Stratified Medicine for AD Drug Development

ISCTM2012 AUTUMN CONFERENCE

TRACK 4B: STRATIFIED MEDICINE AND TARGETED CLINICAL TRIALS FOR ALZHEIMER'S DISEASE
DRUG DEVELOPMENT IN LIGHT OF RECENT PHASE III TRIAL RESULTS: EXAMPLE APOE GENOTYPE

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Financial Acknowledgement

THIS WORK HAS BEEN SUPPORTED
IN PART BY:

ELI LILLY & CO.

THE MERCK FOUNDATION

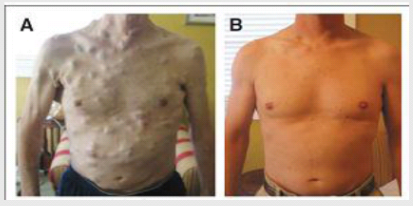
PFIZER, INC.

Finding the Right Patient Can Be Dramatic

Personalizing treatment of Metastatic Melanoma with Zelboraf

Simultaneous approval of drug and test

Roche



Before treatment 15 weeks on Zelboraf

Zelboraf (Vemurafenib)

Positive results in BRAF V600 mutation-positive metastatic melanoma:

- rapid patient response within days
- reduction of risk for disease progression by 74%
- estimated 2 year survival: 38% of patients

cobas® BRAF test

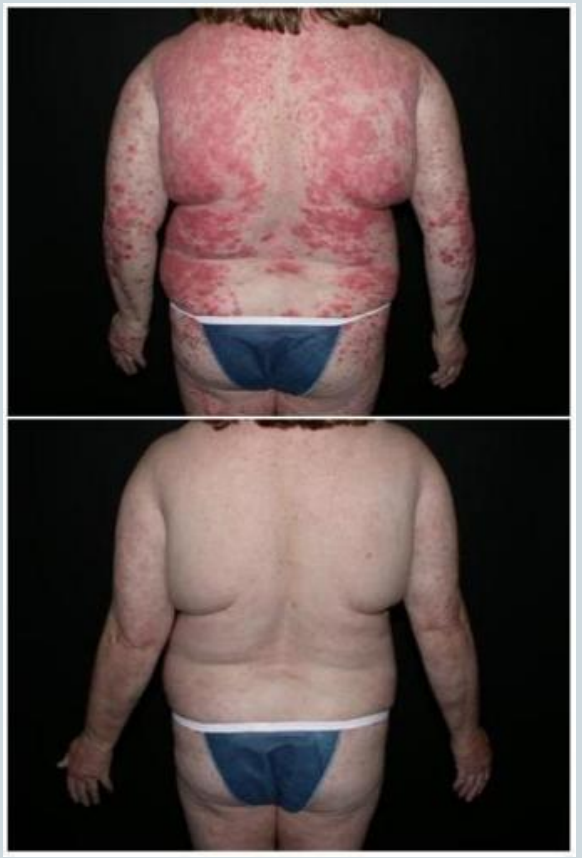
- Identifies patients with BRAFV600E mutation*
- Identifies patients missed by sequencing
- Consistent and reliable results

Source: Michael Cannorile, Roche.
World CDx Summit Europe March 27 2012
Used by Permission

* BRAF gene mutations detected in ~8% of all cancers, over 50% of malignant melanomas

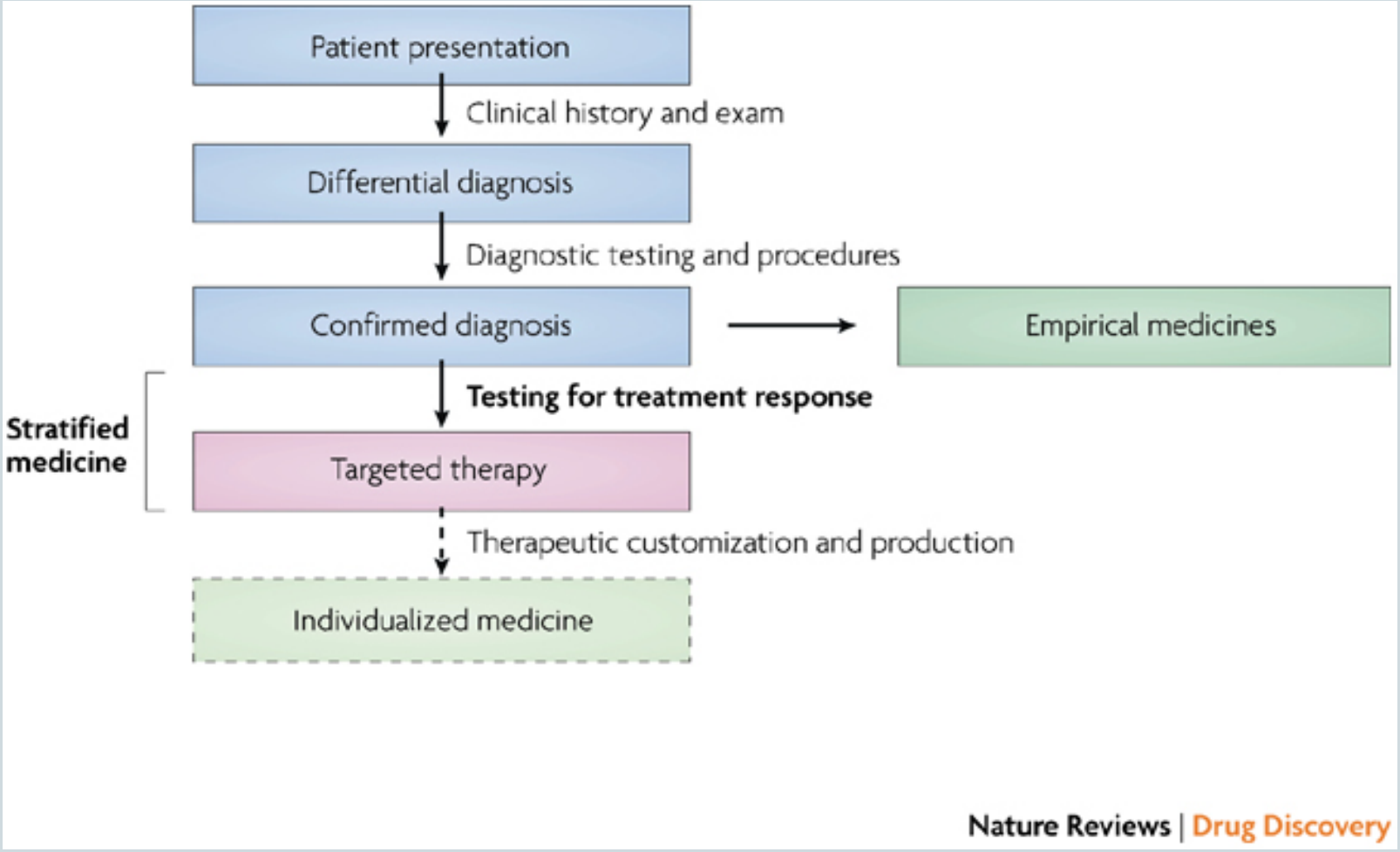
Psorisis: Before and after anti-TNF Treatment

(2 months Remicade)



Source: http://drshibuya.com/PsA-ed.html

Stratified Medicine in the Clinical Context



Bapineuzumab as a Case Study

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

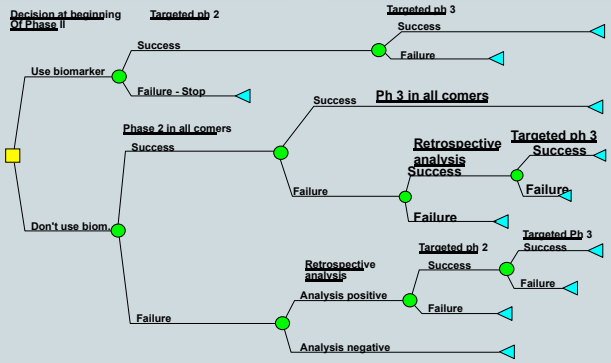
Quantifying factors for the success of stratified medicine

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

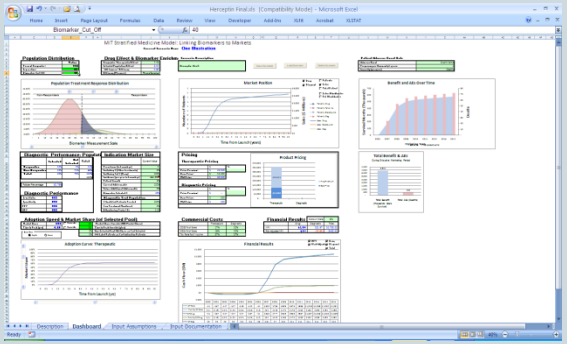
Effort Linked Multiple Tools to Quantitatively Analyze Incentives

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

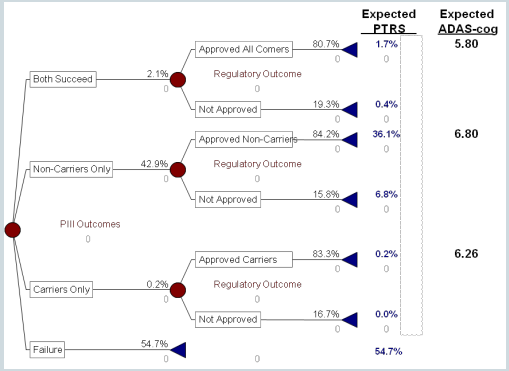


Clinical Design and Simulation models

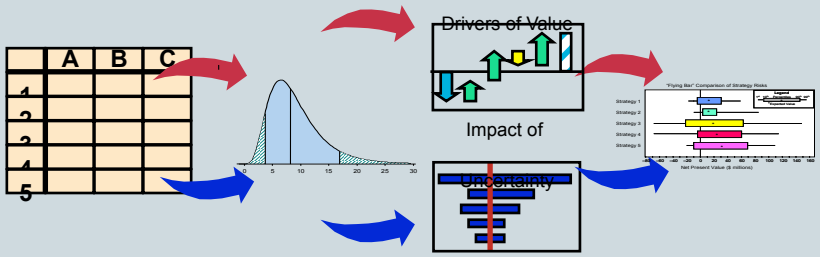
MIT Stratified Medicine Model



PCSD



IMS Health Personalized Medicine Strategy Analysis Tool

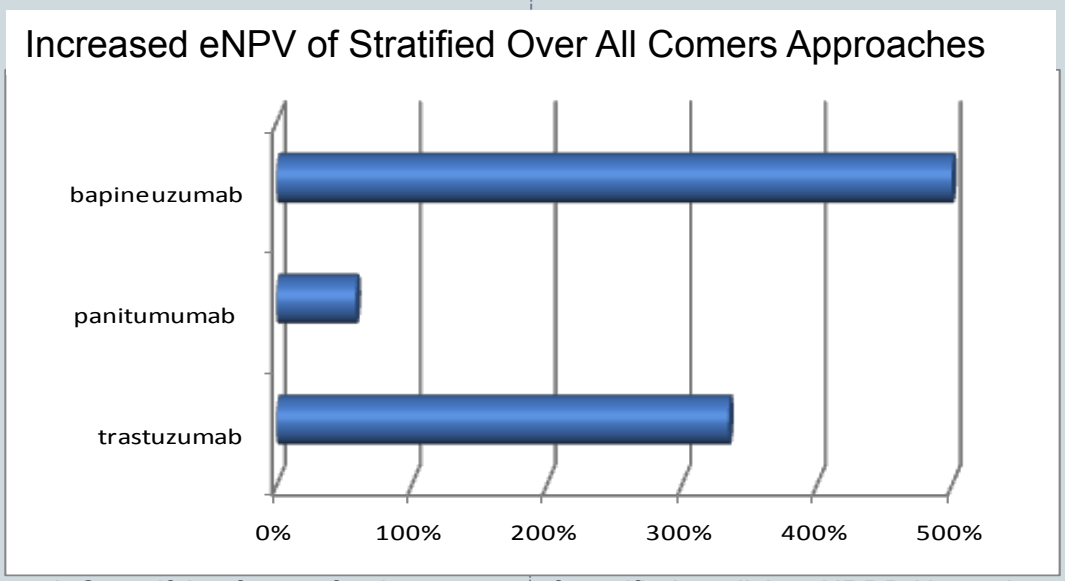


Trusheim et. al. Quantifying factors for the success of stratified medicine. NRDD Nov 2011

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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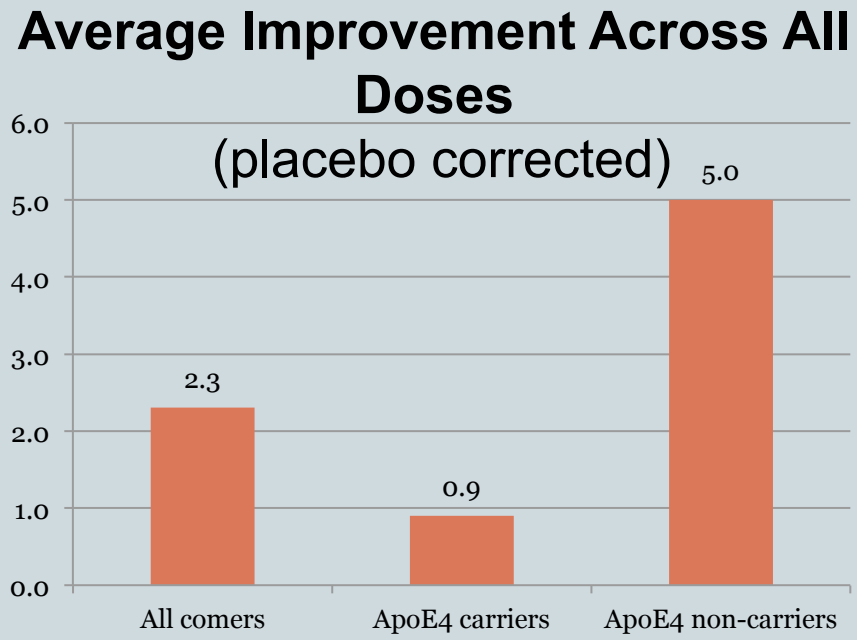
Abeta mAB with ApoE4- Enrichment Chosen As Test Case

- Benchmark: Wyeth/Elan's Bapineuzumab
  - A monoclonal antibody that recognizes the N-terminal of beta-amlyoid
  - Utilized published data from bapineuzumab end of Phase II webcast and information on proposed PIII studies from clinicaltrials.gov
- Key Ph II endpoint: placebo corrected improvement in ADAS-cog change from baseline on a modified intent-to-treat (MITT) basis



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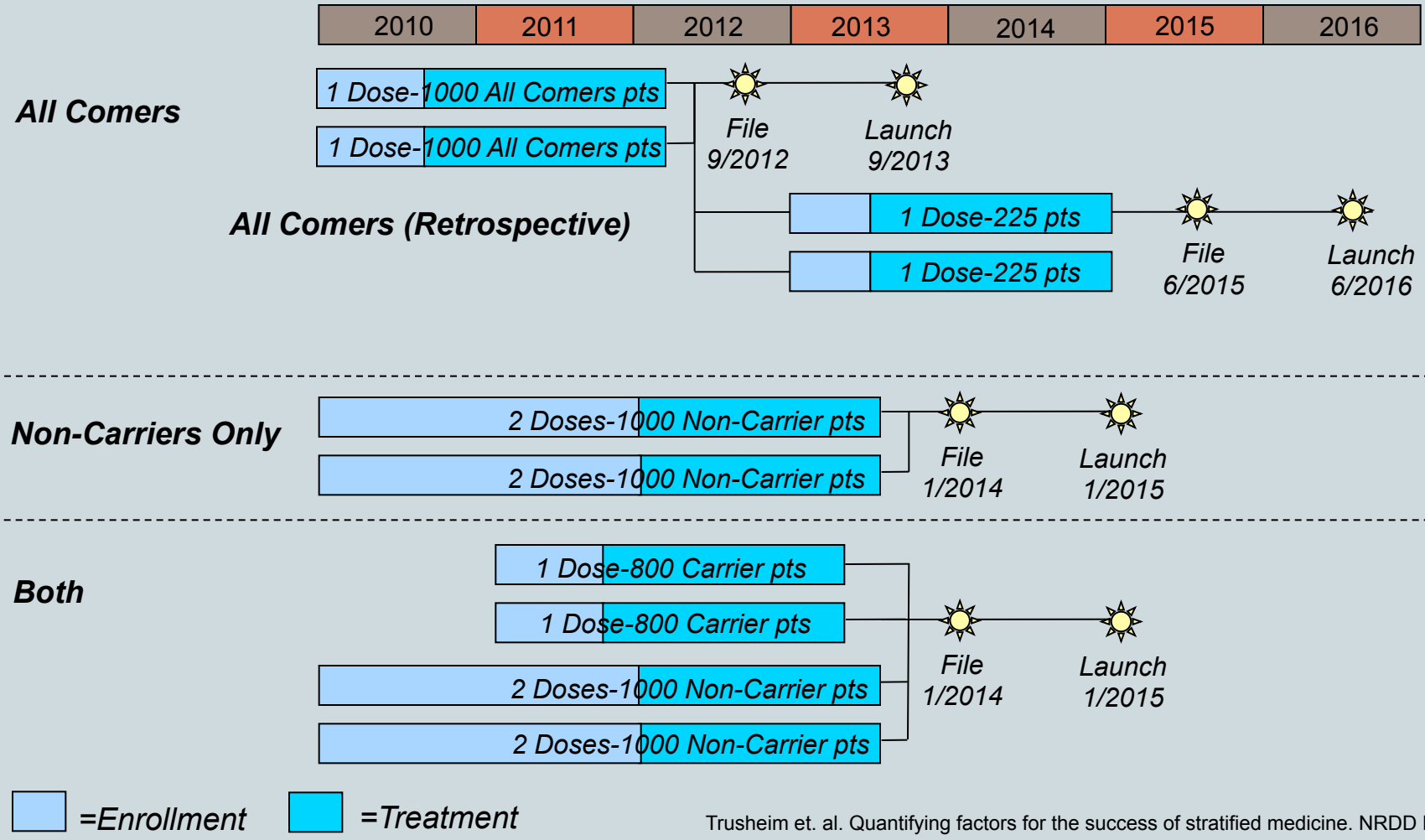
Alternates Considered



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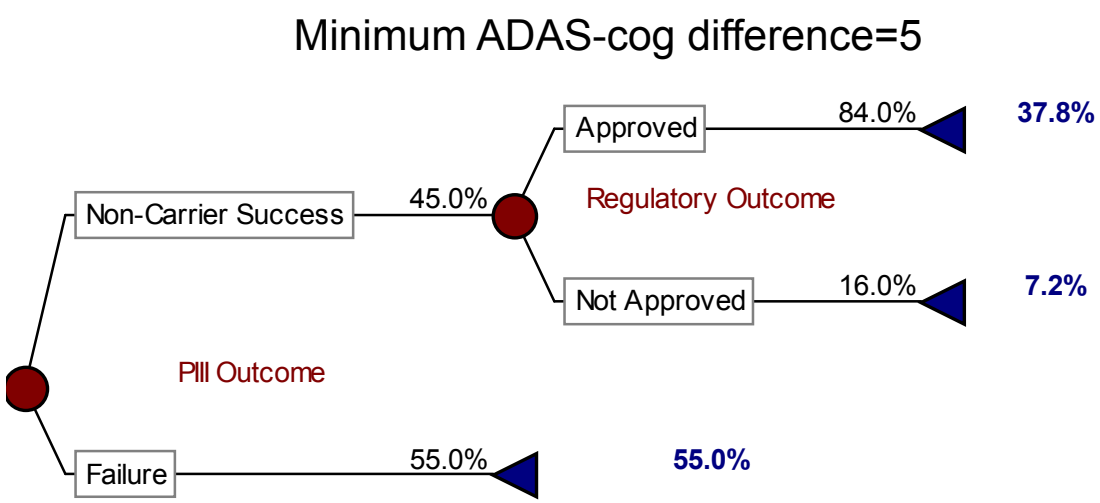
Example Event Tree and Simulation Results: Alzheimer's CDx+ Only (Non-Carriers) PIII Strategy



Minimum ADAS-cog	Probabilities			Expected ADAS-Cog
	PTS	PRS	PTRS	
3	73%	80%	59%	5.74
4	60%	82%	49%	6.21
5	45%	84%	38%	6.79
6	30%	86%	26%	7.46
7	17%	89%	15%	8.23

Technical Success Decreases

Regulatory Success Increases

But Highest PTRS remains at lowest, non-inferior criterion
When does commercial benefit of higher efficacy outweigh risk?

D. Swank, BMS

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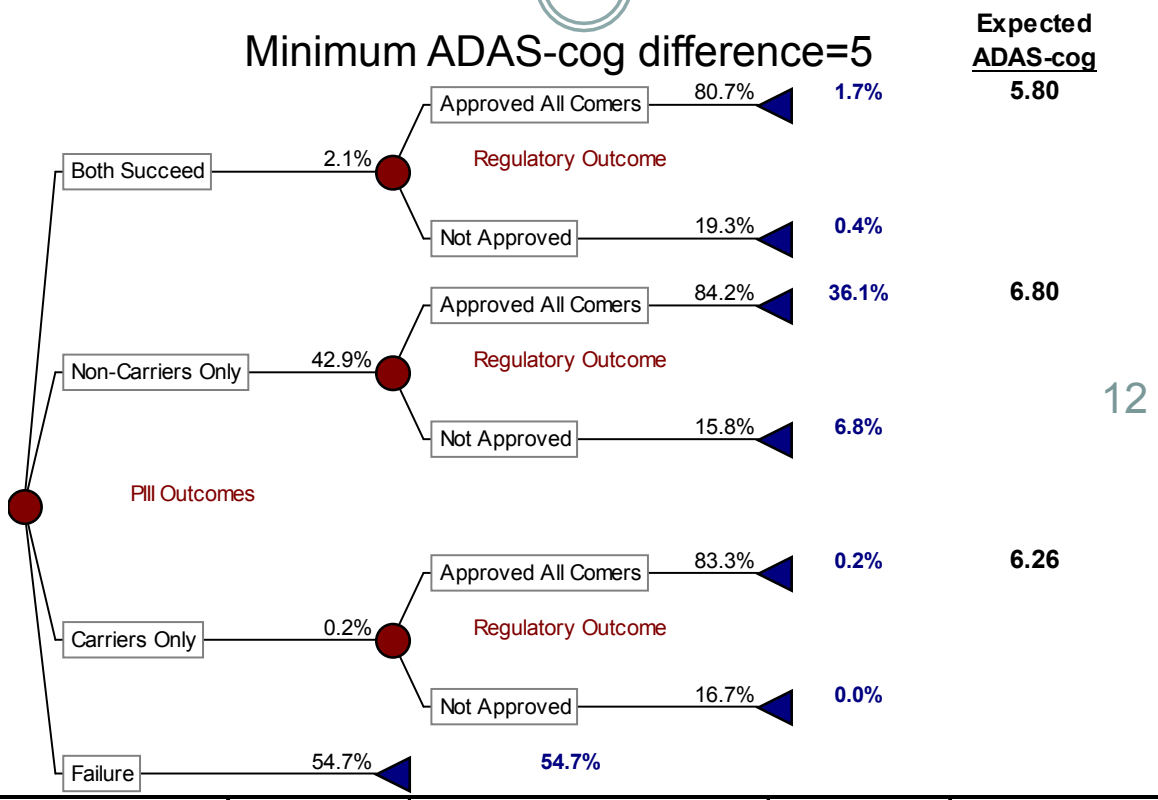
PTRS Study Both Non-carriers and Carriers (4/4)



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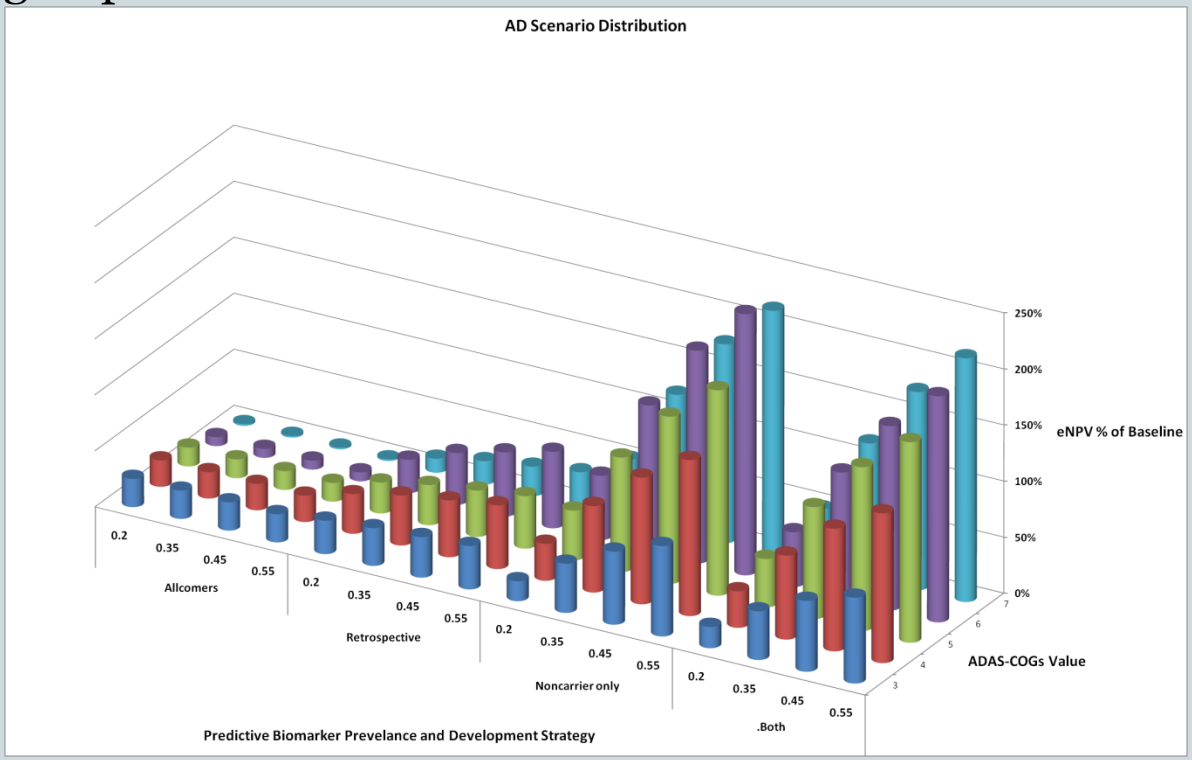
Minimum ADAS-cog	Probabilities For Both			Expected ADAS-Cog	Non-Carriers Only			Expected ADAS-Cog	Carriers Only			Expected ADAS-Cog
	PTS	PRS	PTRS		PTS	PRS	PTRS		PTS	PRS	PTRS	
3	12%	74%	9%	4.12	61%	81%	50%	5.76	0.5%	79%	0.4%	4.77
4	5%	77%	4%	4.95	55%	82%	45%	6.22	0.4%	80%	0.3%	5.47
5	2%	81%	2%	5.80	43%	84%	36%	6.80	0.2%	83%	0.2%	6.26
6	1%	84%	1%	6.65	29%	86%	25%	7.47	0.1%	87%	0.1%	7.09
7	0%	87%	0%	7.43	17%	89%	15%	8.23	0.1%	89%	0.1%	7.90

Biomarker Prevalence, Therapeutic Effect and Development Strategy Combine to Improve Value

- Increasing the biomarker prevalence in the AD population creates greater value across all scenarios – a fourfold increase in eNPV between 20% and 55%.
- The 35% biomarker prevalence scenarios have a 2.3-fold increase over the 20% biomarker group.



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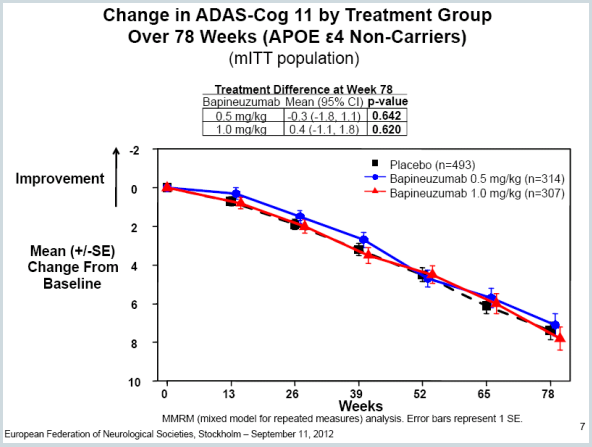
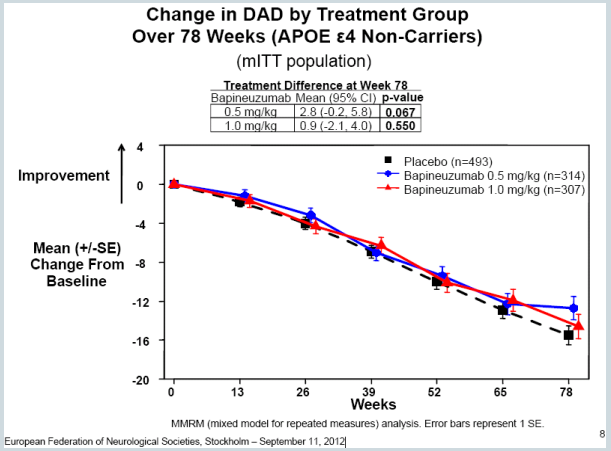
Results of Phase III Trials

ADAS-COGS

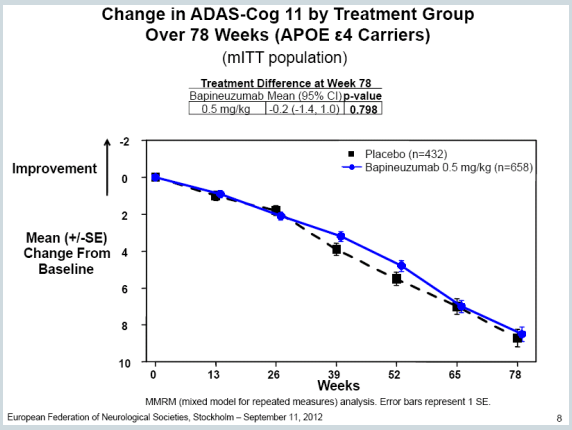
DAD

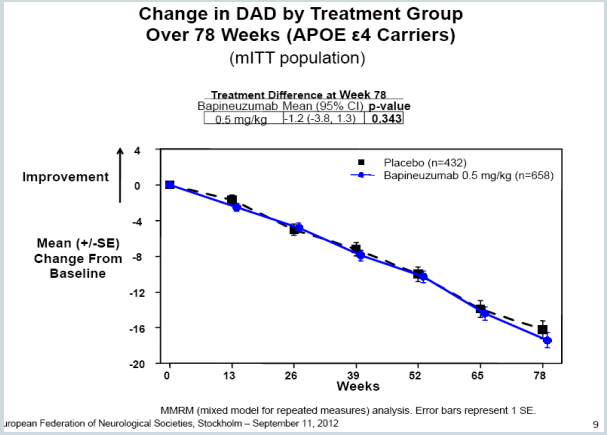
Non-Carriers





Carriers





Salloway et. al. and Sperling et. al. European Federation of Neurological Societies, Stockholm – September 11, 2012

But Some Biomarkers Indicate Limited Effect

Amyloid Burden

Brain Volume

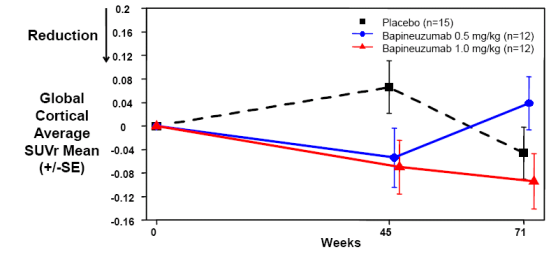
Tau (CSF)

Non-Carriers

Change in Amyloid Burden as assessed by [^{11}C] PiB-PET at Week 71 APOE ε4 Non-Carriers (PiB PET analysis population)

Treatment Difference at Week 71

Bapineuzumab	Mean (95% CI)	p-value
0.5 mg/kg	0.085 (-0.046, 0.215)	0.193
1.0 mg/kg	-0.048 (-0.182, 0.086)	0.466



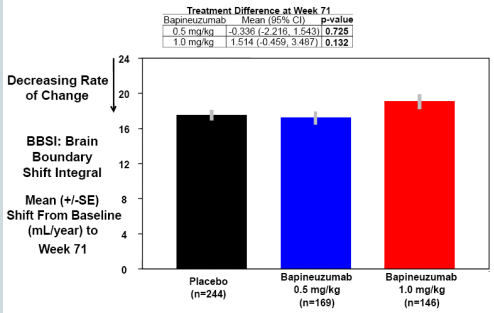
No significant treatment differences between groups; post hoc exploratory analysis suggested a within cohort signal for reduction in PiB PET at 1.0 mg/kg dose (nominal p = 0.057)

(PiB PET analysis population: baseline global cortical average > 1.35; 36.1% did not meet threshold)

Rate of Change in MRI Brain Volume (BBSI) by Treatment Group at Week 71 APOE ε4 Non-Carriers (vMRI analysis population)

Treatment Difference at Week 71

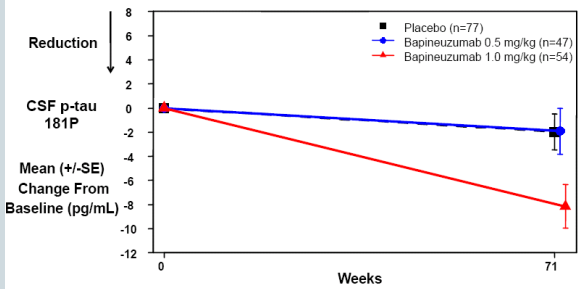
Bapineuzumab	Mean (95% CI)	p-value
0.5 mg/kg	-0.336 (-2.216, 1.543)	0.725
1.0 mg/kg	1.514 (-0.459, 3.487)	0.132



Change in CSF phospho-tau by Treatment Group at Week 71 APOE ε4 Non-Carriers (CSF analysis population)

Treatment Difference at Week 71

Bapineuzumab	Mean (95% CI)	p-value
0.5 mg/kg	0.05 (-4.78, 4.88)	0.984
1.0 mg/kg	-6.19 (-10.82, -1.56)	0.009

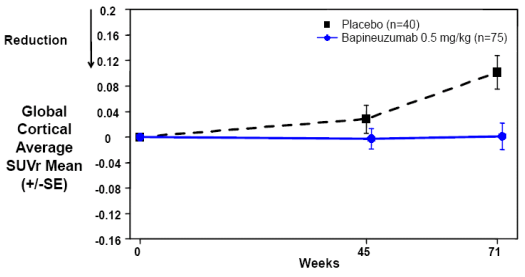


Carriers

Change in Amyloid Burden as assessed by [^{11}C] PiB-PET at Week 71 APOE ε4 Carriers (PiB PET analysis population)

Treatment Difference at Week 71

Bapineuzumab	Mean (95% CI)	p-value
0.5 mg/kg	-0.101 (-0.168, -0.034)	0.004

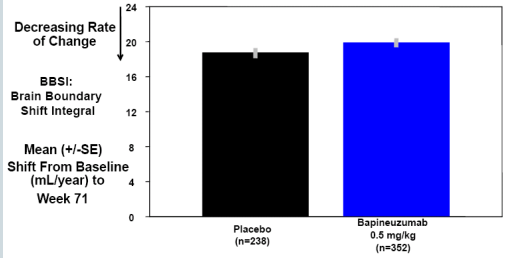


(PiB PET analysis population: baseline global cortical average > 1.35; 6.5% did not meet threshold)

Rate of Change in MRI Brain Volume (BBSI) by Treatment Group at Week 71 APOE ε4 Carriers (vMRI analysis population)

Treatment Difference at Week 71

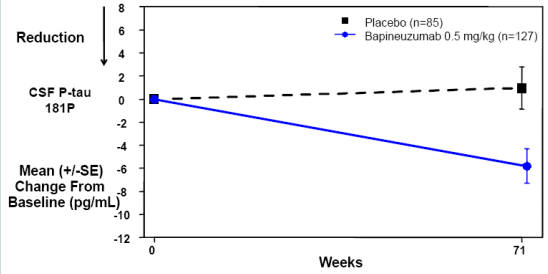
Bapineuzumab	Mean (95% CI)	p-value
0.5 mg/kg	1.175 (-0.340, 2.689)	0.128



Change in CSF Phospho-tau by Treatment Group at Week 71 APOE ε4 Carriers (CSF analysis population)

Treatment Difference at Week 71

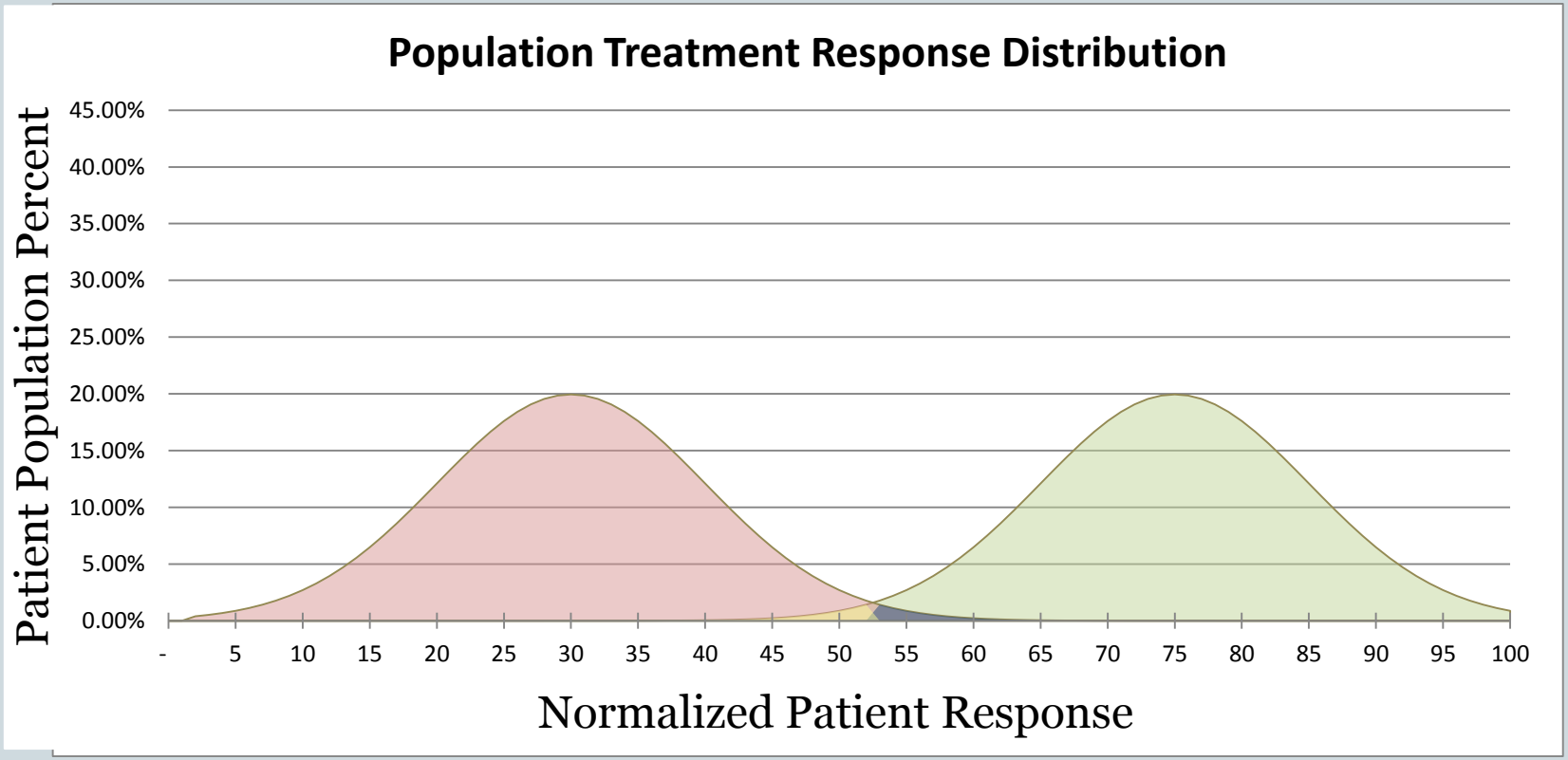
Bapineuzumab	Mean (95% CI)	p-value
0.5 mg/kg	-6.75 (-11.45, -2.06)	0.005



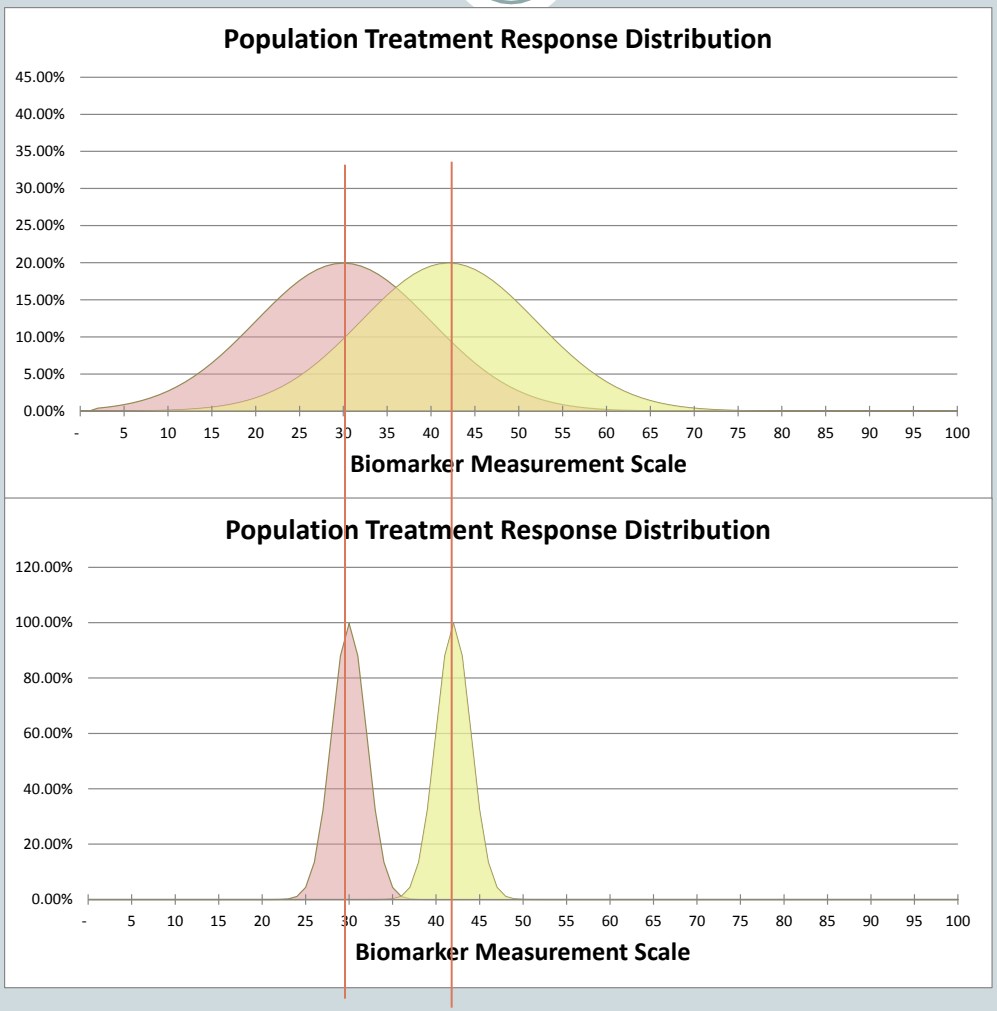
Salloway et. al. and Sperling et. al. European Federation of Neurological Societies, Stockholm – September 11, 2012

Understanding Variance the Key to Stratified Medicine

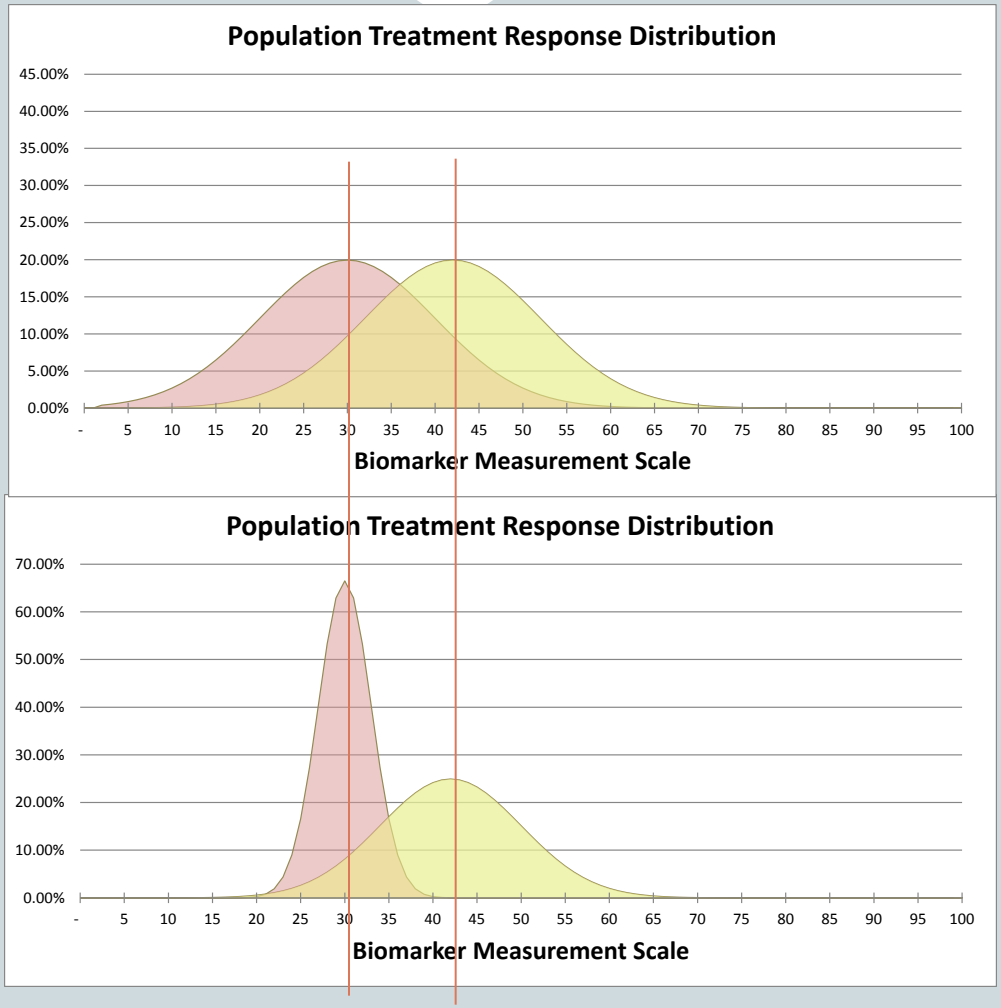
Most Current Clinical Trials Determine Average Differences



But Do Not Provide Much Information on Variance

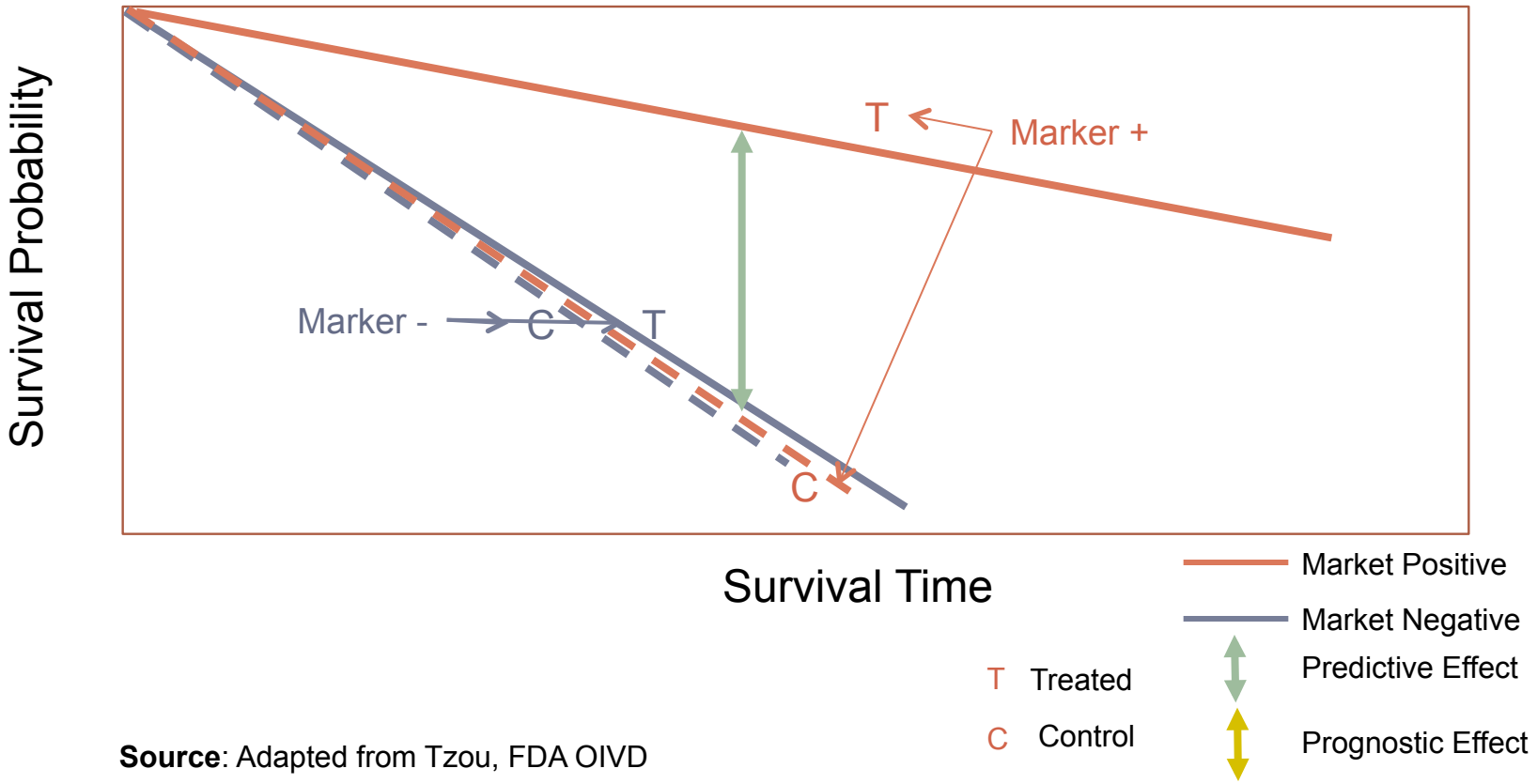


And Symmetry is not Required



While We Seek Predictive Markers

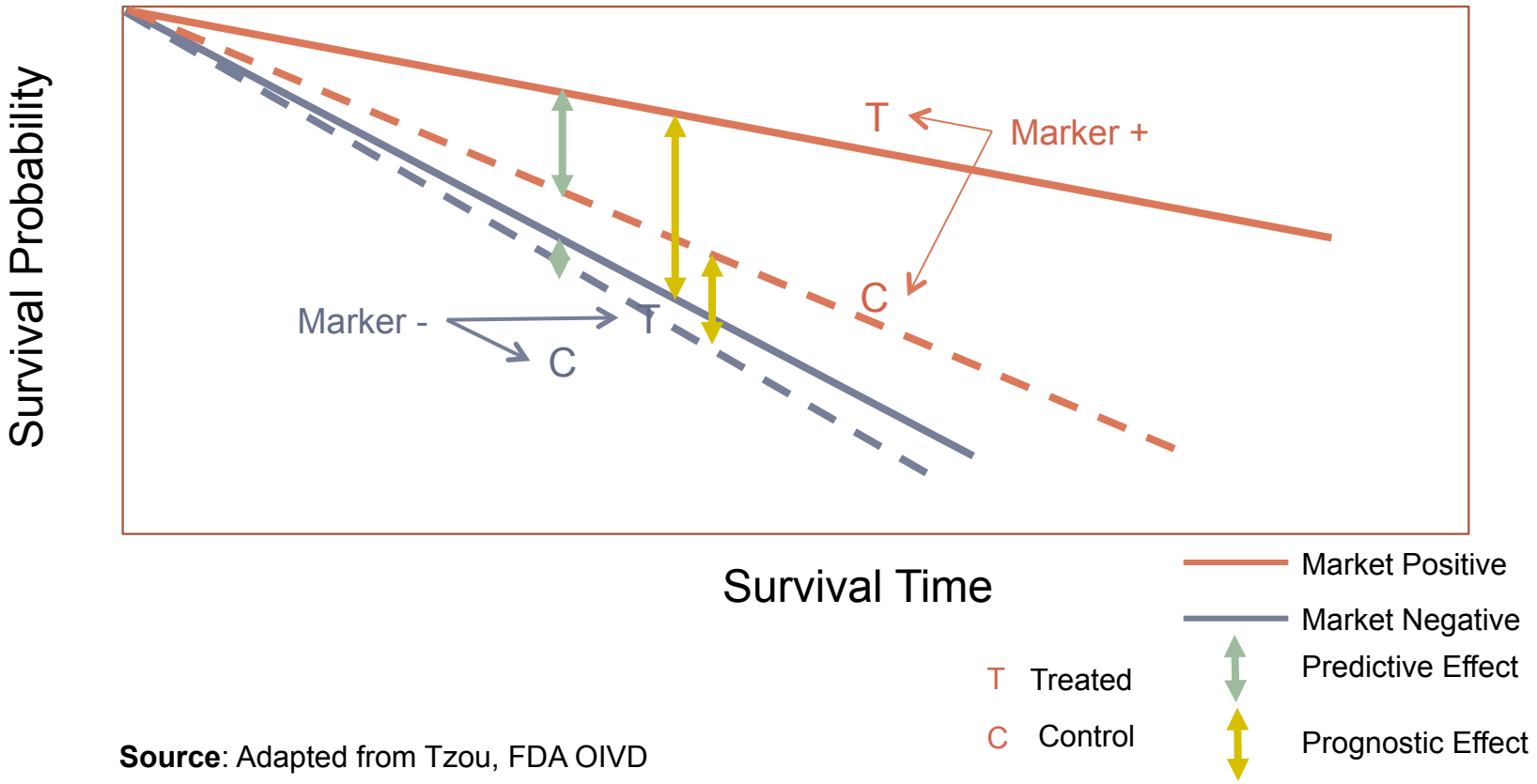
- Biomarker positive have higher survival regardless of treatment



Source: Adapted from Tzou, FDA OIVD

Many Biomarkers May be Both Prognostic and Predictive

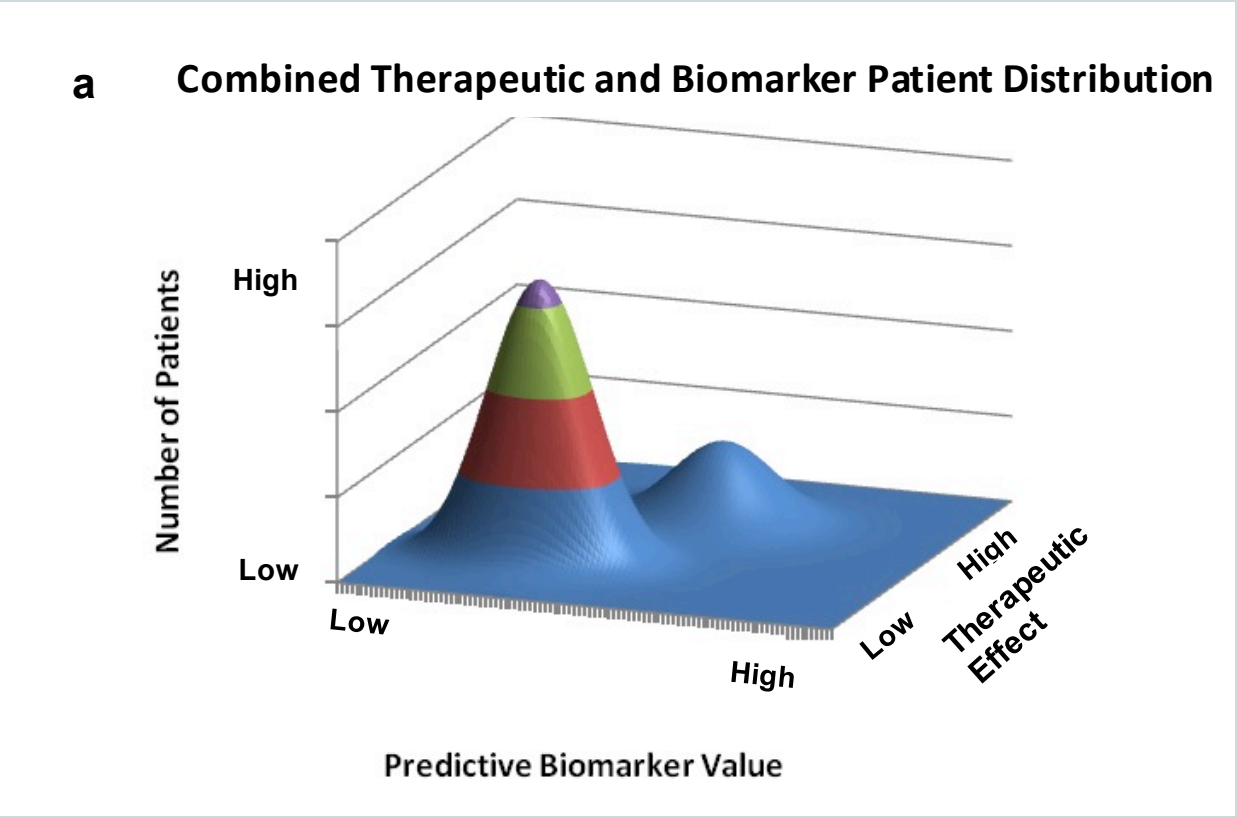
- Biomarkers may exhibit both attributes
- Clinical development & FDA needs to understand both



Source: Adapted from Tzou, FDA OIVD

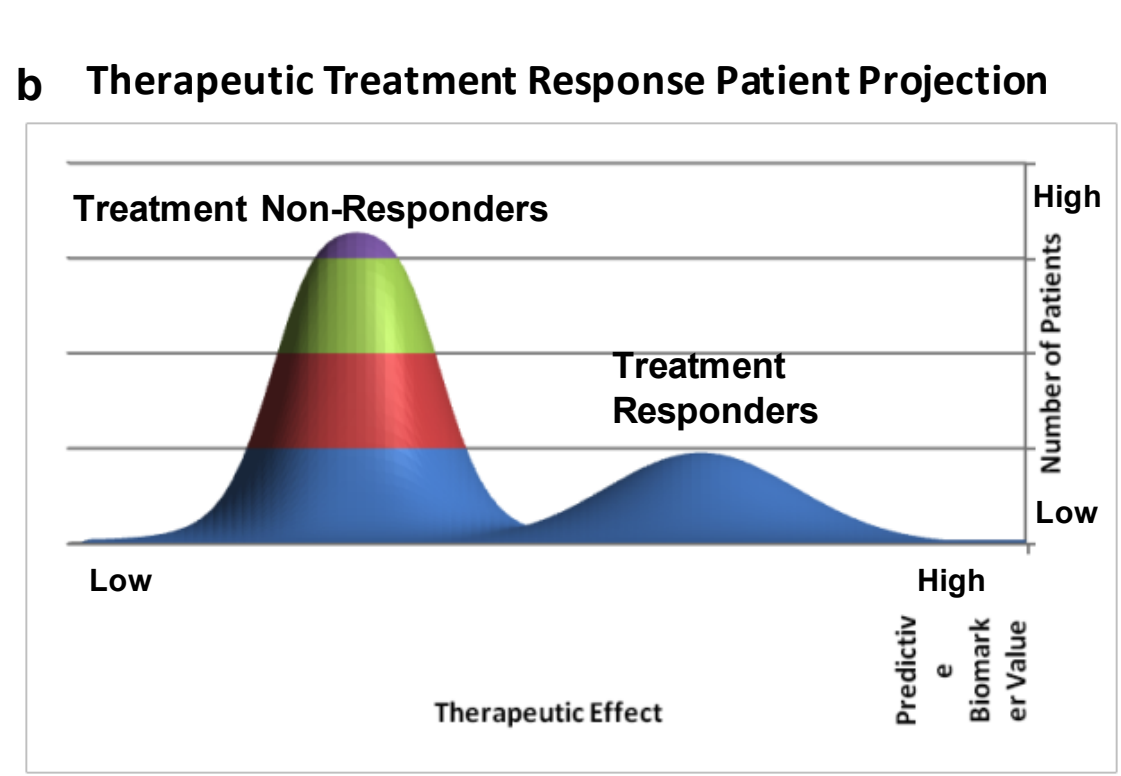
Three Key Factors Define Efficacy Enrichment Potential for a Stratified Medicine

- Therapeutic Effect Distribution
- Biomarker Prevalence
- Companion Diagnostic Clinical Performance



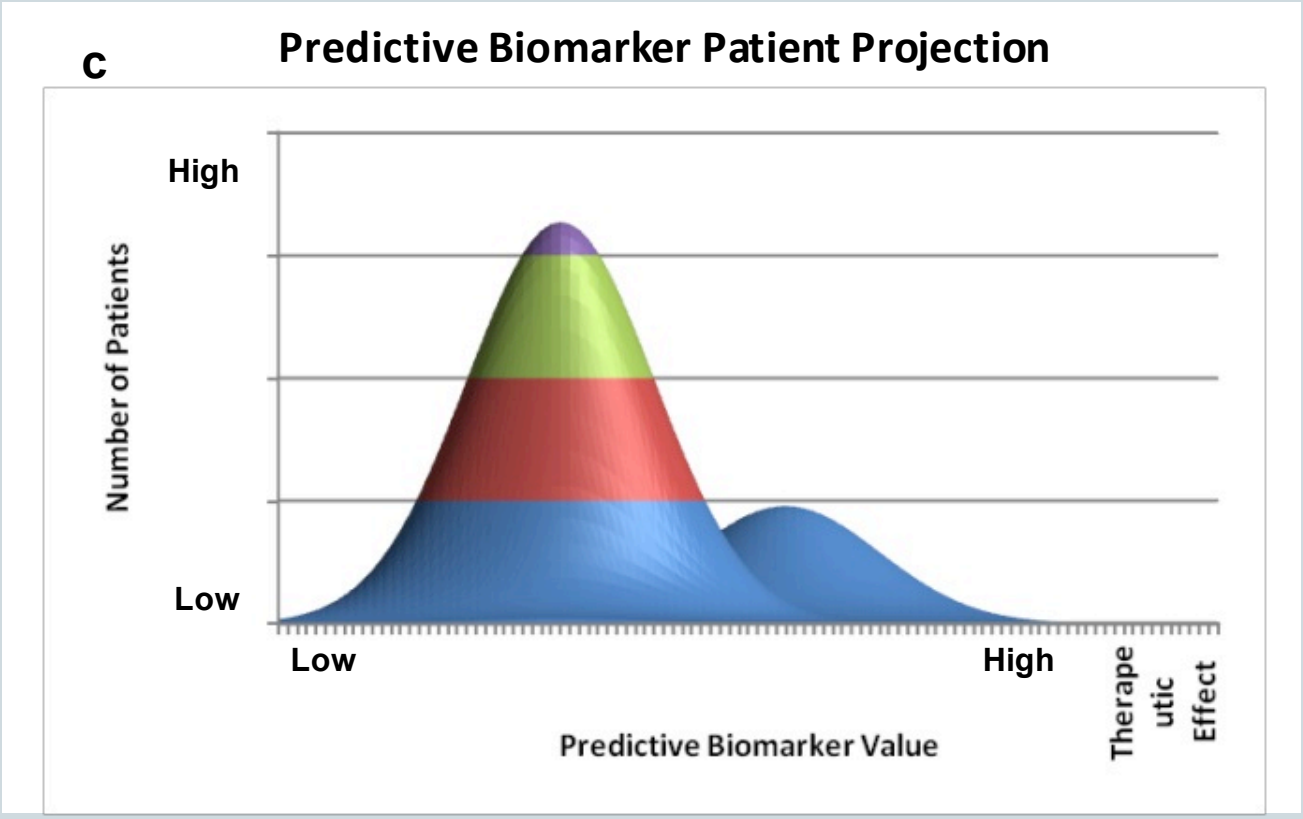
Goal 1: Understand the Therapeutic Variance

- Stratified medicine value derives from the innate variability of patient response to the drug treatment.



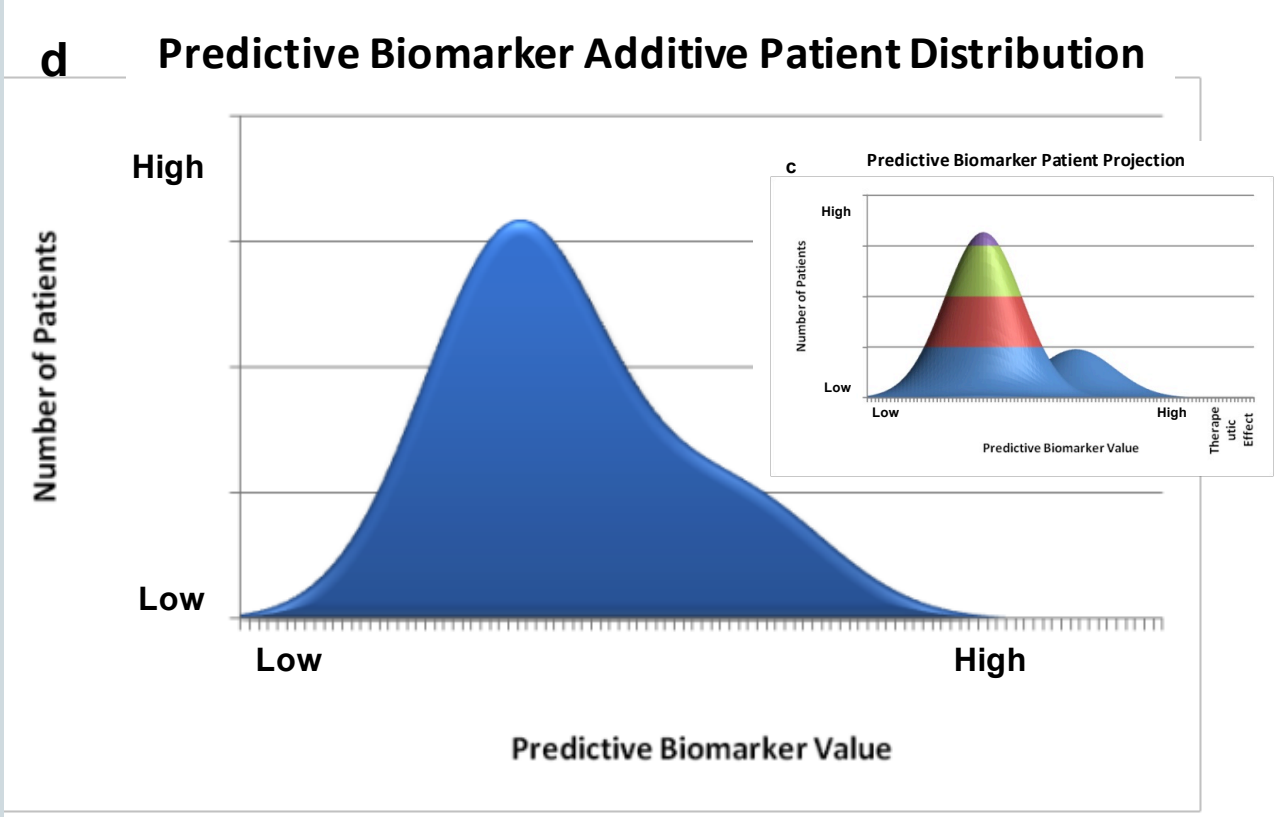
Goal 2: Understand How Imperfectly a Companion Diagnostic Selects Responders

- No companion diagnostic perfectly selects responders
- Do not confuse the shorthand of 'biomarker positive' with 'drug responder'
- Second generation companion diagnostics may perform better (KRAS vs EGFR)

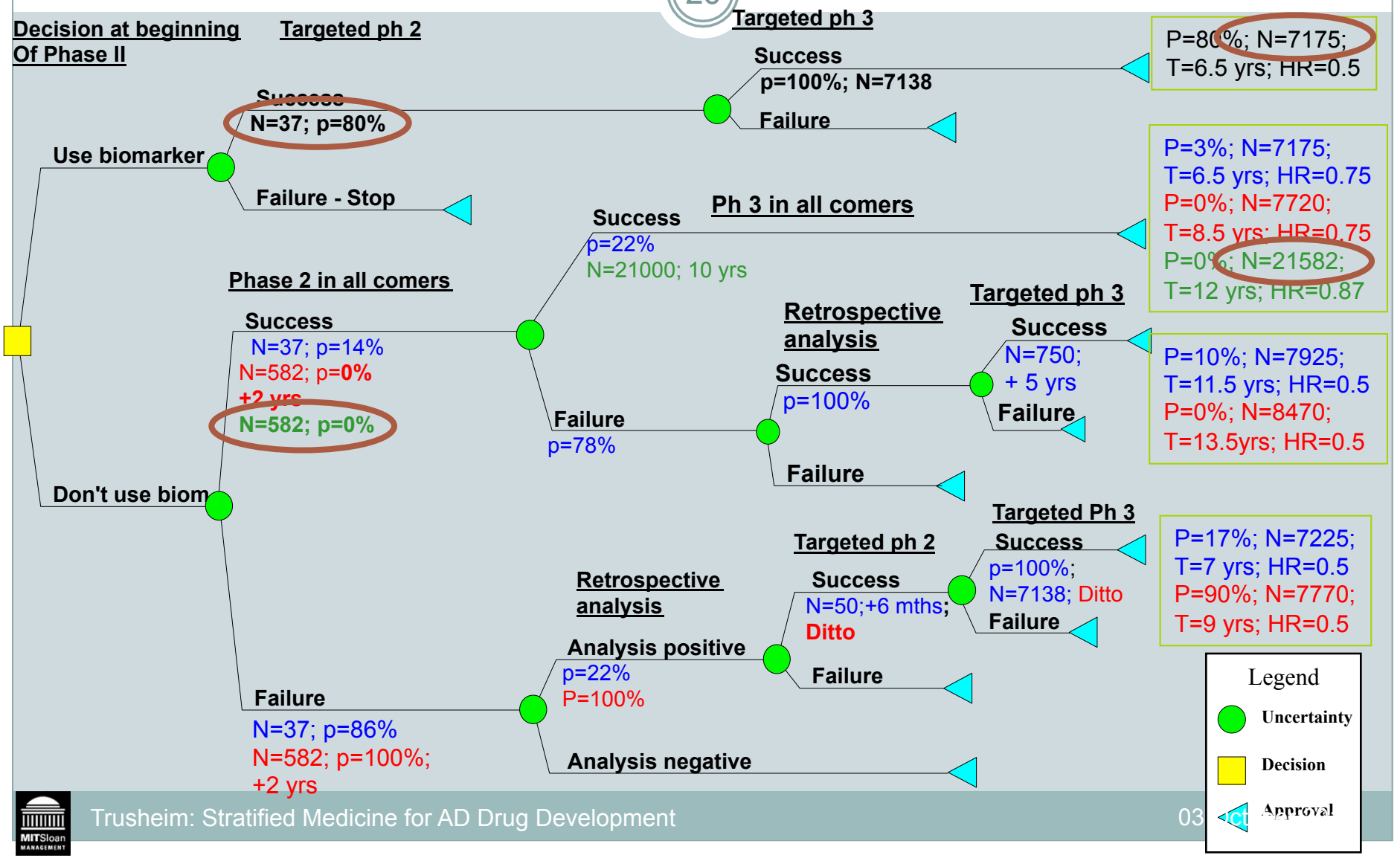


The Underlying Data is Usually Ambiguous

- Without the added information of therapeutic response, the raw biomarker distribution looks like a 'shoulder' rather than dual humps.
- Difficult to interpret with the naked eye



Finding the Responders: Herceptin Clinical Development Options



Power to Prove in Phase II?

- Phase I/Proof of Response studies clearly too small for measuring variance
- Proof of Concept Phase II studies may often be too small (20-60 patients) to discover therapeutic variance or population selection biomarkers.
  - Unless biomarker already assumed in Phase II design: XYZ+ patients
  - Beware of Prognostic vs. Predictive trap
- Sufficiently powered studies are feasible
  - An all-comer study with 324 subjects would have a 90% chance to detect Her2
  - An all-comer study with 120 subjects would have a 90% chance to detect KRAS
- Back to old, large Phase II designs and lose rapid POC?

Translational Studies Often Poorly Designed

Introduction: Validity of biomarkers may be affected if studies do not include certain features in their design. We evaluated ***whether translational research studies of potential biomarkers incorporated design features important for valid clinical associations***.

Methods: We searched 10 journals for translational studies in six systemic autoimmune diseases published in 2004 through 2009. We included studies that reported associations between laboratory markers and the presence of disease, measures of disease activity, or prognosis. We examined the following design features: age, sex, and race matching; control for effects of treatment on expression of the biomarker; inclusion of patients with both early and late disease, or both active and inactive disease; longitudinal or cross-sectional design; and use of validated activity and damage measures.

Results: Among 170 articles, 156 articles examined potential biomarkers for diagnosis, 37 for disease activity assessment, and nine for prognosis; 67 were studies of rheumatoid arthritis (RA); 48, of systemic lupus erythematosus; and 41, of other diseases. Gene-expression profiles were the most commonly examined potential biomarkers (n = 51). Fewer than one half of studies incorporated study-design features important for valid clinical associations. Only 47.4% of studies of biomarkers for diagnosis had groups that were age-matched, 45.5% were sex-matched, and 35.3% controlled for treatment. Studies that examined biomarkers in histologic samples and studies of RA were less likely to include important design features.

Conclusions: ***Fewer than one half of translational studies of potential biomarkers incorporated design features needed for valid interpretation of clinical associations.*** Attention to these features could reduce false-positive and false-negative associations.

Tektonidou and Ward Arthritis Research & Therapy 2010, 12:R179
http://arthritis-research.com/content/12/5/R179
Validity of clinical associations of biomarkers in translational research studies: the case of systemic autoimmune diseases

Stratified Medicine Success in AD Requires Elucidating Multi-Faceted Biomarker Performance

- Understanding Prognostic power
- Understanding Therapeutic variance
- Only then can understanding companion diagnostic predictive performance begin
- Result: Finding those we CAN help and
  Providing new scientific possibilities