



Massachusetts Institute of Technology

Too Personal? Genomics, Biomarkers and the Future of Stratified Medicine

Presentation at “The Future of Pharmaceutical Policy”
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Joint Research with Mark Trusheim, MIT Sloan School of Management

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Stratified Medicines

- **Matching therapies to patient sub-populations with clinical biomarkers**
- **Objective: Do more good (efficacy) or avoid ill (adverse reactions)**
- **Clinical Biomarkers -- Extend beyond genotyping:**
 - **Molecular (gene expression, proteomic, biochemical)**
 - **Imaging**
 - **Clinical observation**
 - **Patient self-reporting**
- **Clinical Biomarker: Any instrument providing information showing a reliable, predictive correlation to differential patient efficacy/safety responses**

What is the goal of “Stratified” Medicine?

“Provide meaningful improved health outcomes for patients by delivering the right drug at the right dose at the right time.”

Goal: Improve individual patient outcomes and health outcome predictability through tailoring drug, dose, timing of treatment, and relevant information

One size fits all

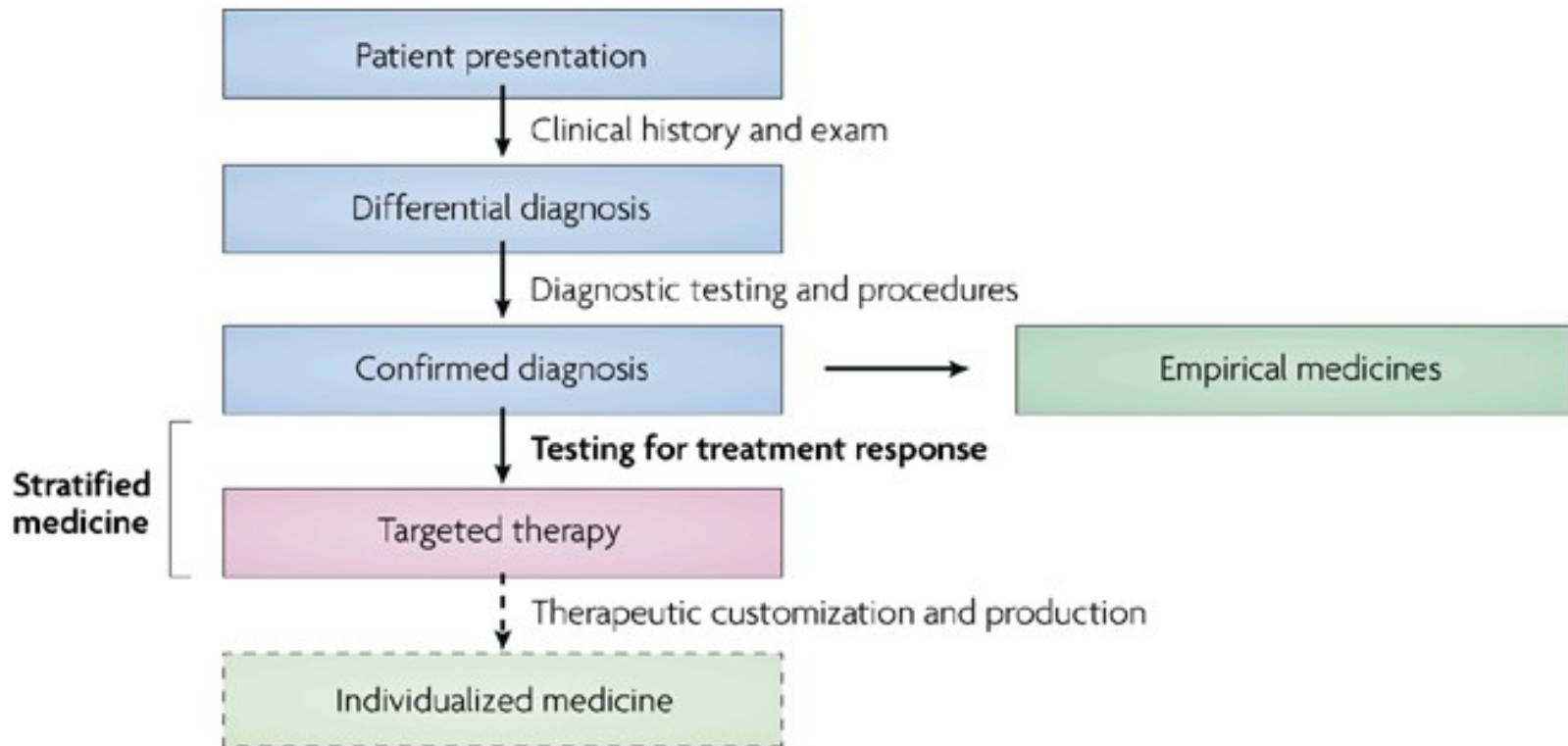
Targeted Therapy

Tailoring

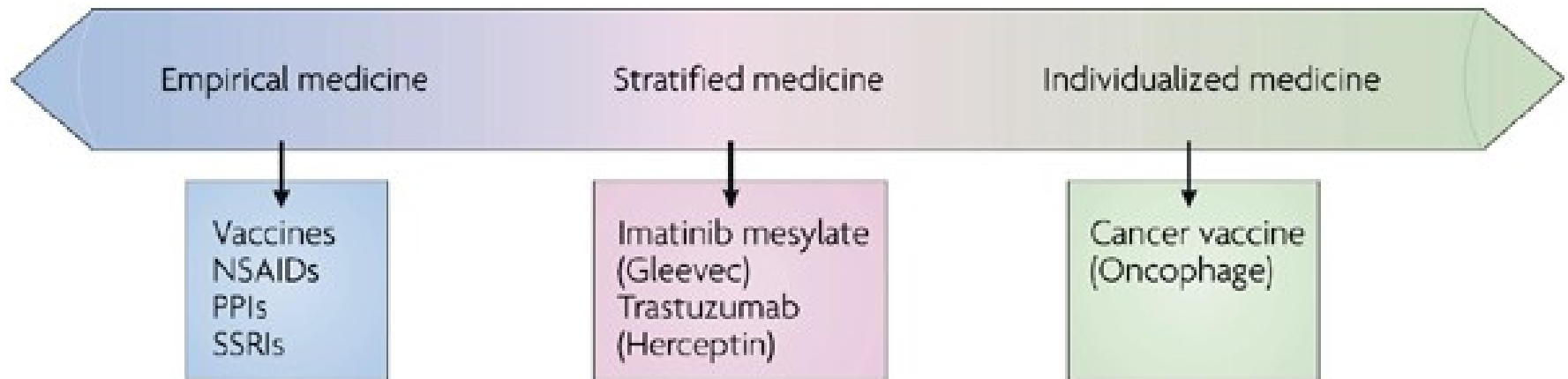
*assess spectrum of patient response to therapy;
stratify patient populations; optimize benefit/risk.*

(e.g. oncology products comprising drug and companion diagnostic)

Stratified Medicine in the Clinical Context



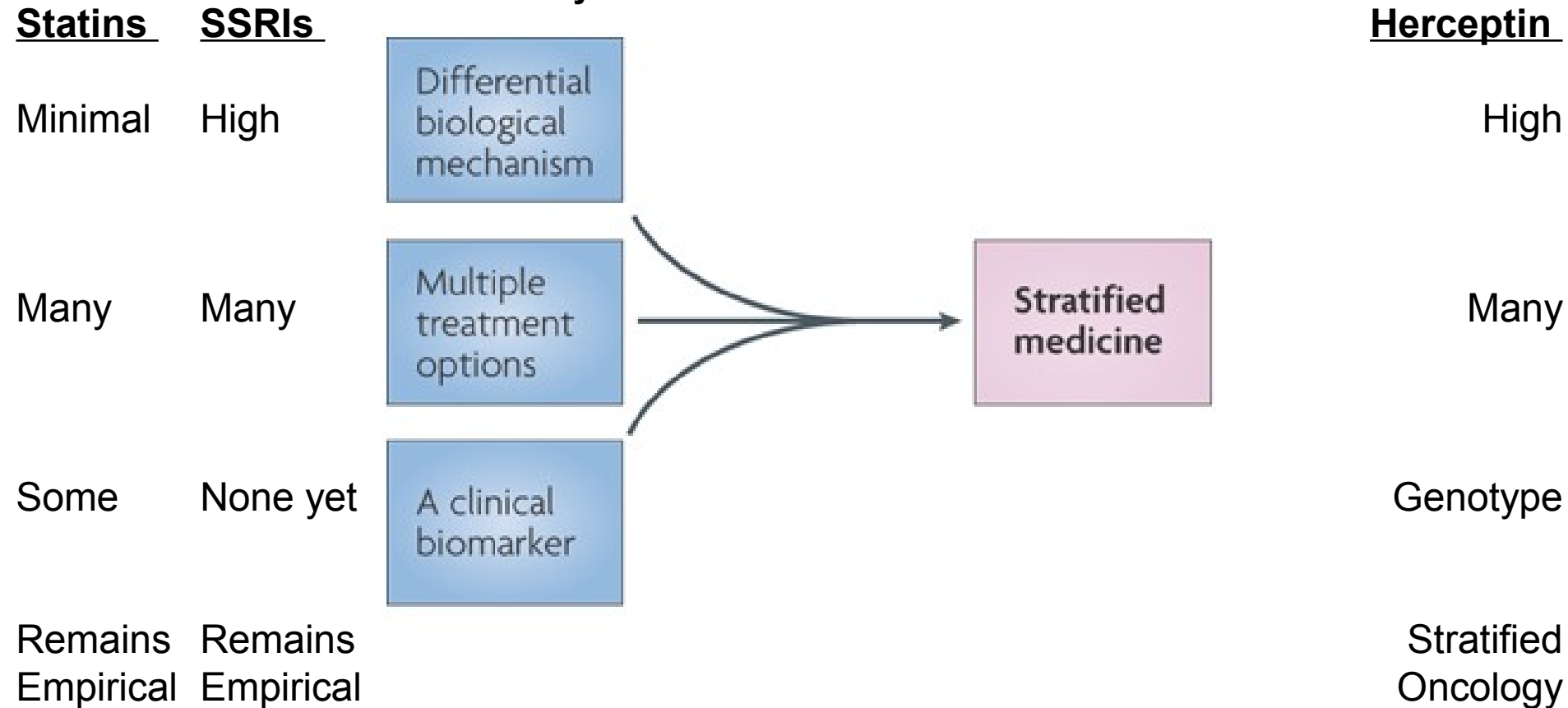
Stratified Medicines, Not Really Personalized



Nature Reviews | Drug Discovery

Why Some Therapeutic Areas Stratify and Others Do Not

Necessary Conditions for Stratified Medicine



Necessary and Sufficient Conditions for Stratified Medicine

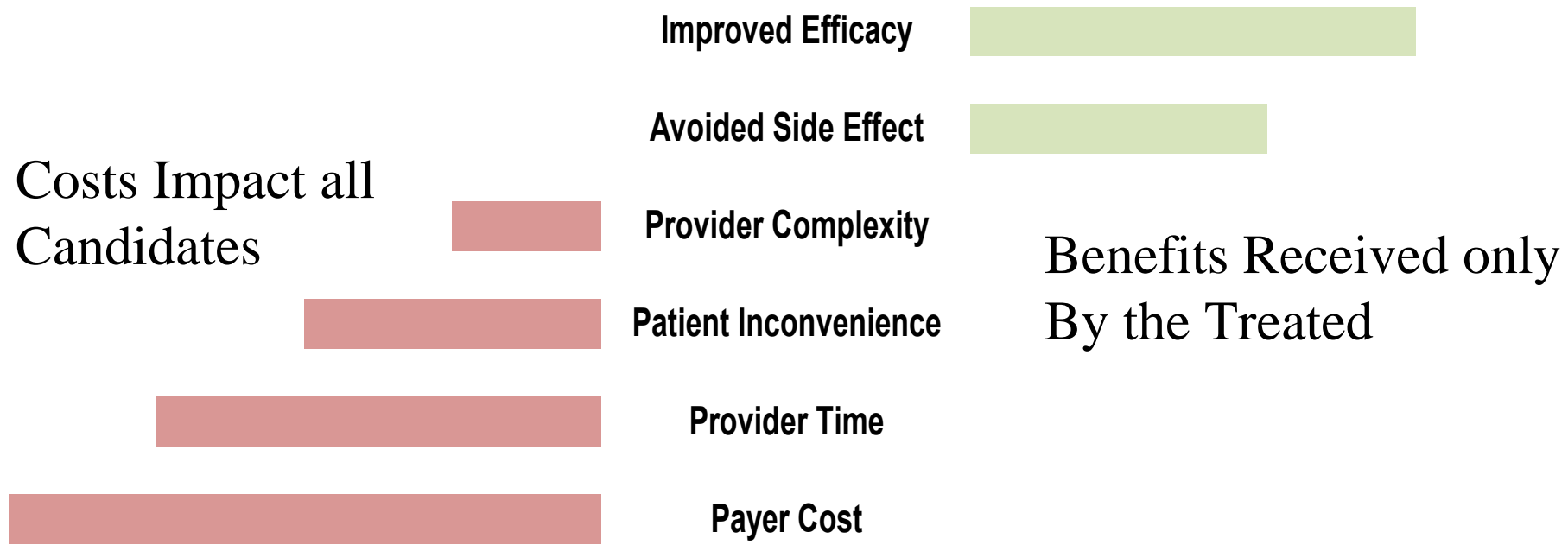
- **Sub-population treatment response is necessary but not sufficient for stratified medicine to emerge**
- **What is also needed is a sustainable, clinically meaningful differential benefit that exceeds the cost of administering the diagnostic clinical biomarker**

Stratification Must Have Clinical Value

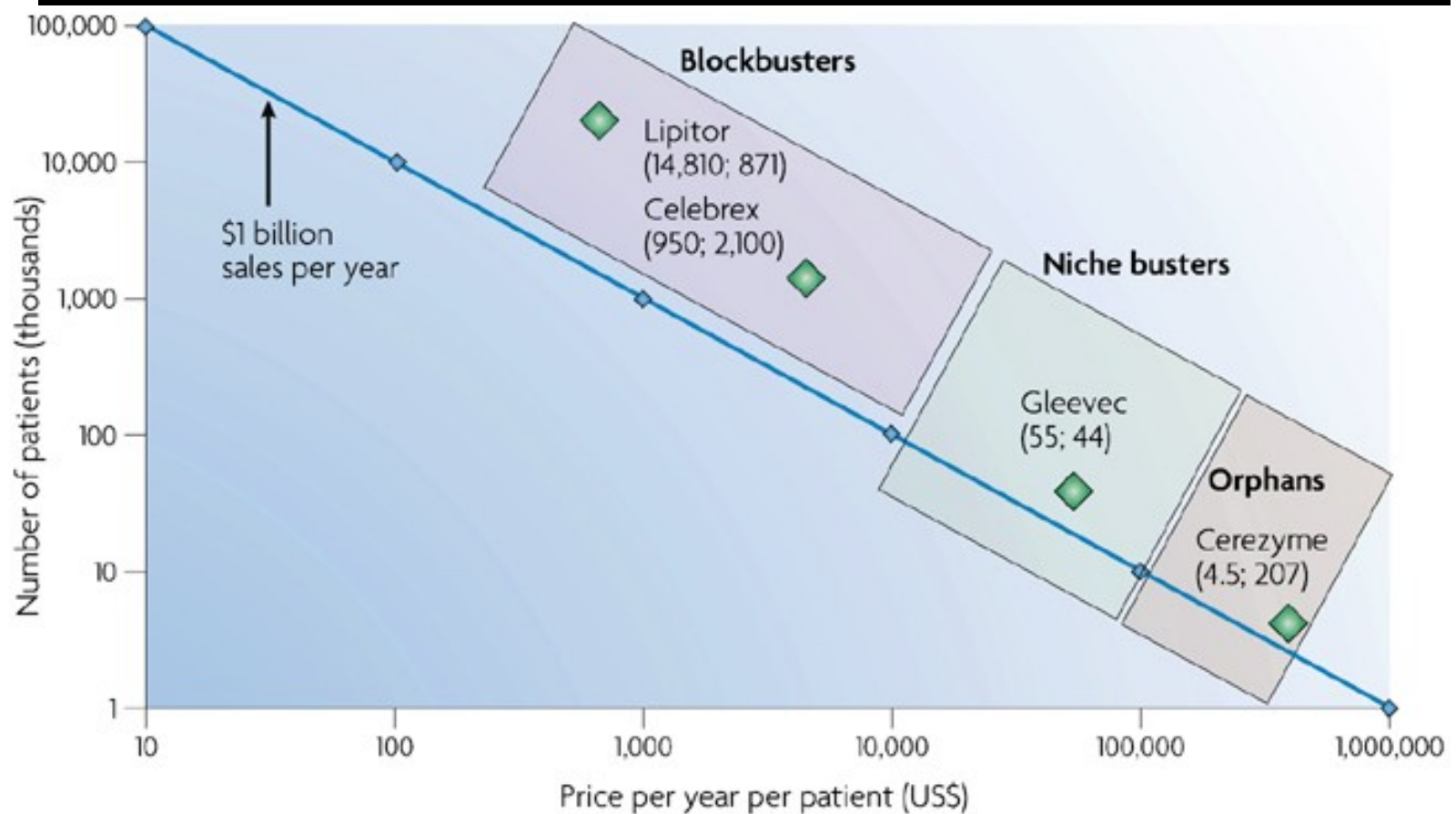
□ Scientific value alone is not sufficient

- Lipid profile differences among patients and varying statin effectiveness among those profiles known for years – BUT THE DIFFERENCES ARE MOSTLY INSIGNIFICANT CLINICALLY

□ Potential clinical benefit must entice behavior change

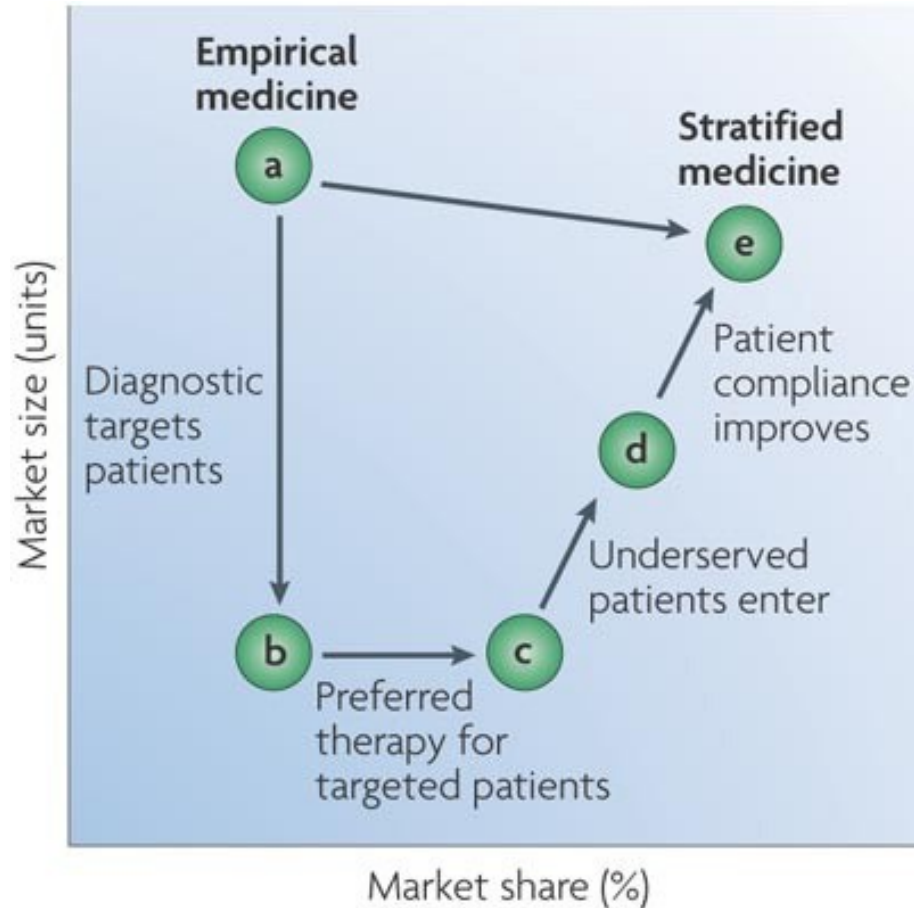


Large Revenues Are Possible



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

The Path to a New Equilibrium



Stratified Medicines: Development Cost Impact

- **Reduced clinical trial sizes, number of trials**
- **Need to develop and validate or “qualify” biomarker**
- **Need to recruit enriched patient pool could entail need for more sites**

Stratified Medicine Impact on Other Stakeholders

- **Regulatory – coordinating approval of the therapy with the biomarker**
- **Payers - Challenges formulary power to limit or prioritize options – premium value of variety**

Three Practical Implementation Criteria



Favorable clinical
positioning & feasibility



Attractive economics
once stratified



A sustainable franchise
against followers

Criterion 1: Clinical Feasibility - Science Necessary but not Sufficient

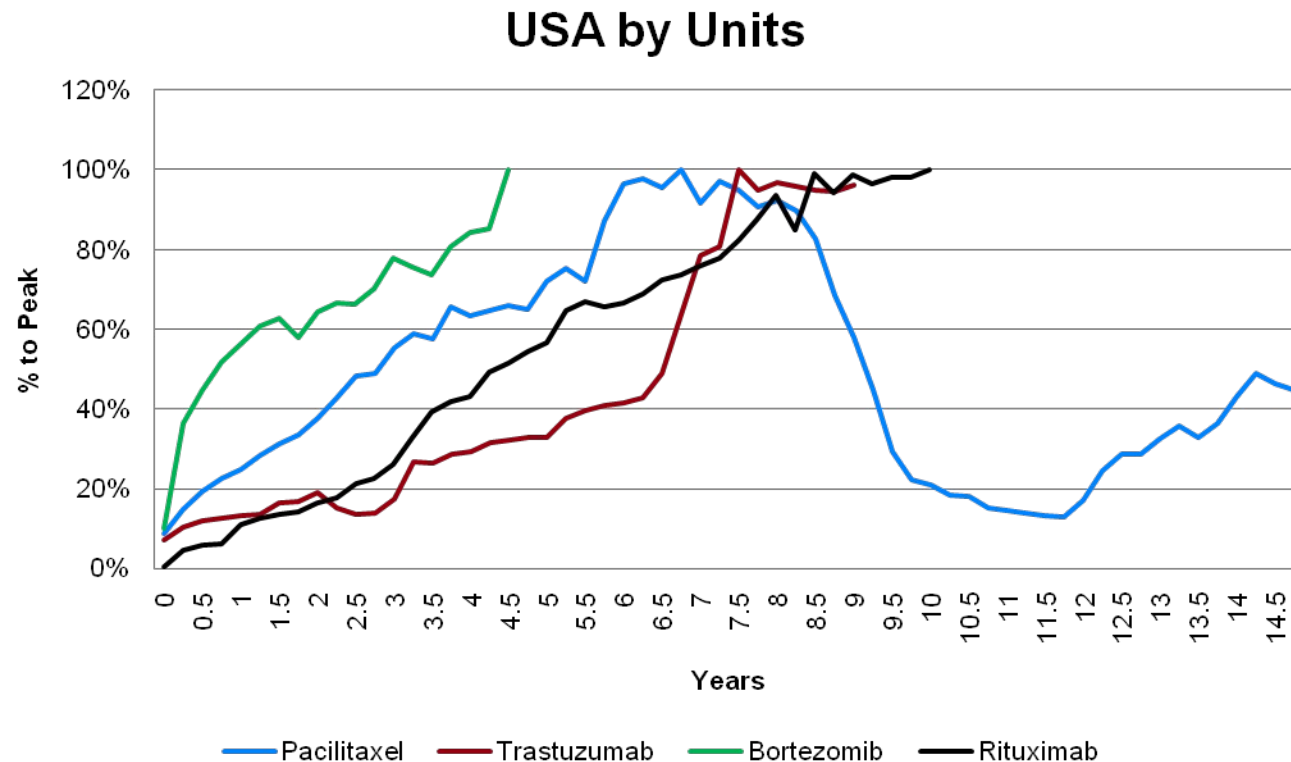


- **Need sufficient scientific evidence for biomarker use**
- + **Therapeutic stratified performance must be substantially superior, not merely “approvable”**
- + **Clinically compatible diagnostic**
 - **Less invasive and costly than treatment**
 - **Sample acquisition ease (observation > swab > urine > blood > tissue)**
- + **Logistically feasible diagnostic**
 - **No -80 degree centigrade storage in outpatient offices**
 - **Test results timely compared to usual clinical decision process**
 - **Appropriate additional patient time, travel and discomfort**

Oncology Adoption Trend Comparison



- Adoption rates for first generation targeted therapies similar to those for a superior cytotoxic therapy



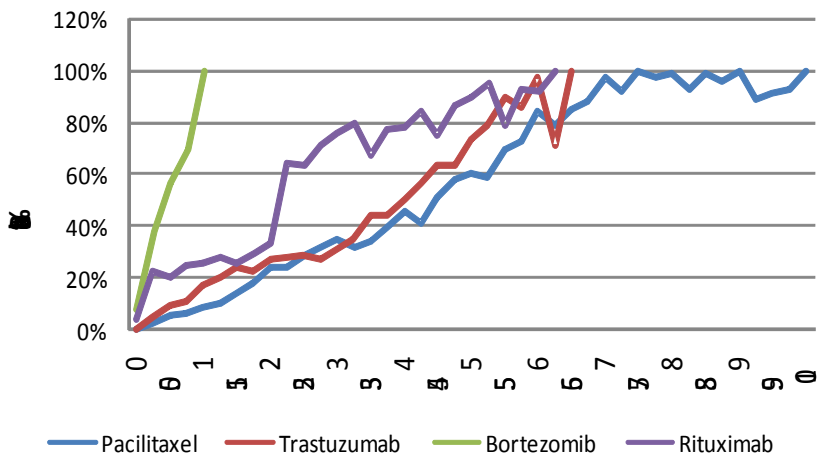
Source: IMS Health, Product-MIDAS, 1993-2007

Japan Shows Somewhat Faster Adoption for Stratified Medicines

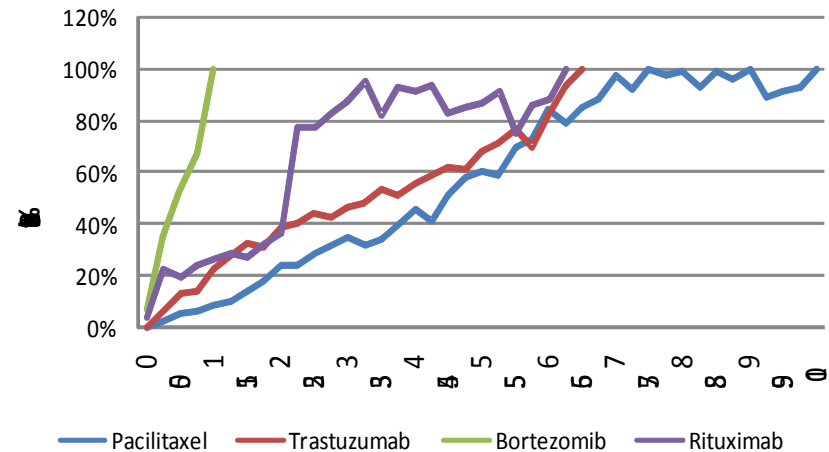


□ But the launch years are somewhat later than in the US

Japan by Units



Japan by Dollars

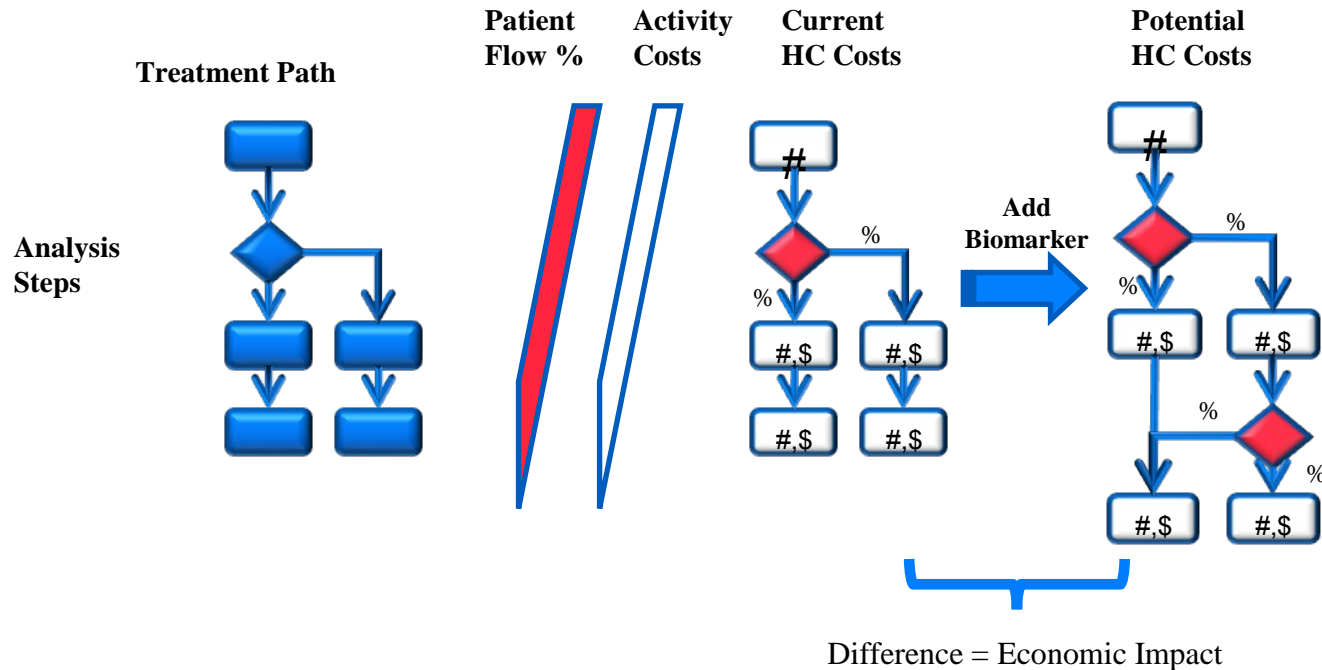


Source: IMS Health, Product-MIDAS, 1993-2007

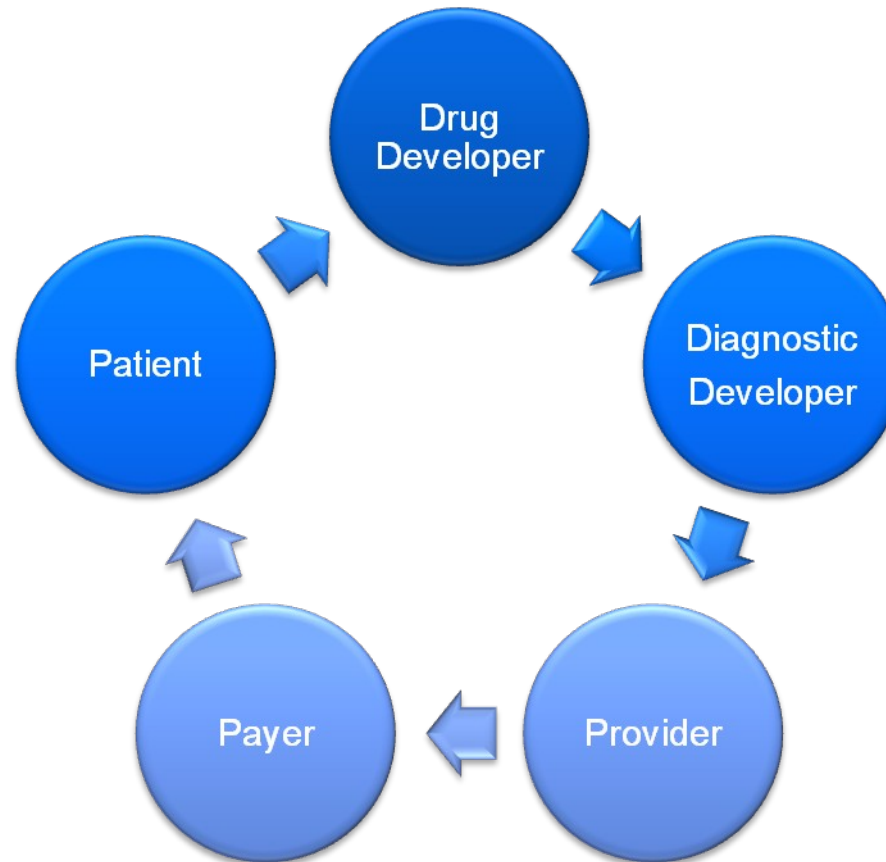
Deepening the Understanding of Adoption: Differential Effectiveness Analysis



- Payer and clinical perspective
- Begin with clinical positioning and patient value rather than scientific possibility alone
- Goal is to provide a tool which naturally incorporates clinical value and payer pay-for-performance perspectives to inform product “target label” objectives and pricing expectations



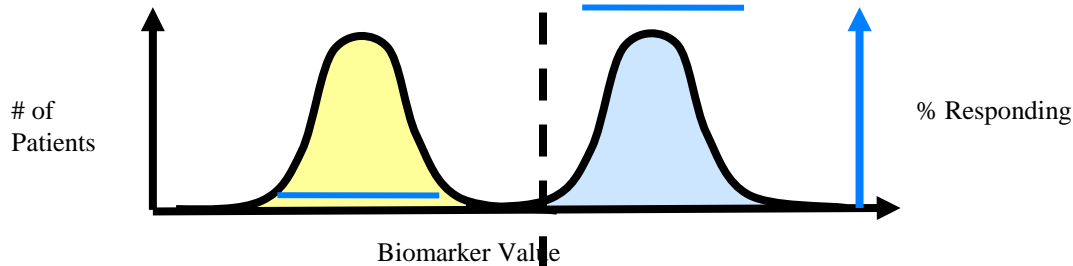
Criterion 2: Attractive Economics – For All Participants



Linking Biomarkers to Markets: Ideal Case

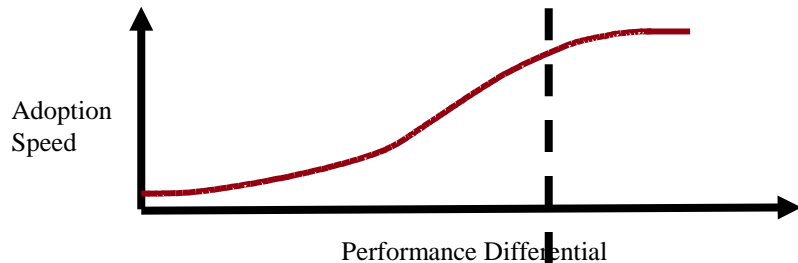


A Biomodal Marker

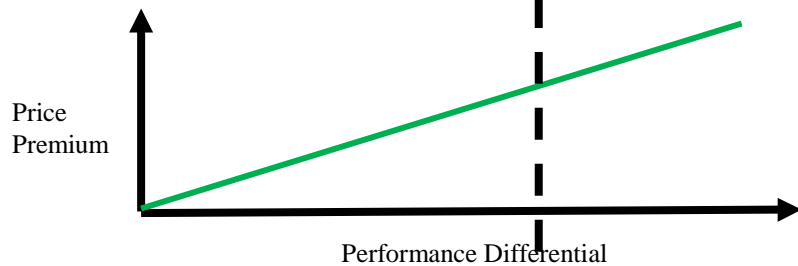
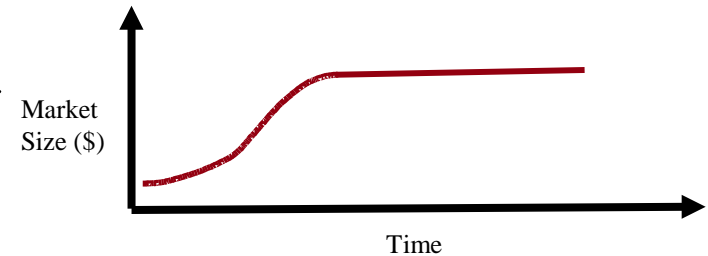


Leads to Rapid
“Niche Buster”

A Superior Drug



Incidence /
Prevalance

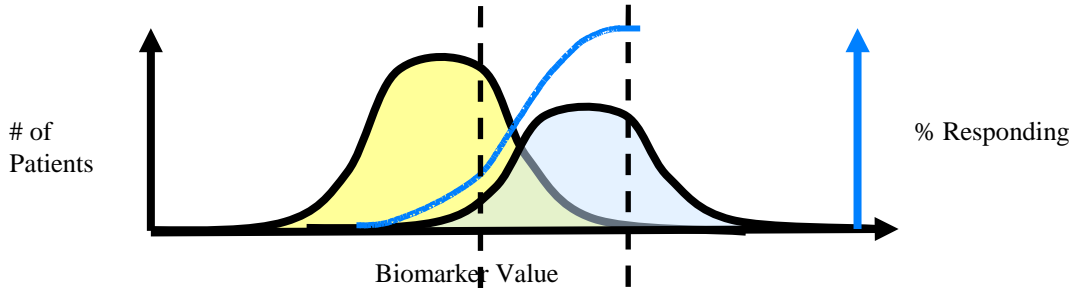


Plus Diagnostics Revenue

Selecting Biomarker Inclusion / Exclusion Criteria Can Prove Complex in Practice

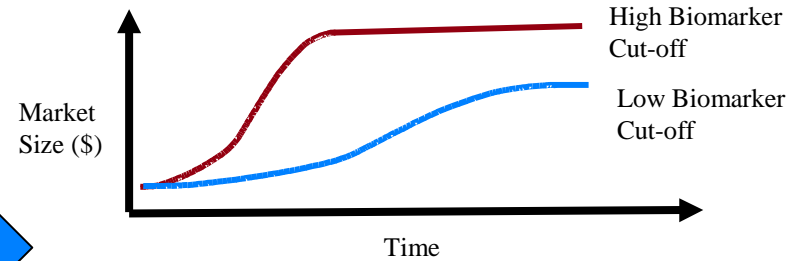


Overlapping Populations

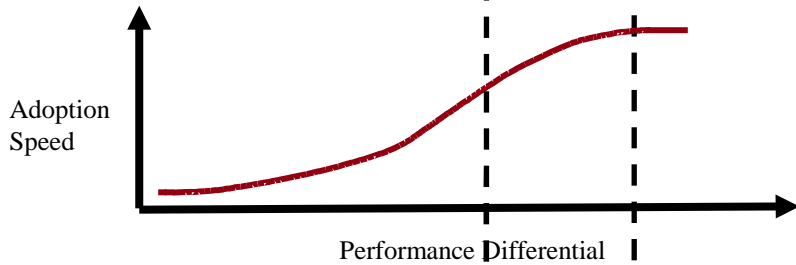


Best Choice is Case Dependent

Case: Larger # of Responders

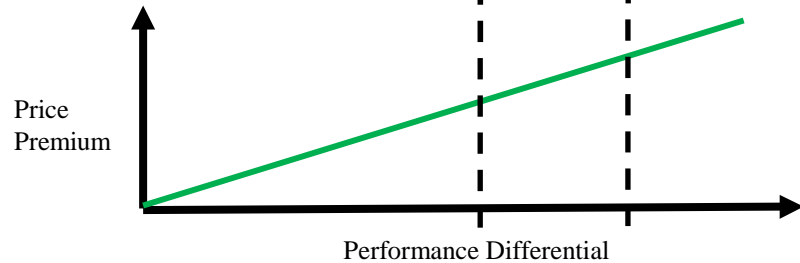
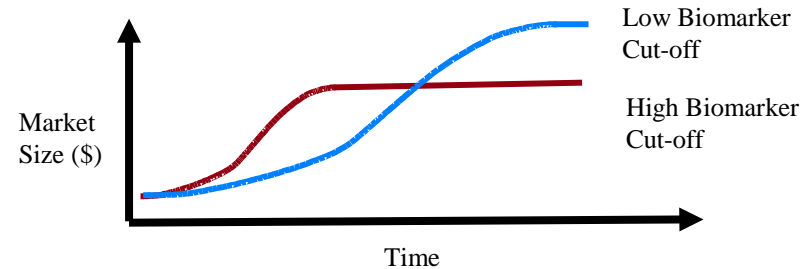


Yields Good to Great Drug



Incidence /
Prevalance

Case: Smaller # of Responders



Herceptin, best of both curves?

Criterion 3: Sustainable Franchise - Anticipate Followers

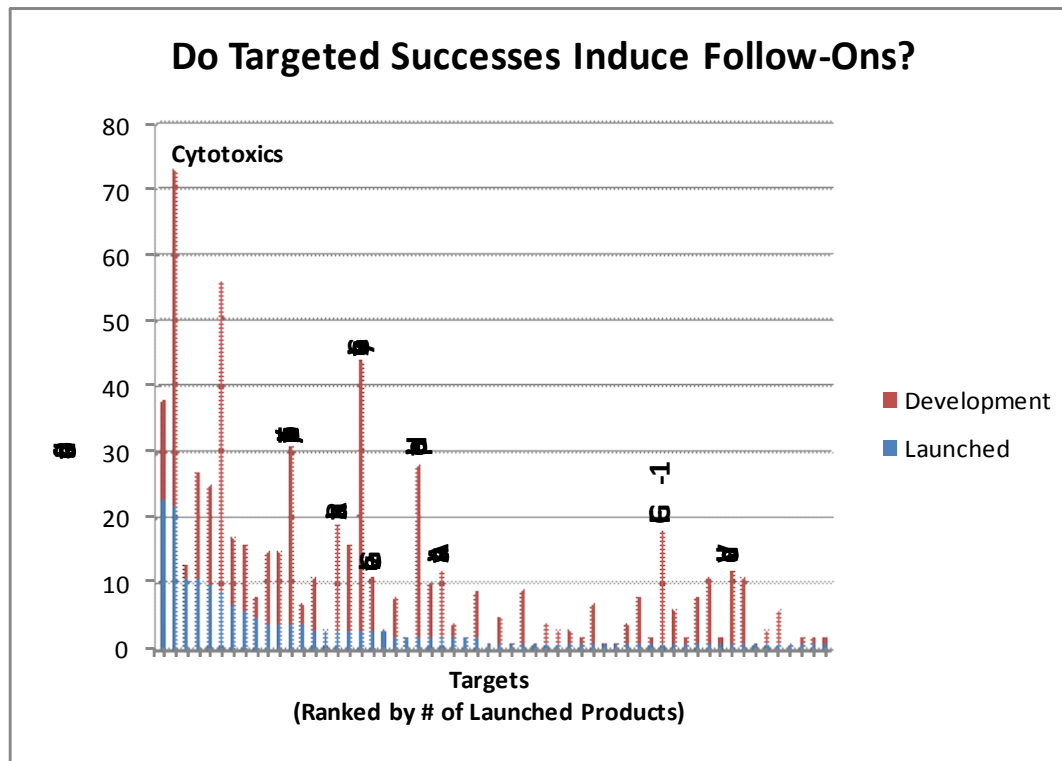


- Followers always seem to arrive
- During development therapeutic performance is often selectable within a range
- Two linked products (treatment and diagnostic) create profit placement choices

Deep Industry Pipelines Behind Launched Stratified Medicines

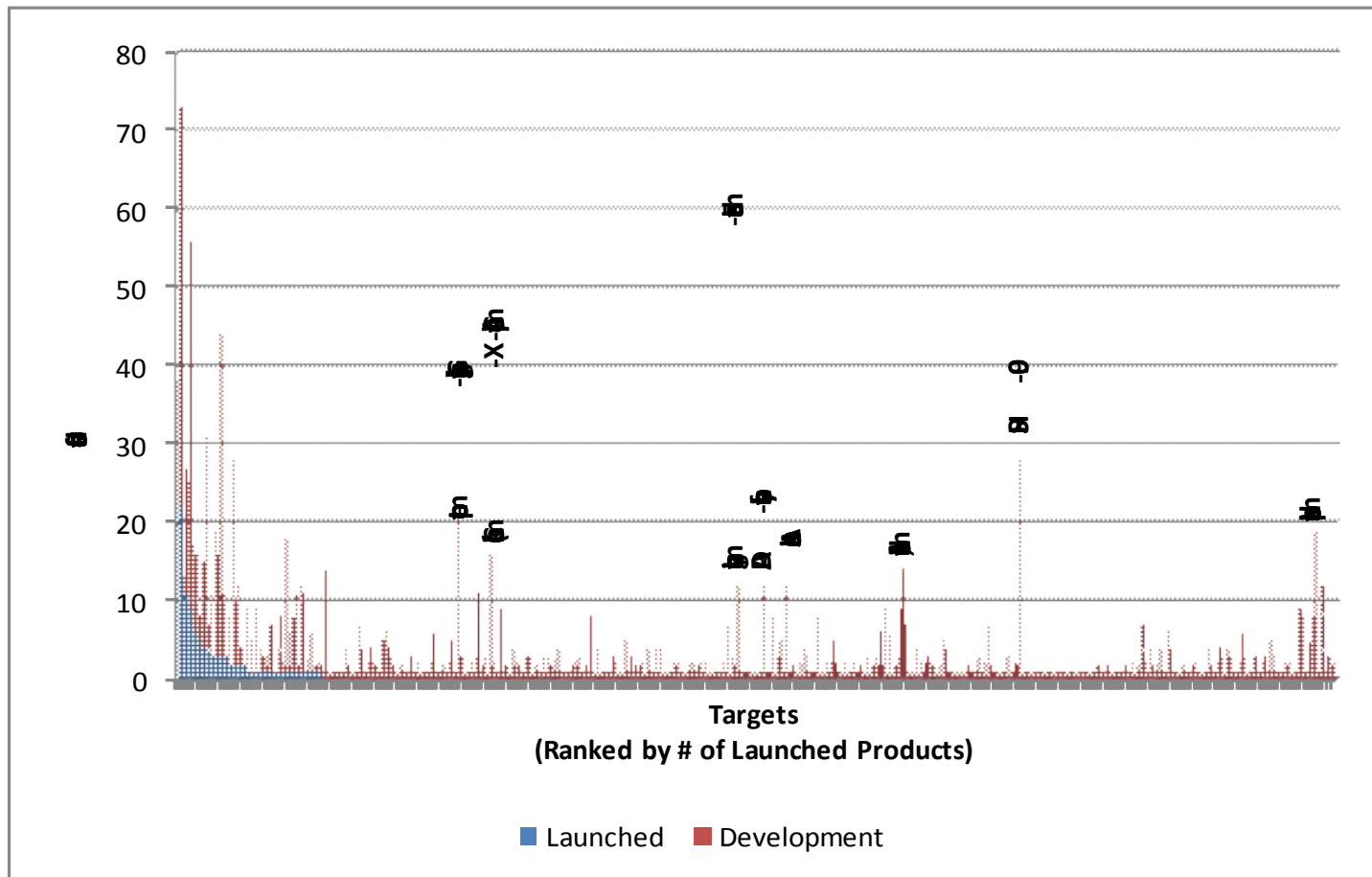


- Traditional follow-on pattern occurring in oncology
- Can smaller niches support a large number of entrants?



PharmaProjects, May 2008. All oncology products and programs with identified mechanisms/targets with that target having at least 1 launched therapeutic

Some Targets with No Launched Products Have over 10 Compounds in Development



PharmaProjects, May 2008. All oncology products and programs with identified mechanisms/targets

And Even Large Players Lack Full Target Coverage or Deep Pipelines for Each Target



Number of Compounds											
Target Family											
Cytokine/Growth factor											3
Cytokine											1
Growth factor											1
Growth factor, non-cytokine											2
(blank)											2
Enzyme	9	4	10	3	6	3	6	3	1		45
Hydroxylase	1	1	1		2						5
Isomerase	2		1		1	2		3			9
Kinase					1						1
Kinase Receptor	2		2	1					1		6
Cytokine receptor	2		2						1		5
Tumour necrosis factor and transforming growth factor family	1										1
(blank)	1		2						1		4
(blank)				1							1
Oxygenase	1		1		2						4
Polymerase	2	1		1					1		5
Protease/peptidase			1						1		3
Synthase			2								2
Transferase	1	2	2	1		1					7
(blank)							3				3
Ion Channel											1
Peptide hormone											3
Receptor	22	14	6	11	7	8	6	8	2		84
Cytokine receptor	7	3	2	5	2			2	1		22
Class I			1	1							2
Class II	2										2
Immunoglobulin family	2	1		1						1	5
Tumor necrosis factor and transforming growth factor family			1	2	1				1		5
Tumour necrosis factor and transforming growth factor family	1			1							2
(blank)	2	2			1				1		6
GPCR		1			3	2					6
5-Hydroxytryptamine						1					1
Cannabinoid						1					1
Endothelin		1									1
Somatostatin					2						2
Somatostation					1						1
Nuclear receptor	1	1	1				1		1		5
Androgen									1		1
Estrogen	1	1					1				3
Retinoic acid			1								1
(blank)	14	9	3	6	2	6	5	5	1		51
Transporter	1										1
Porters (uni-, sym- and anti-)	1										1
(blank)	7	9	8	3	13	9	5	6	1		61
Unspecified	6	11	11	8	3	10	13	8	1		71
Not applicable			1		2	1					4
Grand Total	46	38	38	26	32	32	31	25	5		273

PharmaProjects, May 2008. All oncology products and programs . Note that data does account for latest acquisitions by Pfizer and does not fully account for compounds with joint rights among two or more partners.



Manage Two Linked Product Lifecycles: Not Just the Therapeutic



□ Biomarker/diagnostic a 'gate' through which patients flow

- If poorly distributed initially-can slow adoption by poor access
- If priced high initially-can slow adoption by discouraging use

□ Profit placement strategic choice

- Classic: Most profit in therapeutic
- Nouvelle: Shift profit to proprietary diagnostic-especially if lower priced therapeutic and diagnostic monitors treatment



Stratified Medicine and Pay for Performance: A Faustian Bargain?

- **The great appeal of pay for performance and stratified medicine: Only pay for those treatments that work in the specific patient**
 - **Places risk on the manufacturer**
 - **Provides access to candidate patients**
 - **Restrains costs for governments/payers**
 - **But....**

Downside of Stratified Medicine and Pay for Performance

- **The potential great social compact change: Will manufacturers find themselves incented to manage medicine?**
- **Payers and manufacturers must track (or be told) patient outcomes**
 - **In managing these new risks, manufacturers may need to:**
 - **Audit physician practices to preserve margins, or perhaps even their economic survival**
 - **Find themselves dictating medical criteria under which physicians may prescribe their products**

Final Thoughts on Stratified Medicine

- Exciting science, significant development and regulatory challenges, and novel commercial opportunities – all great topics for pharmaceutical policy researchers!
- Thank you!