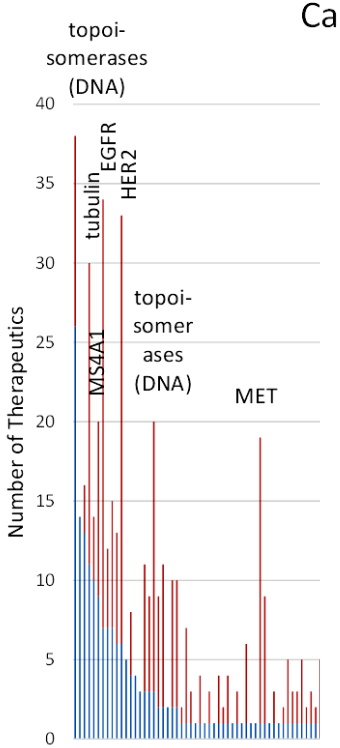


Nature Reviews | Drug Discovery

DYNAMIC COMPETITION AMONG PRECISION MEDICINES FOR SAME TARGET/INDICATION

Competition Begins Early in Precision Medicine

- **Most oncology targets have multiple compounds in competitive development**
- **Signaling for smart players aided by all the public dbs unlike smartphones**



Cancer Therapies Launched or in Ph I, II or III, by Target
(Unspecified, Not Applicable and blank removed)

For the 35 targets in Phase 3 with no approved products, only 12 of 141 compounds had no competitors for their target
Illustrates Schumpeter "Creative Destruction"

Authors' analysis of PharmaProjects pipeline database as of September 2014

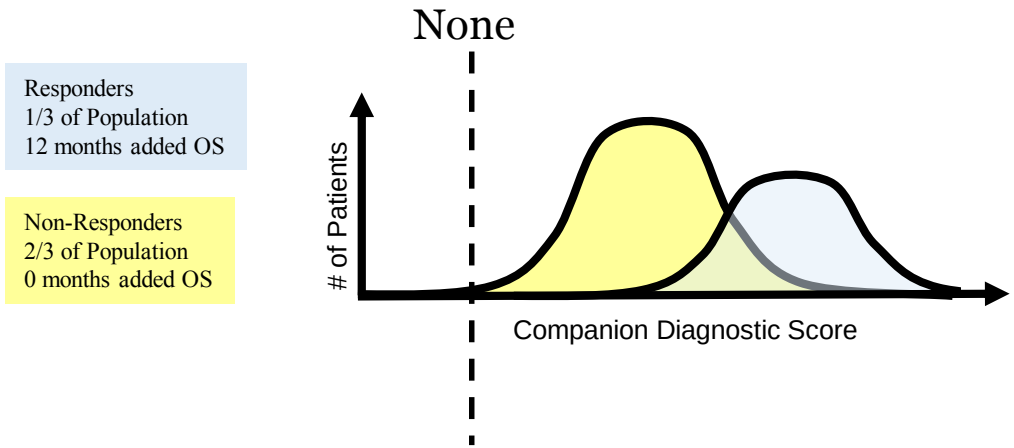
Targets (by # of Launched products then alphabetical)

■ Launched ■ Phase I- III

Trusheim MR, Berndt ER,. NBER Working Paper 21233 June 2015

A Horse Race Among Three Medicines
Firm A: Chooses an Allcomers Approach (No CDx)

- **Consider 3 identical medicines for a 100,000 patient cancer indication**
- **Assume that clinical development efficiencies offset the cost of developing and validating the diagnostic.**



RCT Efficacy (Months OS)	4.0
Sensitivity	100%
Specificity	0%
PPV (Positive Predictive Value)	33%
Patients CDx+	100,000

Firm A chooses an *all-comers* approach with no diagnostic. The average benefit would be 4 months: 1/3(12) + 2/3(0) = 4.

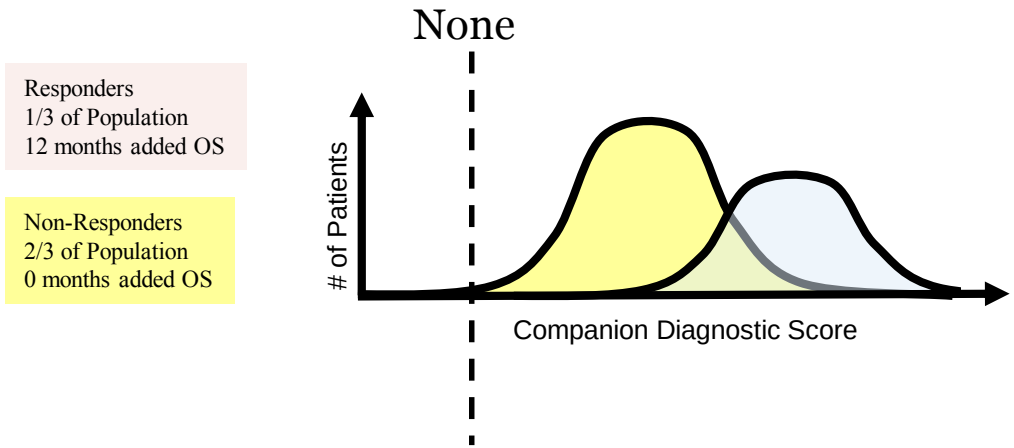
100% sensitivity (selects all patients who might respond) and 0% specificity (excludes none who will not benefit).

RCT: Randomized Controlled Trial
OS: Overall Survival

Trusheim MR, Berndt ER,. NBER Working Paper 21233 June 2015

A Horse Race Among Three Medicines: Firm A: Allcomers Economics

- **All 100,000 patients eligible for treatment**
- **Recent published US oncology ICER of $138,582**
- **To reach $1 billion in annual sales, Drug A must achieve 20% market share (be used by 20,000 patients) at $50,000/year.**



RCT Efficacy (Months OS)	4.0
Price (ICER Based)	$46,000
Benefiting Patients	7,250
Treated Patients	21,750
Payer Cost	$1B

ICER Based Price of $46,000

1/3 of patients respond

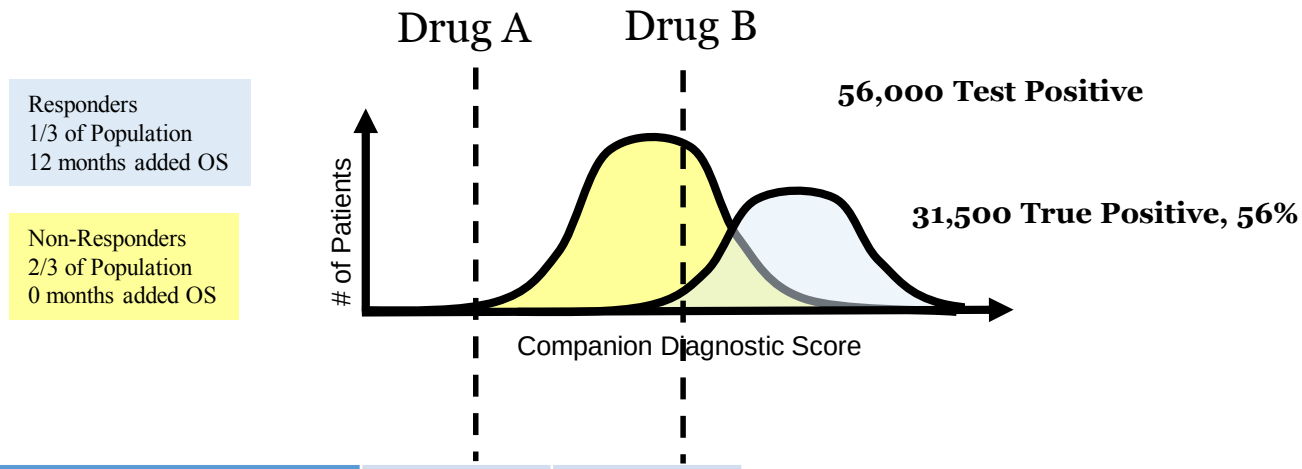
Payers pay $1B

Trusheim MR, Berndt ER,. NBER Working Paper 21233 June 2015

ICER: Incremental Cost Effectiveness Ratio
OS: Overall Survival

A Horse Race Among Three Medicines
Firm B: Low Cut-Off CDx

- **95% sensitivity (31,500 of 33,000) responders CDx+**
- **64% specificity (43,000 of the 67,000 non-responders CDx-, while 24,000 CDx+)**
- **Mean treatment benefit increases 70% to 6.7 months OS**



RCT Efficacy (Months OS)	4.0	6.7
Sensitivity	100%	95%
Specificity	0%	64%
PPV (Positive Predictive Value)	33%	56%
Patients CDx+	100,000	56,000

Firm B, Product efficacy claim increases

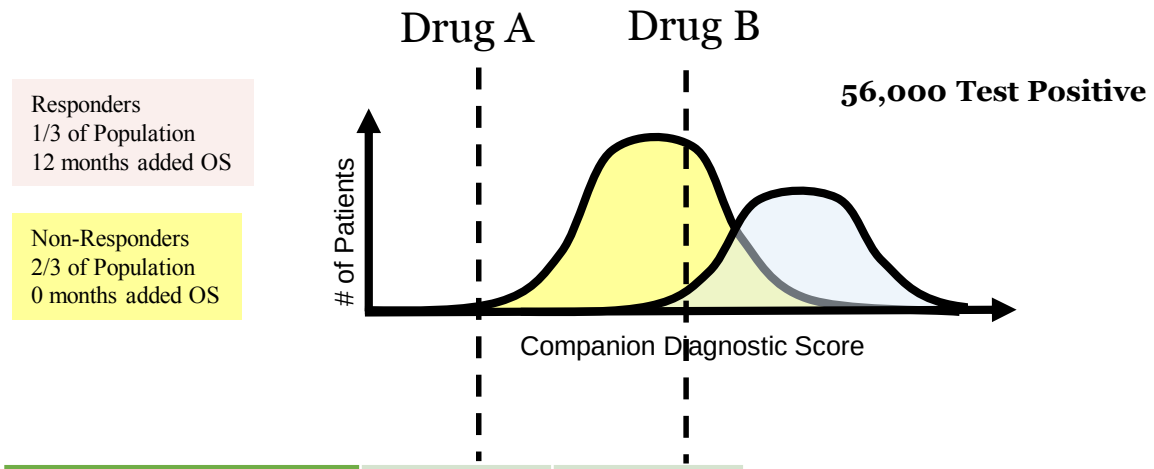
But eligible patients decline

RCT: Randomized Controlled Trial
OS: Overall Survival

Trusheim MR, Berndt ER,. NBER Working Paper 21233 June 2015

A Horse Race Among Three Medicines: Firm B: Low Cut-Off Strategy Economics

- **ICER based price increases 67% due to higher efficacy from CDx selection**
- **Payer Cost (and Drug Revenue) for 7,250 patients to receive benefits remains the same**
- **60% fewer non-responding patients exposed to treatment, side effects and delays (5,750 vs 14,500, Treated - Benefiting)**



RCT Efficacy (Months OS)	4.0	6.7
Price (ICER Based)	$46,000	$77,000
Benefiting Patients	7,250	7,250
Treated Patients	21,750	13,000
Payer Cost	$1B	$1B

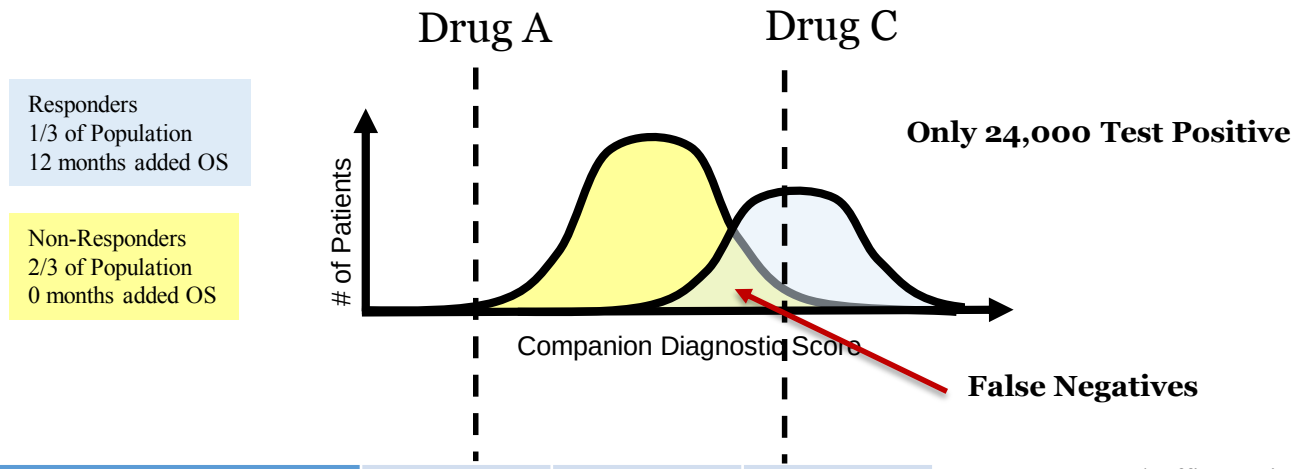
For $1B payer cost (drug revenue) the OVERALL market share declines to 13%
Market share of SELECTED is 23% (13,000/56,000)

Trusheim MR, Berndt ER,. NBER Working Paper 21233 June 2015

ICER: Incremental Cost Effectiveness Ratio
OS: Overall Survival

A Horse Race Among Three Medicines: Firm C: High Cut-Off CDx

- **High 95% specificity so few false positives (~3,000)**
- **Only 64% sensitivity of (≈ 21,000)**
  - **About 12,000 (36%) patients who might benefit test negative, denying them therapy.**
- **Mean treatment benefit increases to 10.3 months OS**



RCT Efficacy (Months OS)	4.0	6.7	10.3
Sensitivity	100%	95%	64%
Specificity	0%	64%	95%
PPV (Positive Predictive Value)	33%	56%	86%
Patients CDx+	100,000	56,000	24,000

RCT reported efficacy increases 2.5X compared to Drug A even though drugs are identical

Selected patient has nearly 9 out of 10 chance of responding

RCT: Randomized Controlled Trial
OS: Overall Survival

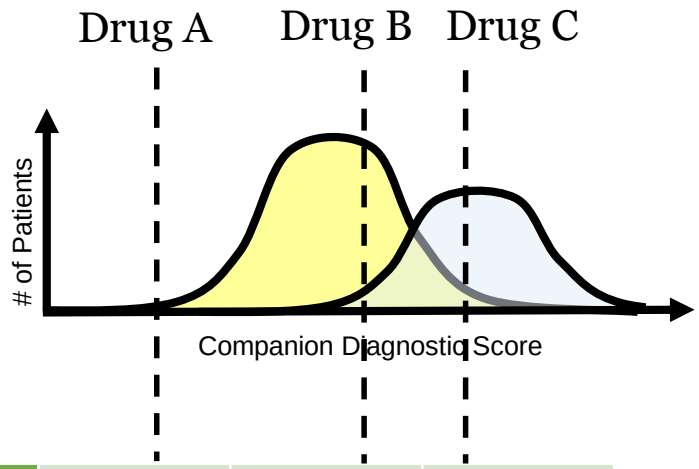
Trusheim MR, Berndt ER,. NBER Working Paper 21233 June 2015

A Horse Race Among Three Medicines: Firm C: High Cut-Off Strategy Economics

- **ICER based ($138,582/QALY) Price increases again due to higher efficacy from CDx selection**
- **Payer Cost (and Drug Revenue) for 7,250 patients to receive benefits remains the same**

Responders
1/3 of Population
12 months added OS

Non-Responders
2/3 of Population
0 months added OS



RCT Efficacy (Months OS)	4.0	6.7	10.3
Price (ICER Based)	$46,000	$77,000	$119,000
Benefiting Patients	7,250	7,250	7,250
Treated Patients	21,750	13,000	8,400
Payer Cost	$1B	$1B	$1B

Trusheim MR, Berndt ER,. NBER Working Paper 21233 June 2015

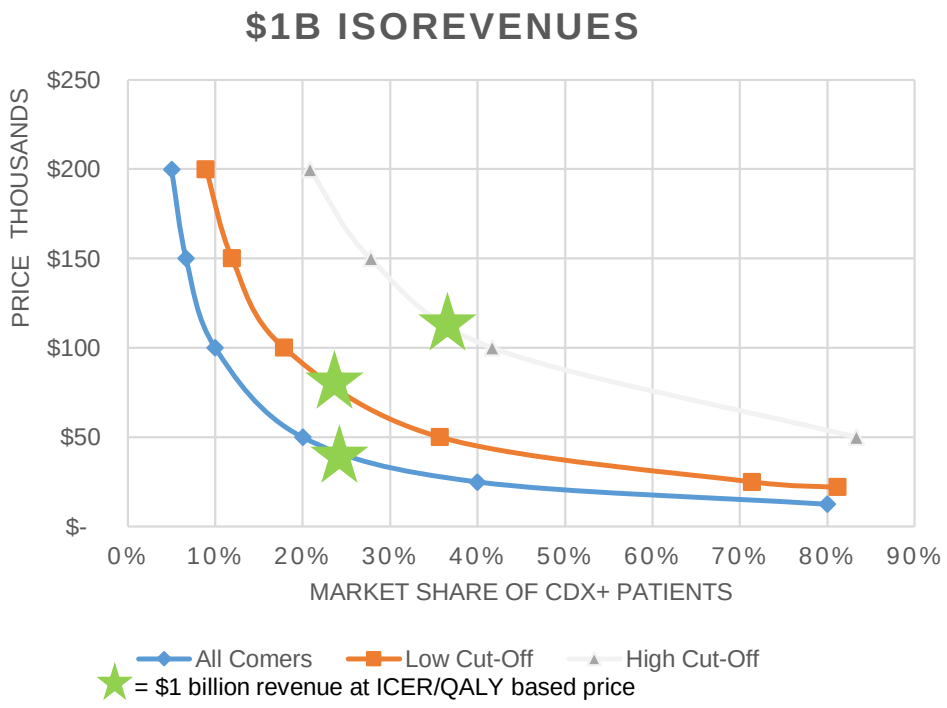
PRICES vary by 150% but VALUE is equal
(Better at higher price since fewer adverse events)

OVERALL market share declines to ~8% to reach 7,250 benefiting patients

ICER: Incremental Cost Effectiveness Ratio
OS: Overall Survival

The 'Scientific Cut-Off Selection' Sets the Commercial Isorevenue Curve as Well

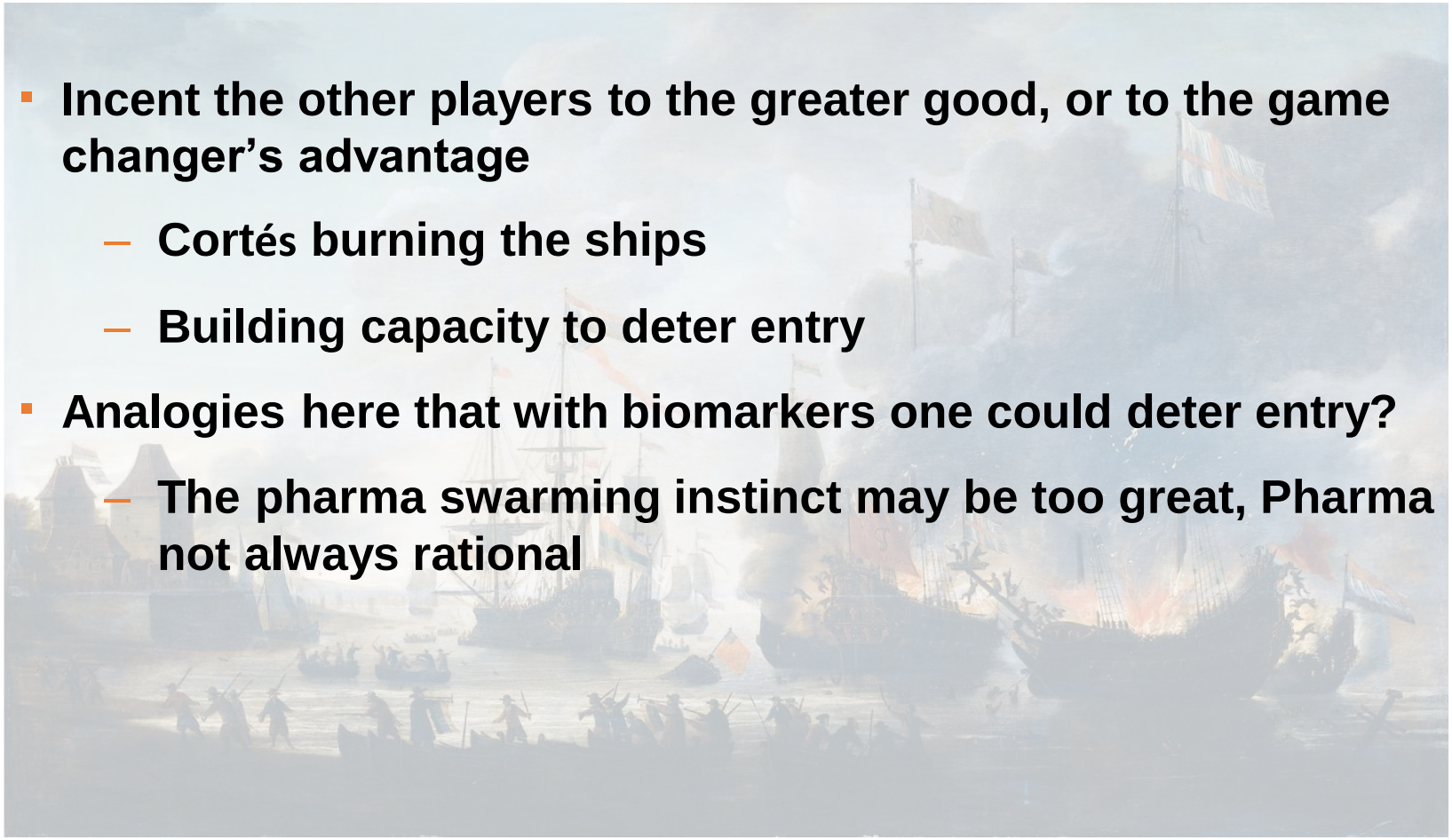
- **The CDx cut-off decision is an economic, and ethical, choice, not simply a scientific judgment**



The Game-Theoretic Outcome?
A beautiful mind or prisoners dilemma with smiley faces

- Drugs B & innately perform no better than Drug A
- Suppose competing Firms A, B and C decided it would be optimal for them to select a low or mid-companion diagnostic cut-off value.
- In practice, Drug A might see a patient population that is responder depleted by Drug B, reducing Drug A's market share and value (called "selection").
- However, each worried that the advantages of a potentially differentiating high-efficacy claim might drive developers to select a high cut-off value.
- If all choose a High cut-off, the overall value might be reduced, with many patients excluded from treatment.
- The potential advantage of a higher cut-off value might prove too alluring, or the fear of a competitor selecting a high cut-off value might drive all to do so.
- Note that this outcome bears considerable semblance to the classic "Prisoners' Dilemma" construct in game theory. Is this where the dynamics of stratified medicine is being propelled?

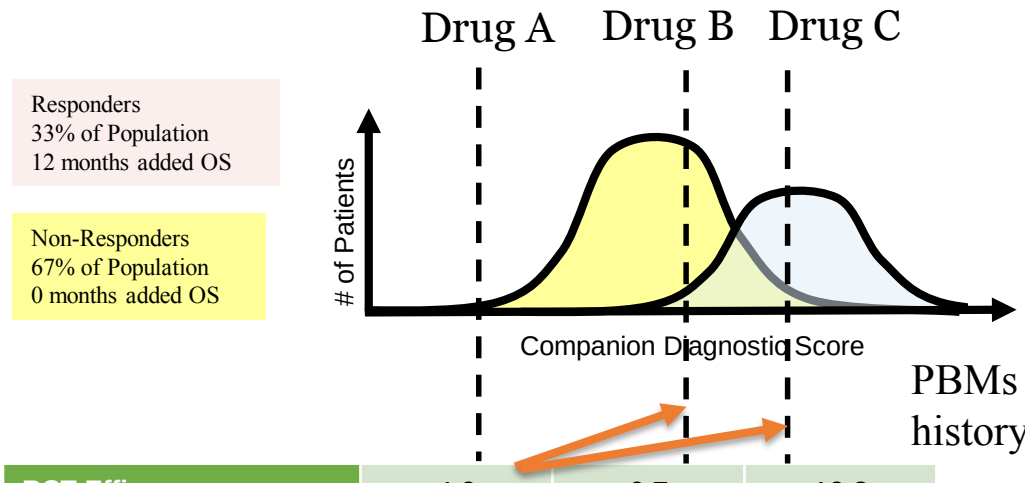
Evolve the Game: Change the Rules



- **Incent the other players to the greater good, or to the game changer's advantage**
  - **Cortés burning the ships**
  - **Building capacity to deter entry**
- **Analogies here that with biomarkers one could deter entry?**
  - **The pharma swarming instinct may be too great, Pharma not always rational**

Beyond the Prisoner's Dilemma: Add the Payer as Player

- **If the payer learns that the drugs are essentially identical**
- **AND if the guidelines or practice move to one of the biomarker approaches**
- **The payer could prefer (or switch) patients to the lower ICER and price drug for use on CDx+ patients**



PBMs have long and strong history of patient drug switching

RCT Efficacy (Months OS)	4.0	6.7	10.3
Price (ICER Based)	$46,000	$46,000	$46,000
Benefiting Patients	7,250	7,250	7,250
Treated Patients	21,750	13,000	8,400
Payer Cost	$1B	$0.6B	$0.4B

Payer could save 40-60%
By Changing the Rules

Trusheim MR, Berndt ER,. NBER Working Paper 21233 June 2015

Precision Medicine a Greater Dilemma

- **In practice, this is more than a single period, non-cooperative game**
  - **Sequential, Multi-period game with incomplete information**
  - **Possible timing differences of drug entries, sequential game**
- **Adding the payer mixes a second game with the developer cut-off game**
- **Prices can be adjusted over multiple periods, and the cut-off for a drug can be changed after new trials. So it is a repeated game**
- **Other drugs may be developed by the players, so learning and training may also apply.**

Additional Games to be Developed

- **Cut-off migration game:**
  - Begin with high cut-off and then migrate lower over time to provide access to false negative patients and increase population size.
  - HER2/Herceptin case
- **Multi-indication game:**
  - Set cut-off high for initial, early indication to generate reputation and then lower for later indications.
  - PCSK-9 of orphan homozygous to statin intolerance. Express Scripts indication pricing to break the game.

Additional Games to be Developed (Continued)

- **Multi-marker game:**
  - Use a different assay or marker than competitors.
  - Immuno-onc PD1/PDL1 products. Setting standards literature. Tirole textbook on industrial organization.
- **Multi-marker over time game:**
  - A newer, more accurate marker may emerge.
  - Cetuximab (Erbitux) case of KRAS marker replacing EGFR

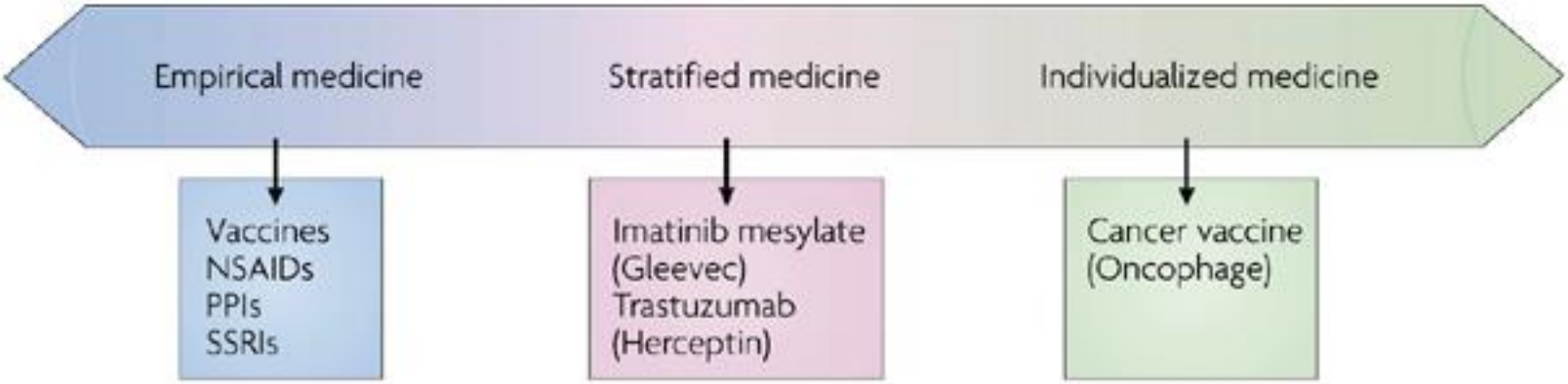
Selecting a Cut-Off Value: Some Final Thoughts: Get Used To It

- Precision medicine tightens the links among clinical, economic, and ethical considerations. Setting the companion diagnostic cut-off value is a crucial shared connection among all three, with no easy rule of thumb to guide the choice.
- Precision medicine renders the traditional split between the R&D scientists and the commercial marketers obsolete. Is this a new instance of the Hippocratic oath to "do no harm"?
- Other questions: Why are only novel medicines being paired with companion diagnostics – why not legacy medicines? Why aren't payers developing companion diagnostics? Hint: Payers want to play medicines off against one another to gain discounts. precision medicine makes this more difficult. Note that micro-economic theory teaches that to avoid higher prices from double marginalization, it is preferable that the companion diagnostic and therapeutic be produced and sold by the same firm.

Stratified and Precision Medicines

BACKGROUND MATERIAL

The Patient Therapeutic Continuum



Nature Reviews | Drug Discovery

Major Drugs Ineffective for Many

Hypertension Drugs 10-30%
ACE Inhibitors

Heart Failure Drugs 15-25%
Beta Blockers

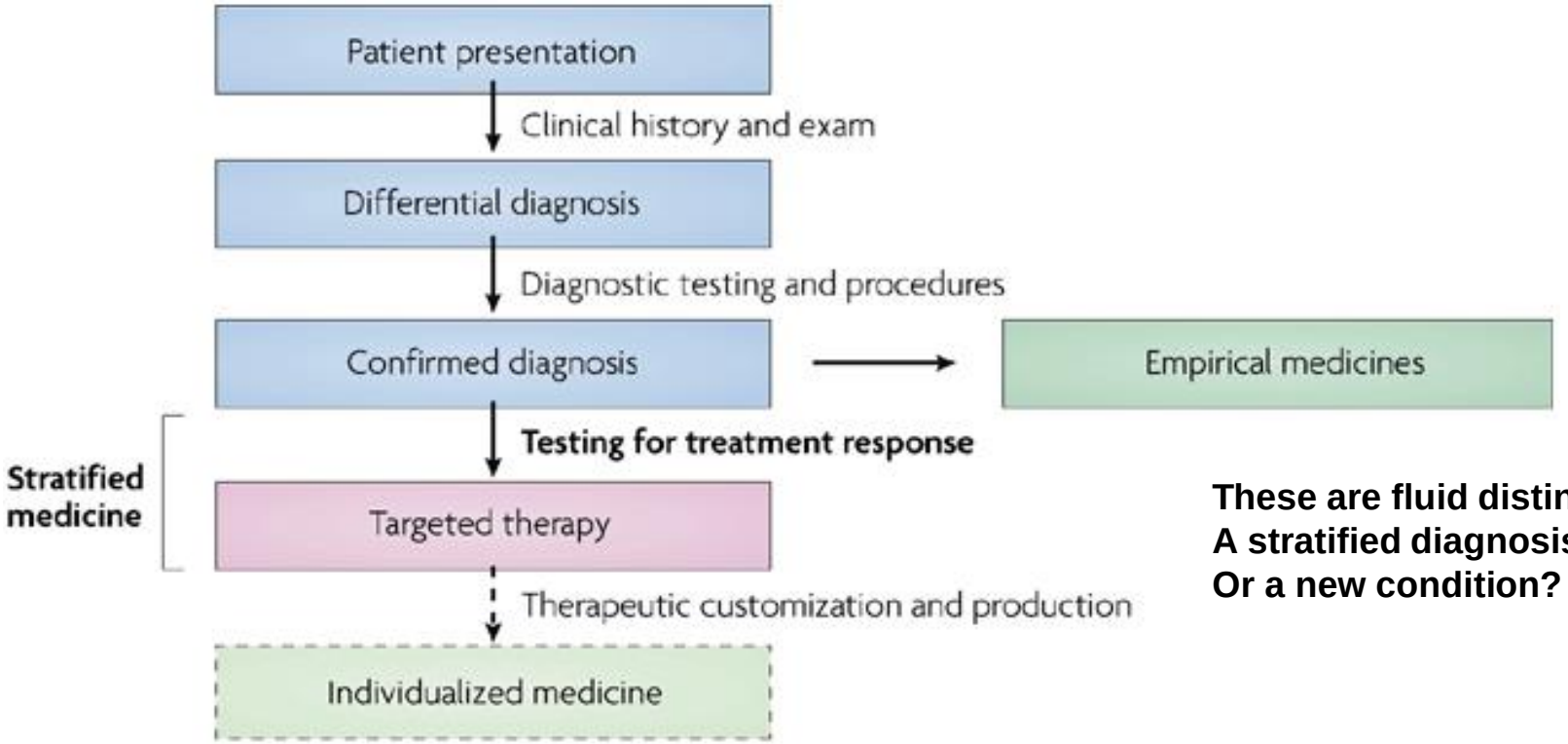
Anti Depressants 20-50%
SSRIs

Cholesterol Drugs 30-70%
Statins

Asthma Drugs 40-70%
Beta-2-agonists

Source: Abrahams Presentation of Spear B, Heath-Chiozzi M, Huff J Clinical Trends Molecular Medicine 2001; 7(5):201-4.

Stratified Medicine in the Clinical Context



These are fluid distinctions:
A stratified diagnosis,
Or a new condition?

Diagnostic Biomarkers are Imperfect

- Test scores can be binomial or continuous; many diagnostics convert a continuous metric to a binomial one using some cutoff or threshold value
- Sources of imperfection in Diagnostic Biomarkers: Molecular properties may make measurement difficult; some phenomena are inherently subjective (e.g., pain), patient heterogeneity occurs in relationship of the analyte to the gross clinical phenotype of interest, collecting and handling of sample specimens can compromise accuracy
- Implication: Diagnostics will typically yield false positives and false negatives so that positive predictive values and negative predictive values for a diagnostic are typically less than 100%