Economic Incentives for Genetic and Genomic Strategies: Stratified Medicines

PRESENTATION AT IOM WORKSHOP

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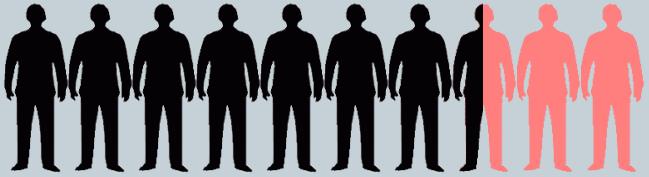
Potential & Current Impact

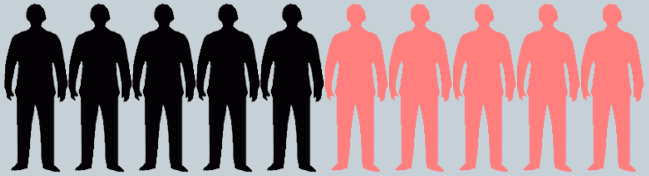
Major Drugs Ineffective for Many

Hypertension Drugs 10-30%
ACE Inhibitors

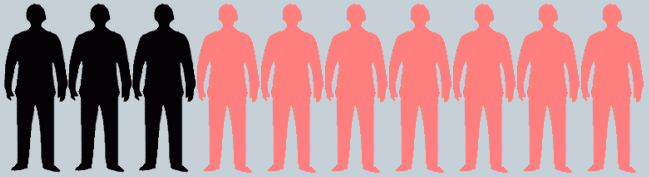
Heart Failure Drugs 15-25%
Beta Blockers



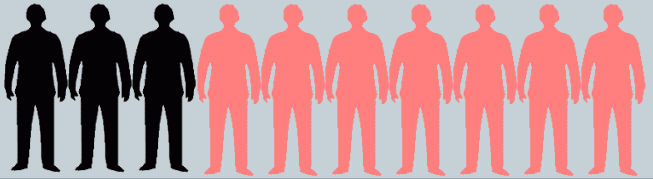
Anti Depressants 20-50%
SSRIs



Cholesterol Drugs 30-70%
Statins



Asthma Drugs 40-70%
Beta-2-agonists

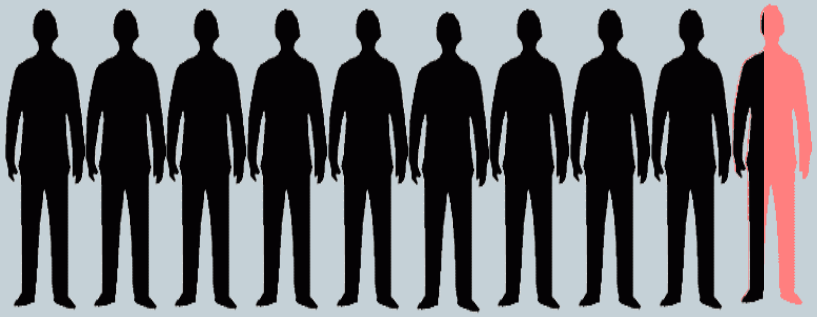


Source: Abrahms Presentation of Spear B, Heath-Chiozzi M, Huff J Clinical Trends Molecular Medicine 2001; 7(5):201-4.

Ineffective Therapies Can Cause Harm

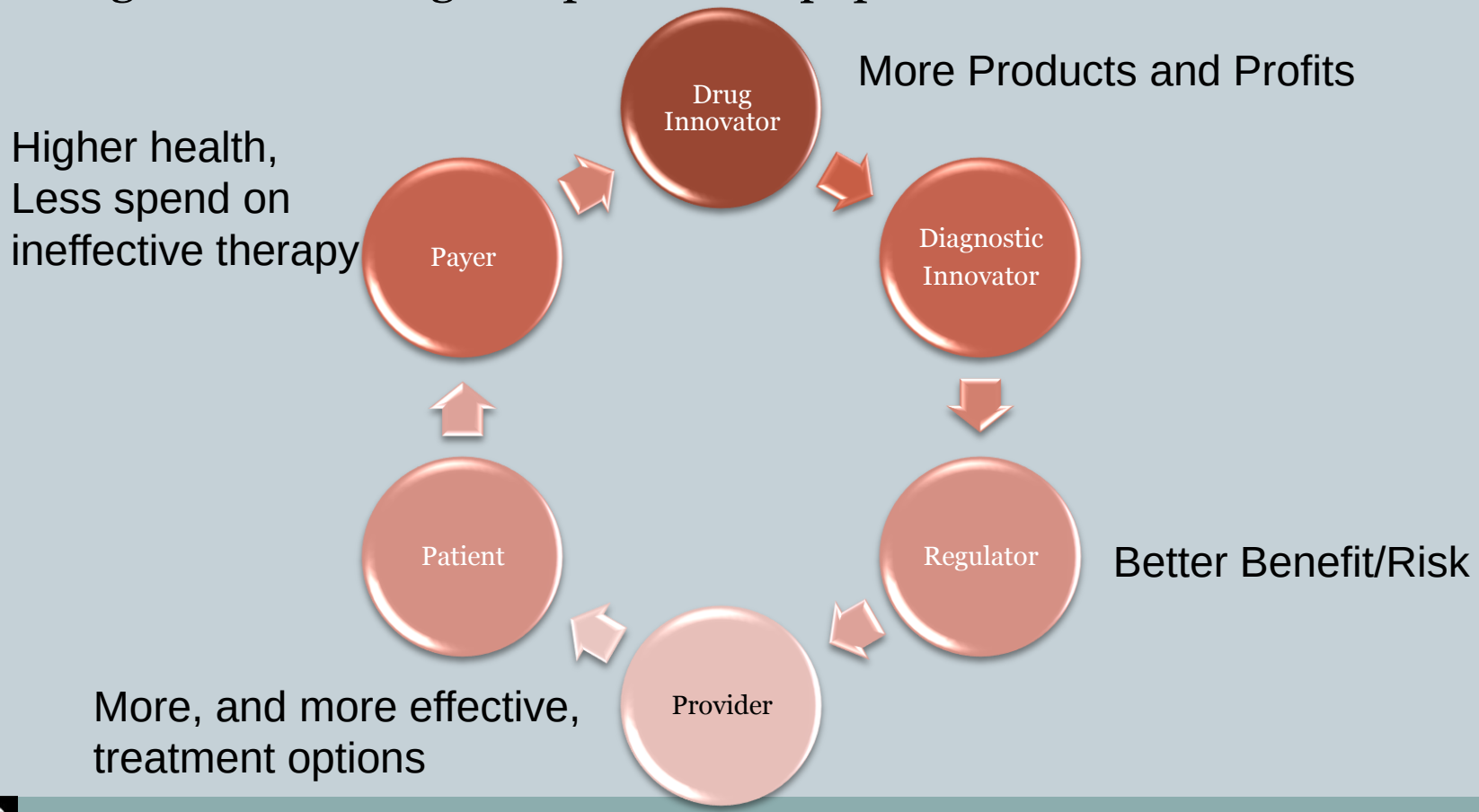
Adverse Events

- Estimated 100,000 deaths per year (in 1994; Lazarou et al 1998)
- 6th leading cause of death in the US
- Experienced by approximately 7% of patients (2.2 million) per year
- Medication-related health problems account for an estimated 3% to 7% of hospital admissions (Pirmohamed M, et al 2004)
- During their hospital stay, 15% of patients experienced adverse drug reactions (Davies, et al 2009)
- Increased patient non-compliance

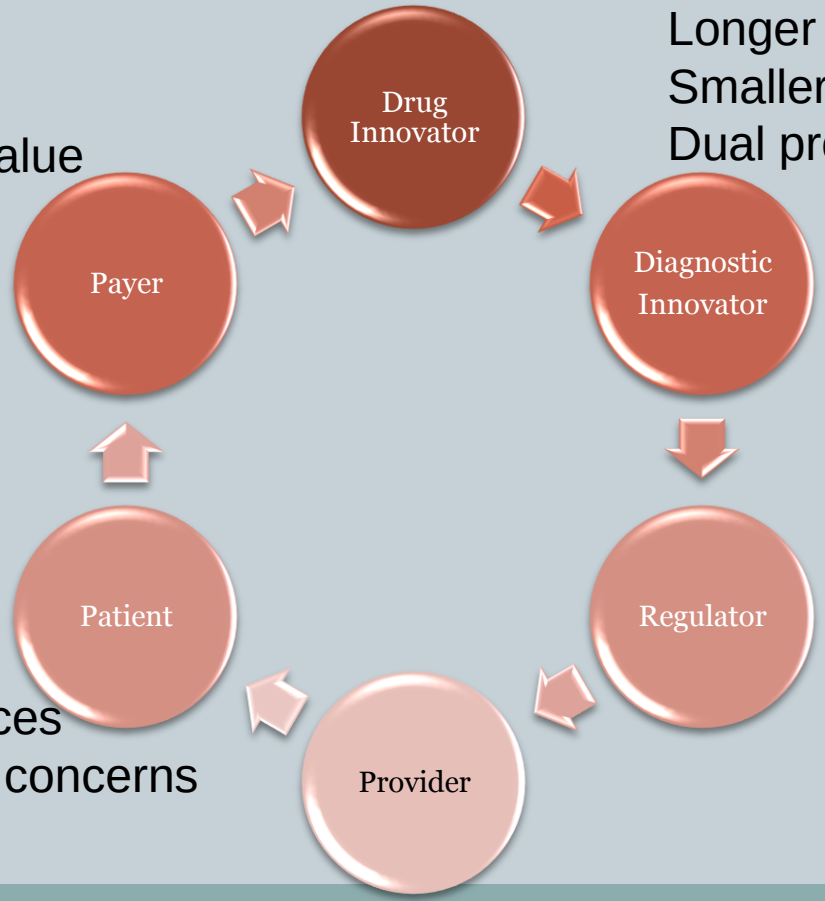


Stratified Medicine Provides Opportunities for All Participants

- Stratified Medicine: A therapeutic combined with a companion diagnostic that targets a patient subpopulation for treatment.



Stratified Medicine Provides Challenges for All Participants



Longer dual development,
Smaller markets,
Dual product risk

Dual approvals
Evidence standards
Workload

More confusing choices
Cost/reimbursement concerns

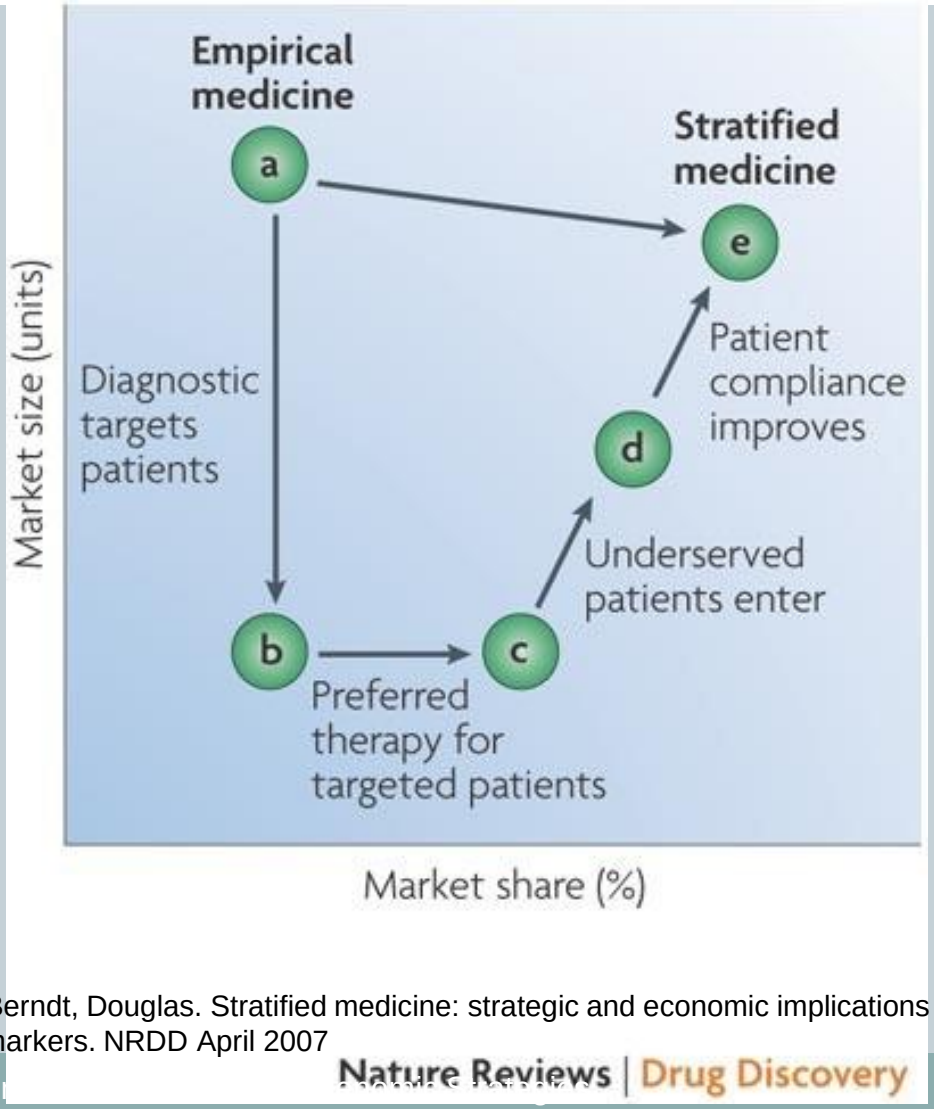
Unclear benefit & value
Higher spending

Examples of Positive and Negative Economic Impacts

- Positive Prospectively Stratified Medicines:
  Xalkori/ALK-EML4 Fusion, BRAF inhibitors, HER2
- Positive Diagnostics:
  OncotypeDx Value to payers, patients, less clear to company
- Mixed Impact:
  - Retrospectively Stratified EGFR inhibitors: Value to provider/payer, likely negative to developer
  - Retrospective dose optimization: Warfarin
- Failure to Find:
  Avastin, 100+ candidate stratifiers, none demonstrated so far

Economic Incentive Dynamics

Recognize the Market Size Dynamics

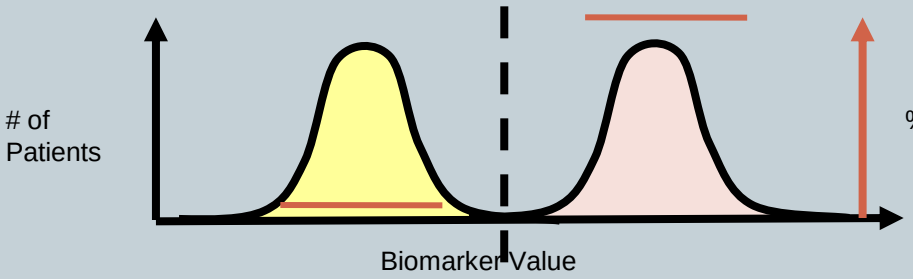


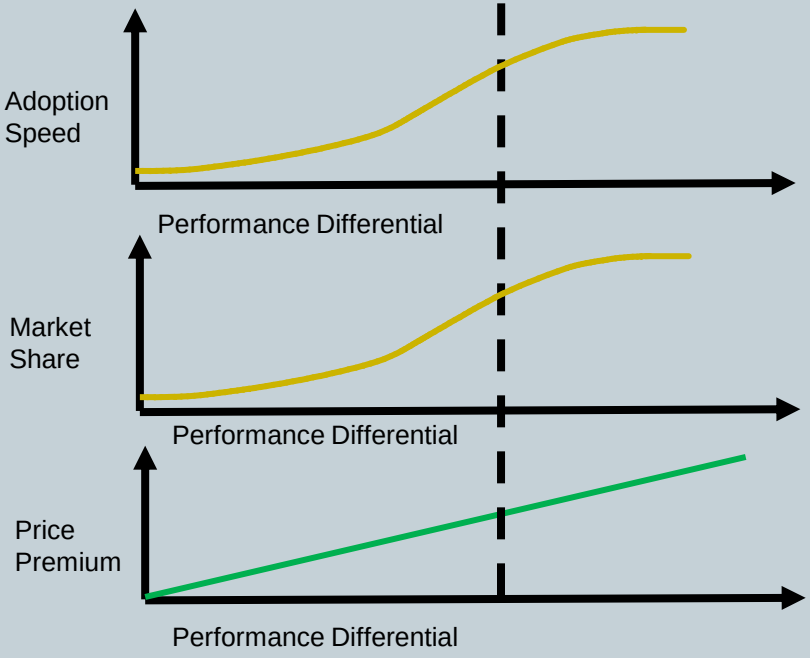
Trusheim, Berndt, Douglas. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. NRDD April 2007

Nature Reviews | Drug Discovery

Linking Biomarkers to Markets: Ideal Case

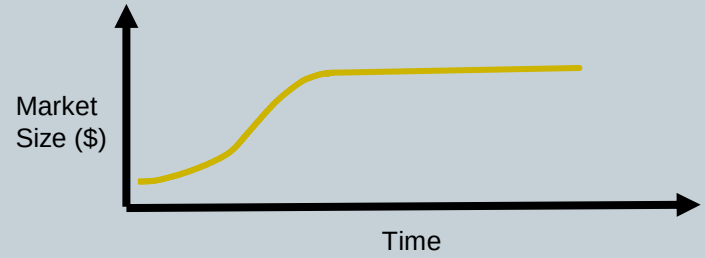
A Biomodal Marker





Incidence / Prevelance

Leads to Rapid "Niche Buster"

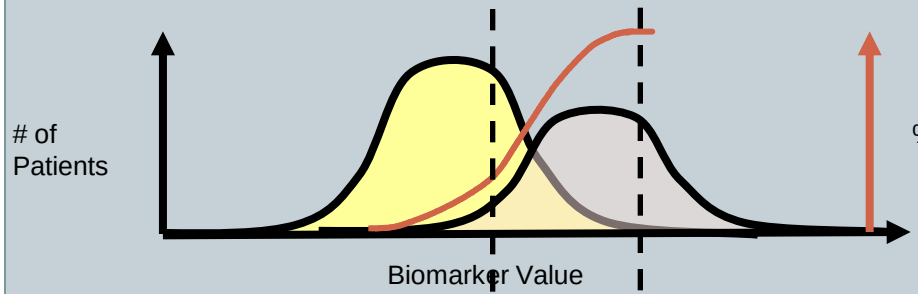


Plus Diagnostics Revenue

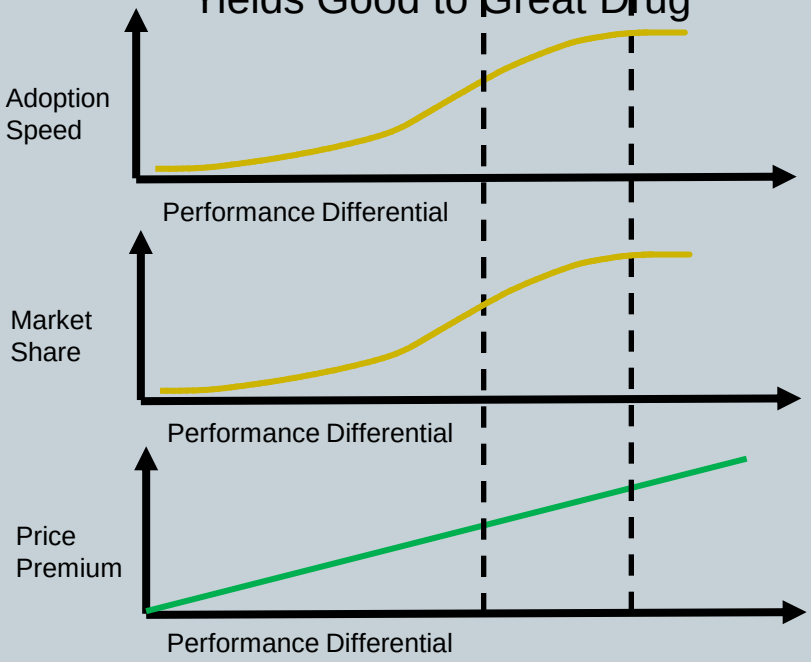
Critical relationship:
Clinical performance drives commercial performance

Ambiguous Biomarker Threshold Introduces Incentive Uncertainties

Overlapping Populations



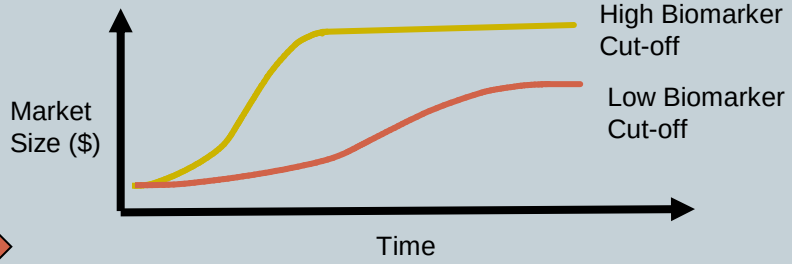
Yields Good to Great Drug



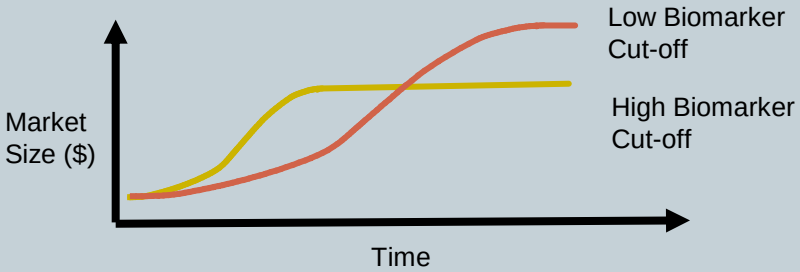
Incidence / Prevalence

Economic Choice is Case Dependent

Case: Larger # of Responders



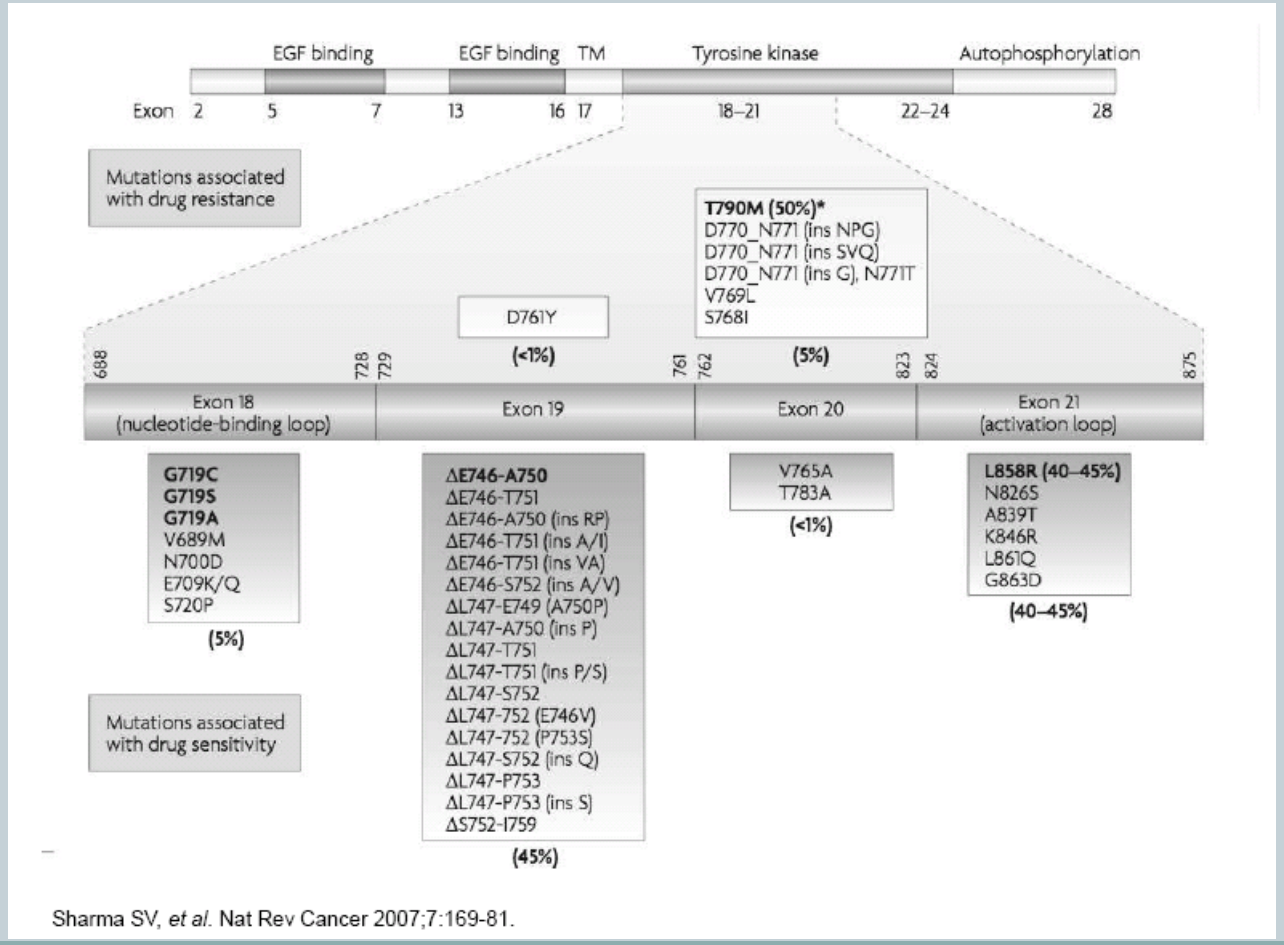
Case: Smaller # of Responders



Herceptin, switching curves?
New life cycle mgmt approach?

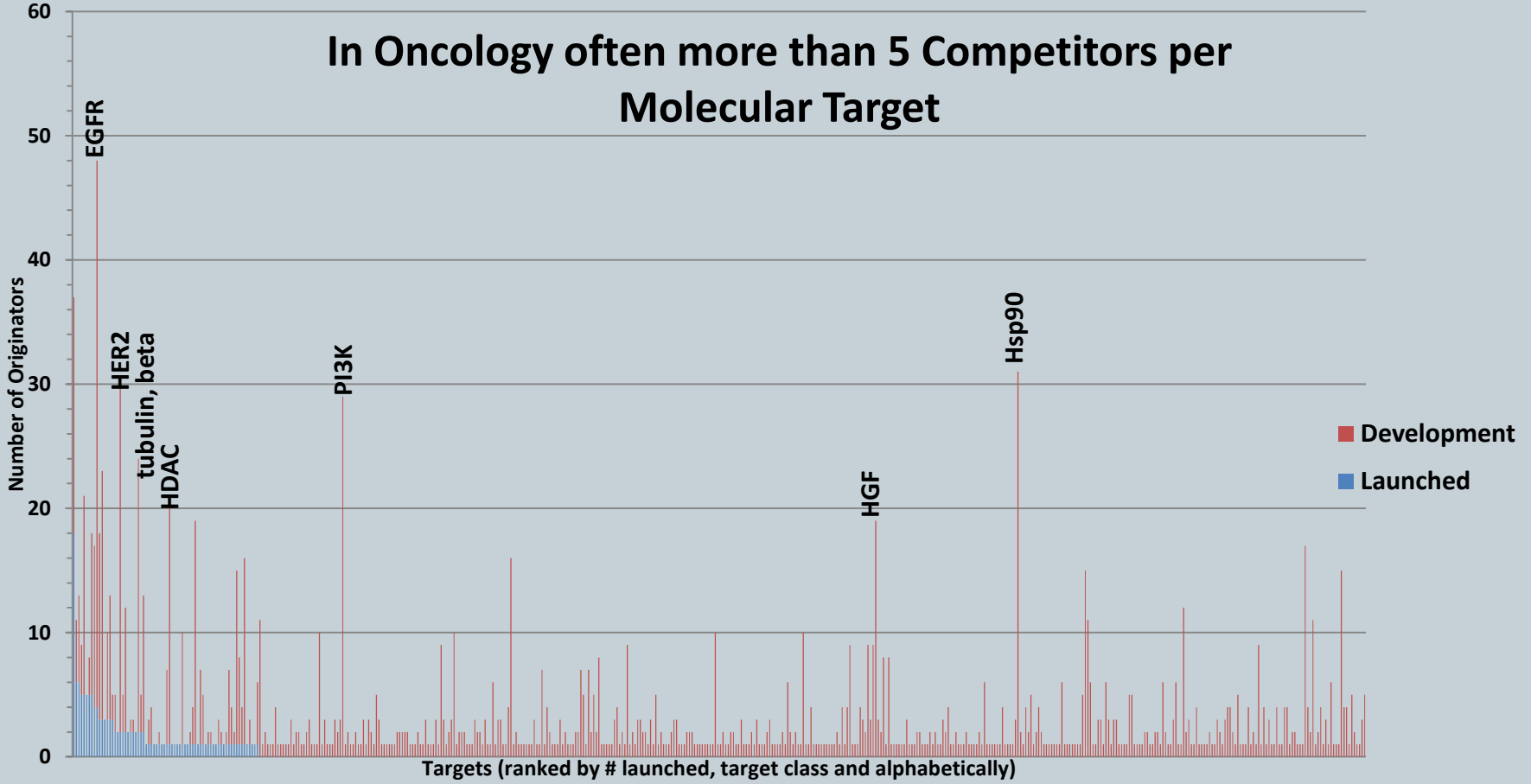
Even Genetic Markers Provide Biomarker Threshold Flexibility

- Many alternative mutations usually exist: EGFR



Sharma SV, *et al.* Nat Rev Cancer 2007;7:169-81.

Stratified Medicines Face Competition even in Small Markets – Monopolistic Power Unlikely



Source: PharmaProjects, June 2010. All oncology products and programs with identified mechanisms/targets

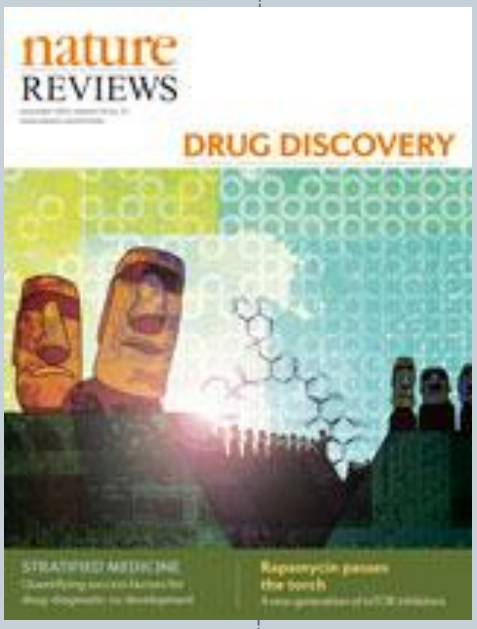
Stratified Medicines: Development Cost Impact

- Benefit: Reduced clinical trial sizes & number of trials, but may be off-set by safety database requirements and biomarker negative studies
- Cost: Need to discover, develop and validate biomarker into a companion diagnostic
- Cost: Need to recruit enriched patient pool could entail need for more sites

Examples of Quantifying Positive and Negative Impacts

Thanks to Consortium Collaborators & Colleagues

- A wide range of organizations
  - Adaptive Pharmacogenomics
  - Bristol-Myers Squibb
  - CMS
  - Eli Lilly and Company
  - FDA
  - Genzyme
  - Glaxo SmithKline
  - IMS Health
  - Merck
  - MIT
  - Monogram Biosciences
  - Novartis
  - Roche
  - Van Andel Research Institute



Analysis feature

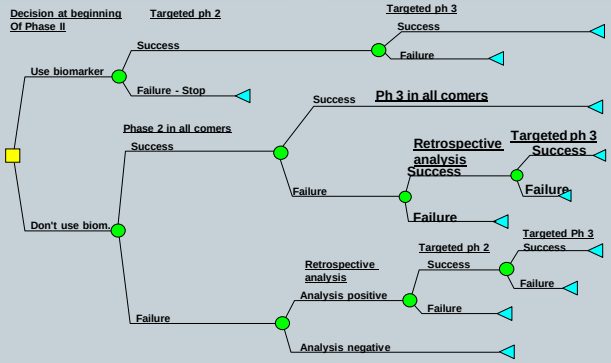
Quantifying factors for the success of stratified medicine

November 2011

- And MIT Colleagues
  - Ernst Berndt
  - Fiona Murray
  - Scott Stern
  - Adrian Bignami
  - Amir Goren
  - Lindsay Johnson
  - Brian Newkirk
  - Samir Sabir
  - Joe Sterk
  - Anushree Subramaniam
  - Heather Vitale

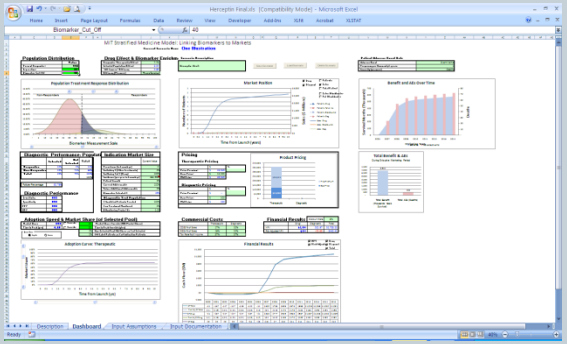
Effort Linked Multiple Tools to Quantitatively Analyze Incentives

Phase II → Phase III → Regulatory → Clinical → Commercial/ Reimburse

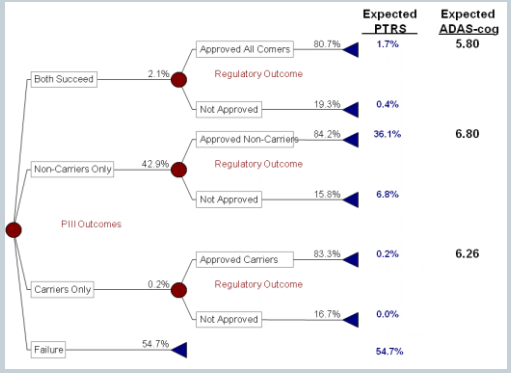


Clinical Design and Simulation models

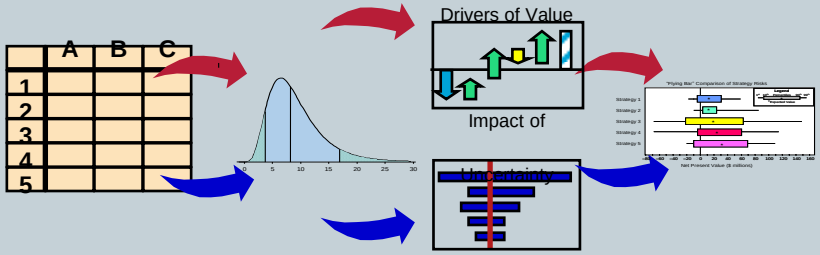
MIT Stratified Medicine Model



PCSD



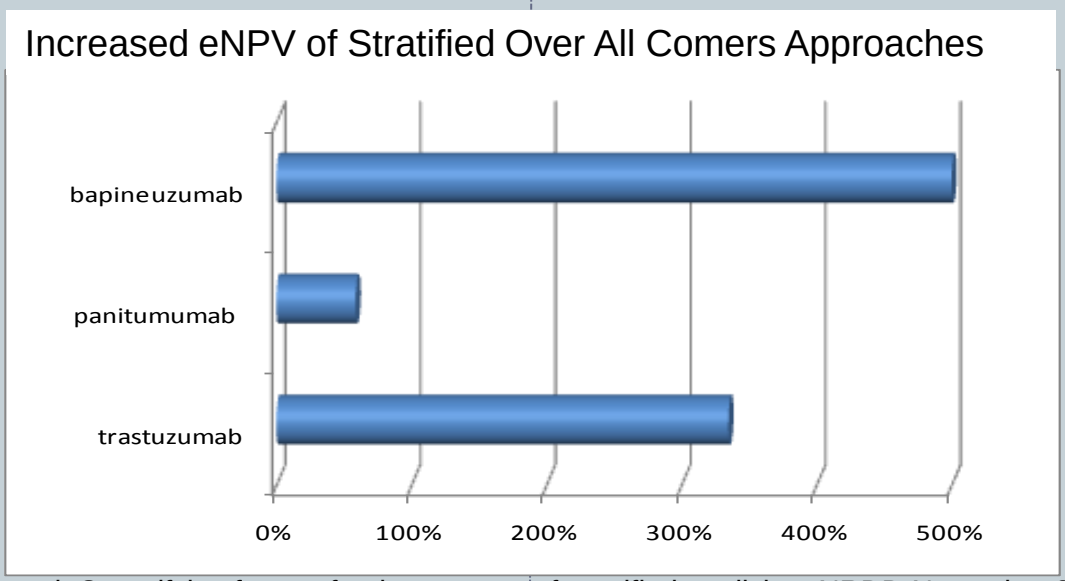
IMS Health Personalized Medicine Strategy Analysis Tool



Stratified Approach Proved Superior in All Cases

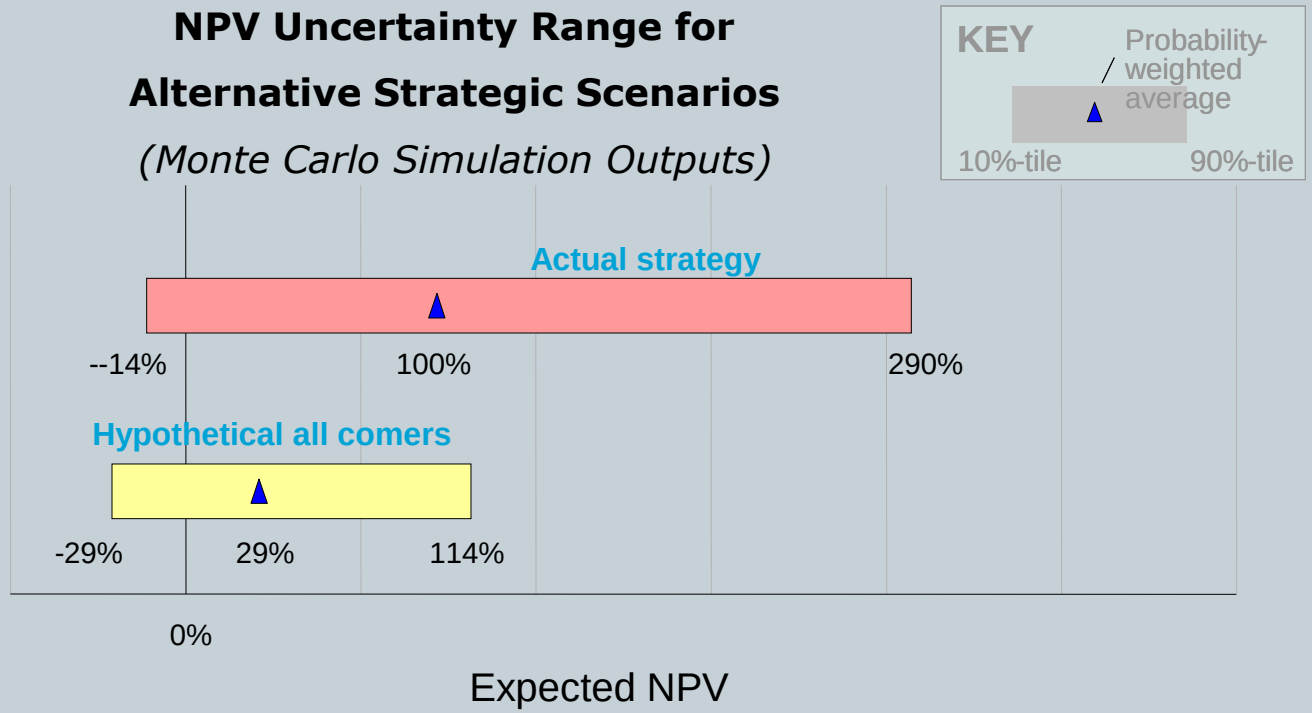
- Oncology
  - Trastuzumab (Herceptin)
  - Panitumumab (Vectibix)
- Alzheimer's Disease
  - Bapineuzumab

- Focus
  - Phase II – therapeutic exclusivity expiry
  - First in class, first indication, first region



Trusheim et al. Quantifying factors for the success of stratified medicine. NRDD November 2011

With all uncertainties factored in by the IMS tool, the biomarker strategy dominates all-comers for Herceptin



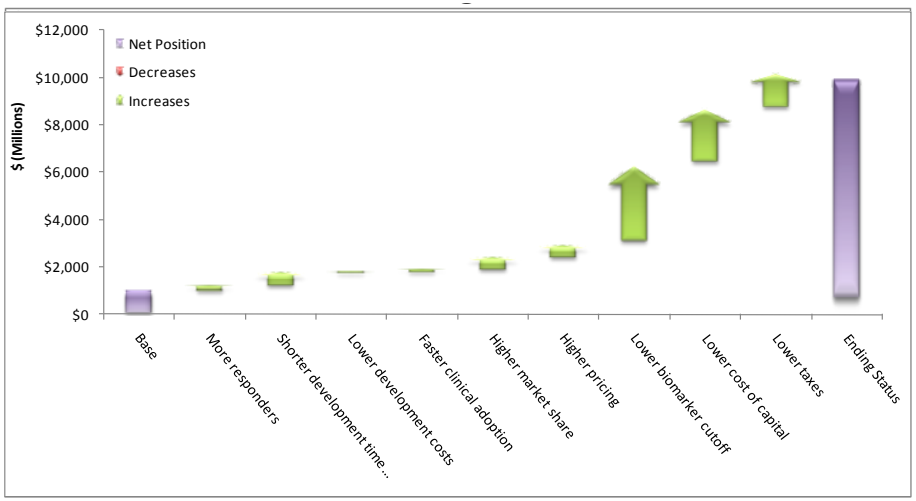
Adapted from Trusheim et al. Quantifying factors for the success of stratified medicine. NRDD November 2011

Landscape & Opportunities in Next 5 Years: Economic Forces at Play

Alternative Future Worlds
Moving Beyond Sensitivity Scenarios

- In Personalized Medicine Development, the factors are not just additive, but multiplicative
- $1B NPV stratified medicine example
- 9 factors +/- 25% from development time to clinical adoption speed to market share

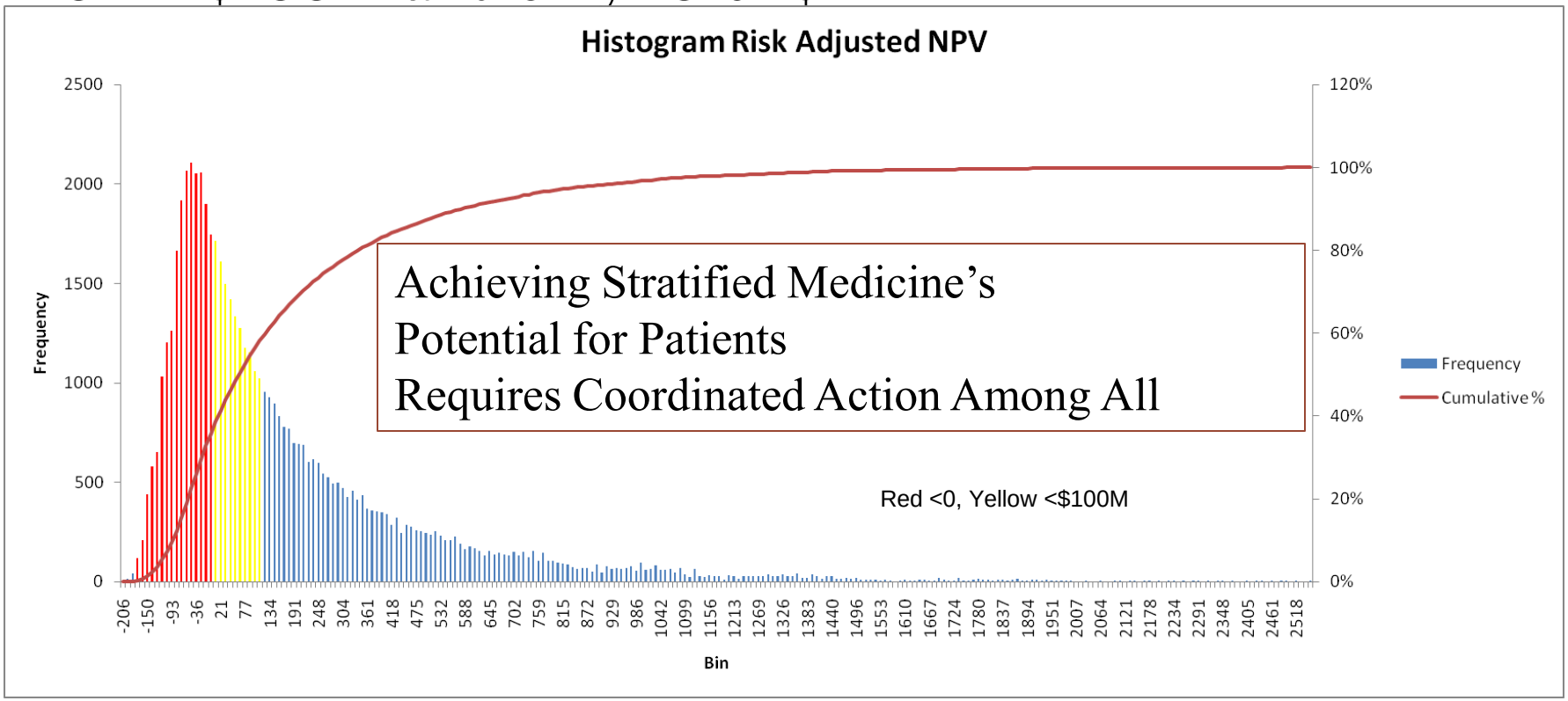
Nirvana



Adapted from Trusheim et al. Quantifying factors for the success of stratified medicine. NRDD November 2011

More Poor Futures than Rich Futures

- >500,000 potential futures exist by combining 12 factors
- 36% of cases are negative risk adjusted NPV, 21 % 0<x<$100M and only 10%>$1B



Adapted from Trusheim et al. Quantifying factors for the success of stratified medicine. NRDD November 2011

Increasing Pressures on Economic Incentives Moving towards Pharmageddon Scenarios

Regulatory
CLIA lab restriction
Multi-variate test guidance
Rejection of retrospective data

Product Exclusivity
Biosimilar 7-12 year period
Diag Patent restrictions
Unclear Orphan designation

Drug Reimbursement
Asymmetric post-launch adjustment
4th Tier formulary

Provider Adoption
Poor Adherence to EBM
Restricted product education/detailing

Diagnostic Reimbursement
Remains 'cost plus' rather than value
No payer investment in R&D

Academic Research Standard Assymetry
New biomarker claims often statistically underpowered
Retrospective, Meta analysis not confirmed prospectively (KRAS)

Possible Incentive Actions: Other than Price

Traditional Tools

- Faster to market (Accelerated approval)
- Patent extensions (Pediatric)
- Exclusivity periods (Orphan)
- Guaranteed market (Advance Purchase Agreements)
- Subsidized development (R&D Tax Credit, SBIR Grants)
- Direct gov't development (NIH biomarkers, DOD defense program procurement, NASA)

New Tools

- Sub-populations designated as qualified 'Orphan' conditions
- Contingent, staged early regulatory approvals
- Automatic reimbursement for defined time period
- Accept advanced trial designs

Conclusion

- **Opposing Forces:** Increasing power of platforms & increasing genomic potential opposed by increasing evidence standards, lower economic returns, higher privacy and sample access hurdles
- **Constrained Funding:** private sector funding constrained by investor returns and constrained public sector funding due to fiscal deficits & constrained foundation/philanthropic funding due to low endowment returns and difficult fund raising environment
- **Incentives Trending Downward:** Incentives high in principle but being lowered by local optimization by stakeholders