Challenges in Developing and Disseminating Stratified Medicines: Observations and Policy Options

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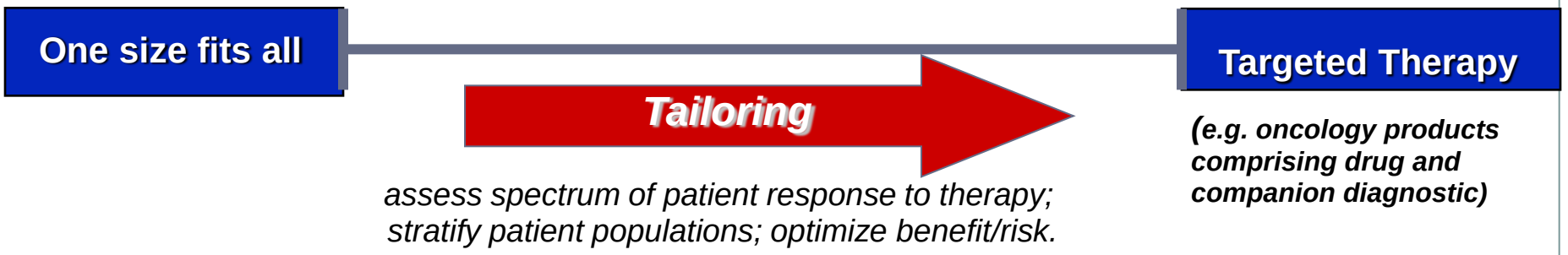
What is the goal of "Stratified" Medicine?

"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**



Dr. Eiry Roberts, Eli Lilly at CBI 2006 Summit

The Patient Therapeutic Continuum

Major Drugs Ineffective for Many

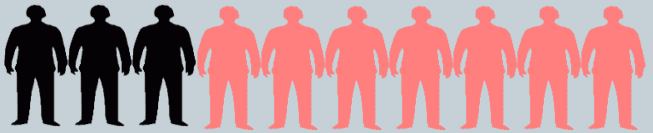
Hypertension Drugs 10-30%
ACE Inhibitors

Heart Failure Drugs 15-25%
Beta Blockers

Anti Depressants 20-50%
SSRIs

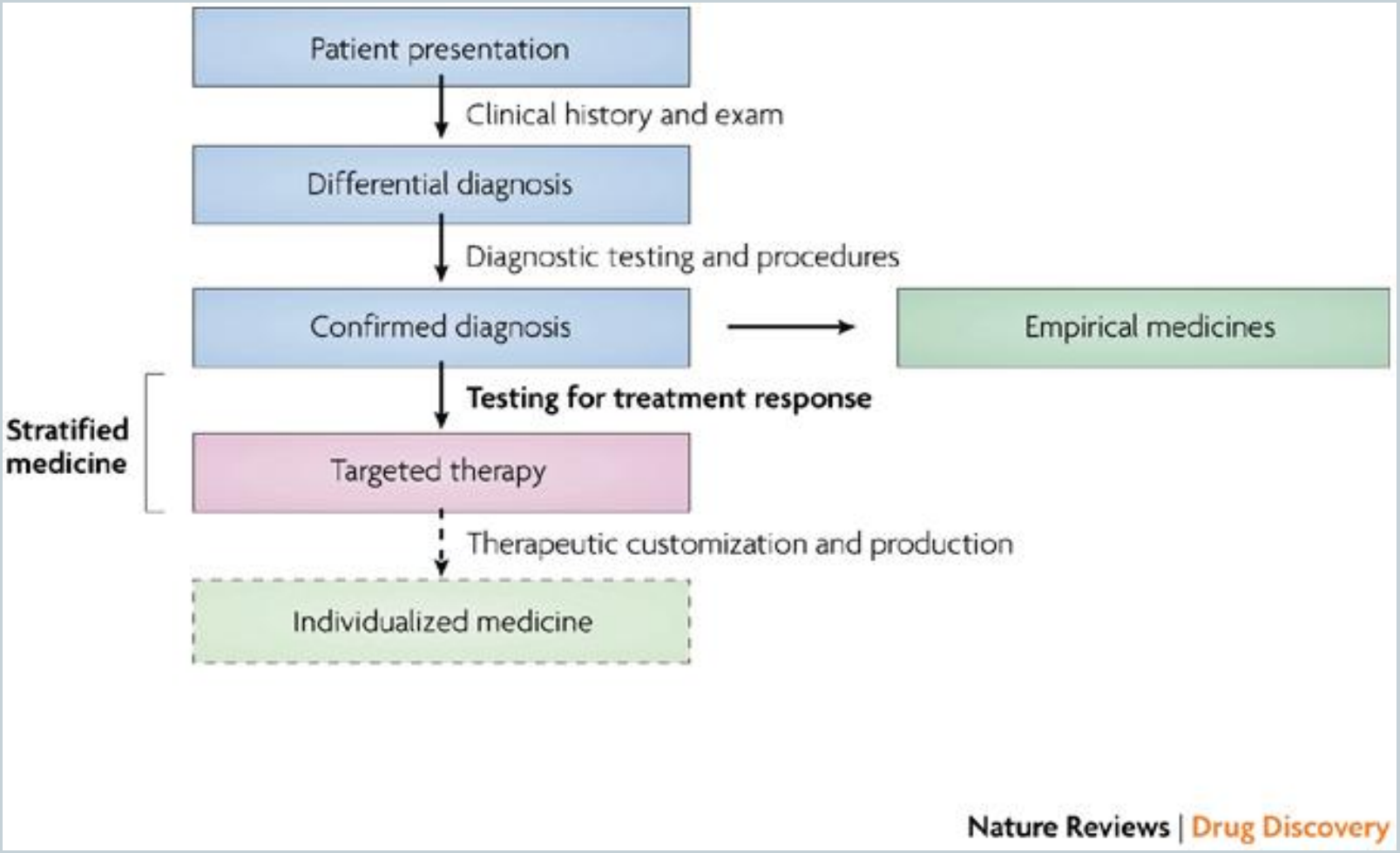
Cholesterol Drugs 30-70%
Statins

Asthma Drugs 40-70%
Beta-2-agonists



Source: Abrahams, E., Silver M., The case for personalized medicine. *J Diab Sci & Tech.* **3**(4) 680-684 July 2009

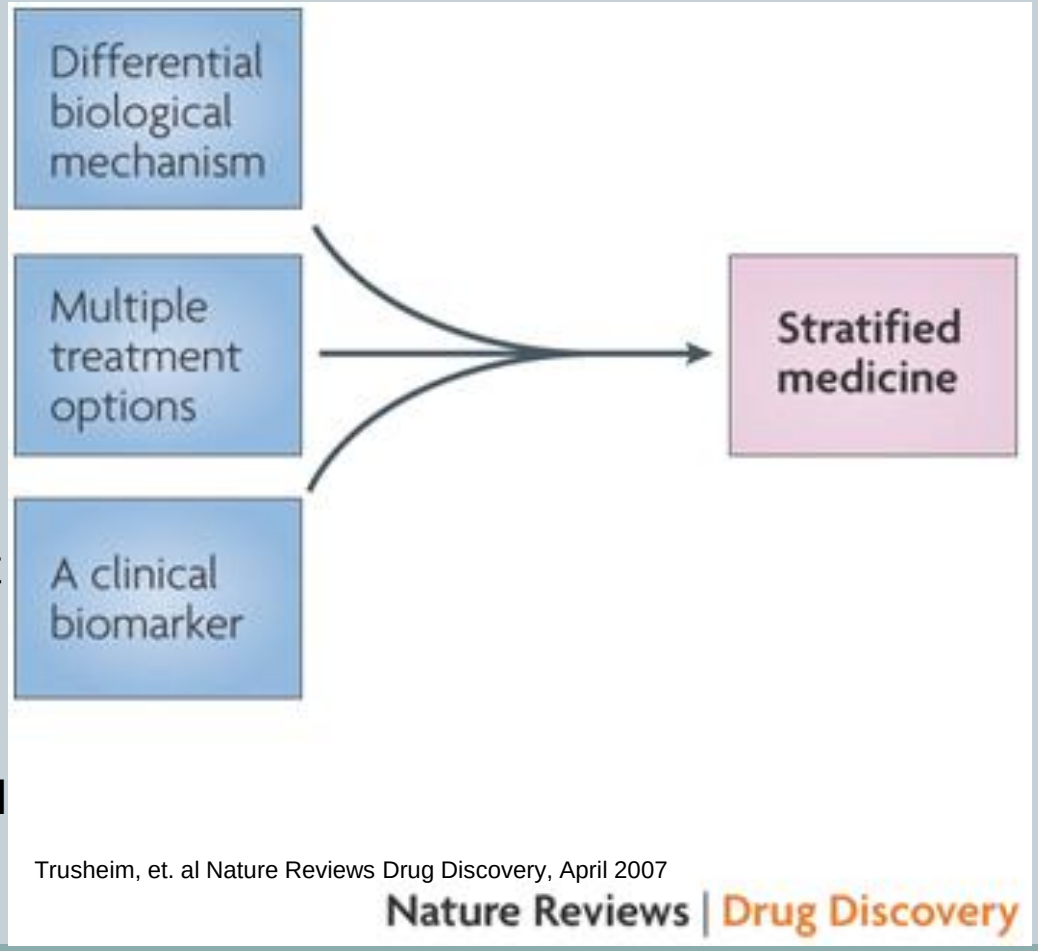
Stratified Medicine in the Clinical Context



Why Some Therapeutic Areas Stratify and Others Do Not

Statins	SSRIs	Herceptin
Minimal	High	High
Many	Many	Many
Some	None yet	Genotype
Remains Empirical	Remains Empirical	Stratified Oncology

Necessary Conditions for Stratified Medicine



Trusheim, et. al Nature Reviews Drug Discovery, April 2007

Nature Reviews | Drug Discovery

Stratified Medicines Only $20B of ~$650B BioPharmaceutical Market

- Unpublished chart redacted

Hu, Trusheim, Berndt, Aitken, Epstein: Identifying personalized medicine therapeutics and quantifying their utilization, draft manuscript 2011

While Initially Leading, US Usage is Declining

- Unpublished chart redacted

Hu, Trusheim, Berndt, Aitken, Epstein: Identifying personalized medicine therapeutics and quantifying their utilization, draft manuscript 2011

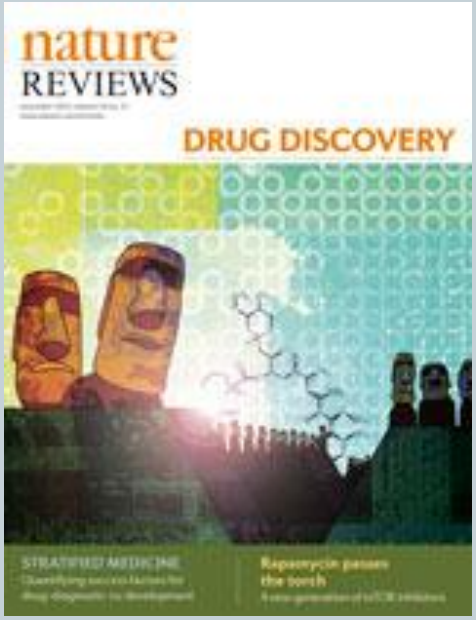
Modeling the Codevelopment of Biomarkers and New Drugs

INSIGHTS GAINED FROM AN ACADEMIC, REGULATORY AND INDUSTRY COLLABORATIVE PROJECT

FDA, MIT, Industry Consortium Examining the Complexity of Co-Developing Stratified Medicines

Consortium Aspirations

- Understand impediments and incentives for Personalized Medicine-focus on Stratified Medicines
- Facilitate multi-stakeholder dialogue
- Develop insights based on evidence and quantitative analysis
- Develop and compare easy-to-use tools



Analysis feature

Quantifying factors for the success of stratified medicine

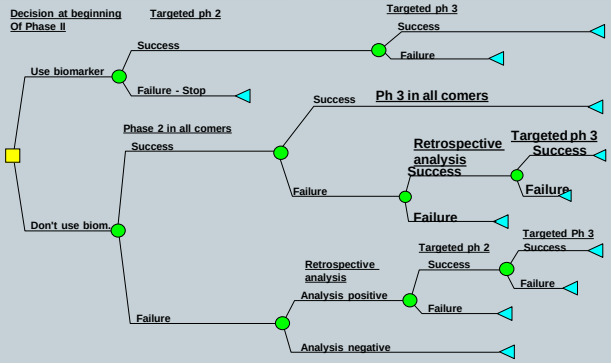
November 2011

Consortium Membership

- The team benefited from a wide range of organizations
  - Adaptive Pharmacogenomics
  - Bristol-Myers Squibb
  - CMS
  - Eli Lilly and Company
  - FDA
  - Glaxo SmithKline
  - IMS Health
  - Merck
  - MIT
  - Novartis
  - Roche
  - Van Andel Research Institute
- And functional specialties
  - Biomarker Development
  - Commercial Development
  - Economics
  - Finance & Planning
  - Regulatory
  - Statistics
  - Strategy & Portfolio Analysis

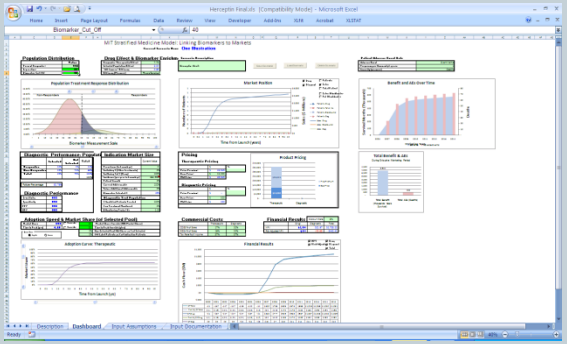
Effort Linked Multiple Tools to Achieve Goals

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

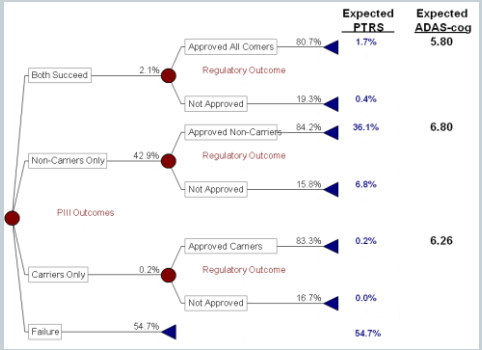


Clinical Design and Simulation models

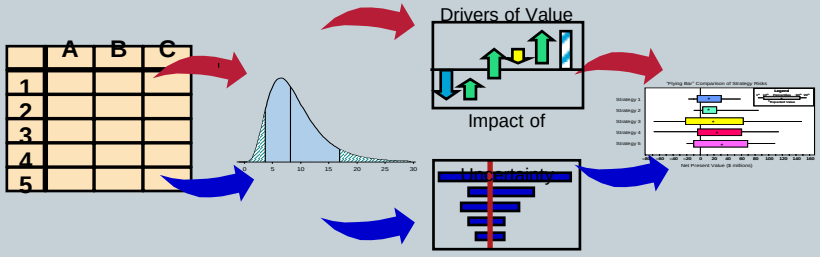
MIT Stratified Medicine Model



PCSD



IMS Health Personalized Medicine Strategy Analysis Tool



Trusheim et al. Quantifying factors for the success of stratified medicine. *Nat. Rev. Drug Disc.* **10**(11)817-833 November 2011

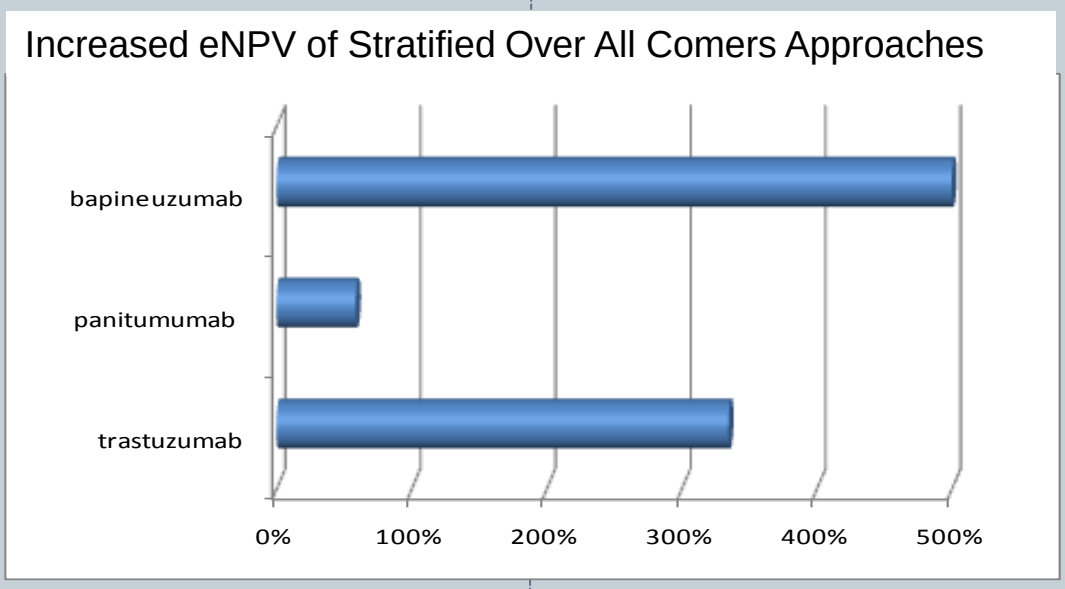
Alternative Development Plans Considered

- All Comers: No stratification
- Retrospective Rescue: Stratification subsequent to Phase III all comers negative results
- Dual development: Prospective development with both biomarker positive and biomarker negative populations
- Biomarker sub-population only

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



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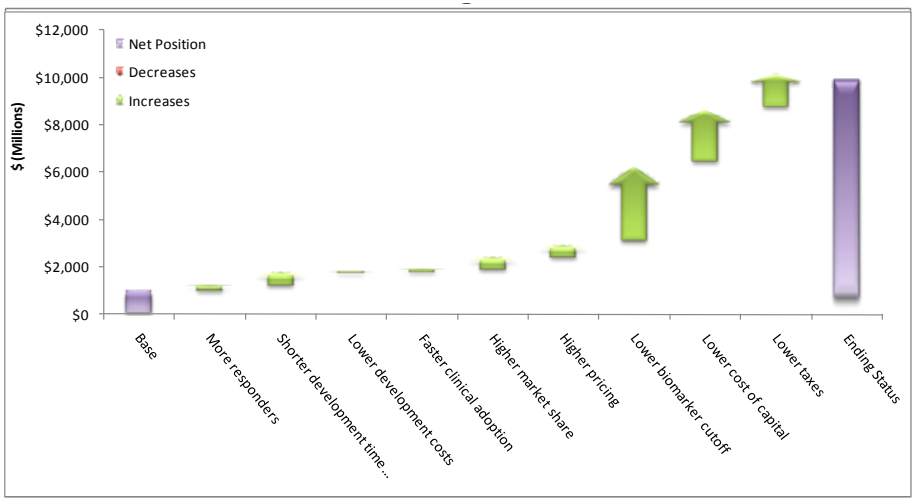
Compounding Connections

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



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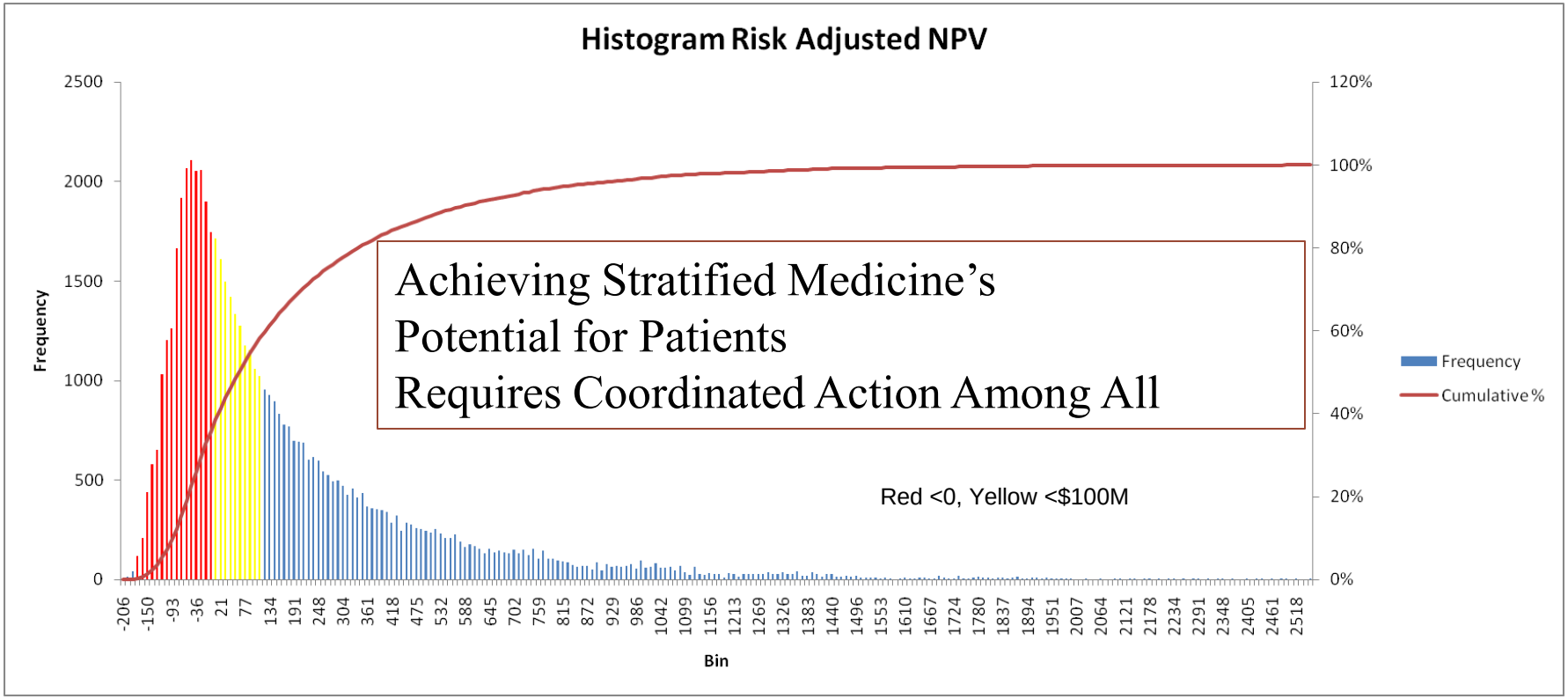
More Poor Futures than Rich Futures

- >500,000 potential futures exist by combining 12 factors
- 36% of cases are negative risk adjusted NPV, 21 % 0<x<$100M and only 3%>$1B (not including tax rate and cost of capital cases)



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Broader Institutional Environment Materially Impacts Factors Analyzed

Factor Analyzed	Policy Environment Impact
Drug responder rate	Low/indirect
Development time and trial size	High/indirect
Development costs	High/indirect
Clinical adoption	High/direct
Market share	Low
Pricing	High/direct
Biomarker selection level	Low/indirect
Cost of capital	Medium/indirect and indirect
Taxes	High/direct
Therapeutic effect	Low/indirect
Disease incidence	Low/indirect
Probability of technical and regulatory success	High/direct

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 Asymmetry
- New biomarker claims often underpowered (poor science)
- Retrospective, Meta analysis

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