# Quantitative Approaches to Informing Clinical Decisions – Where does Systems Pharmacology Fit In?

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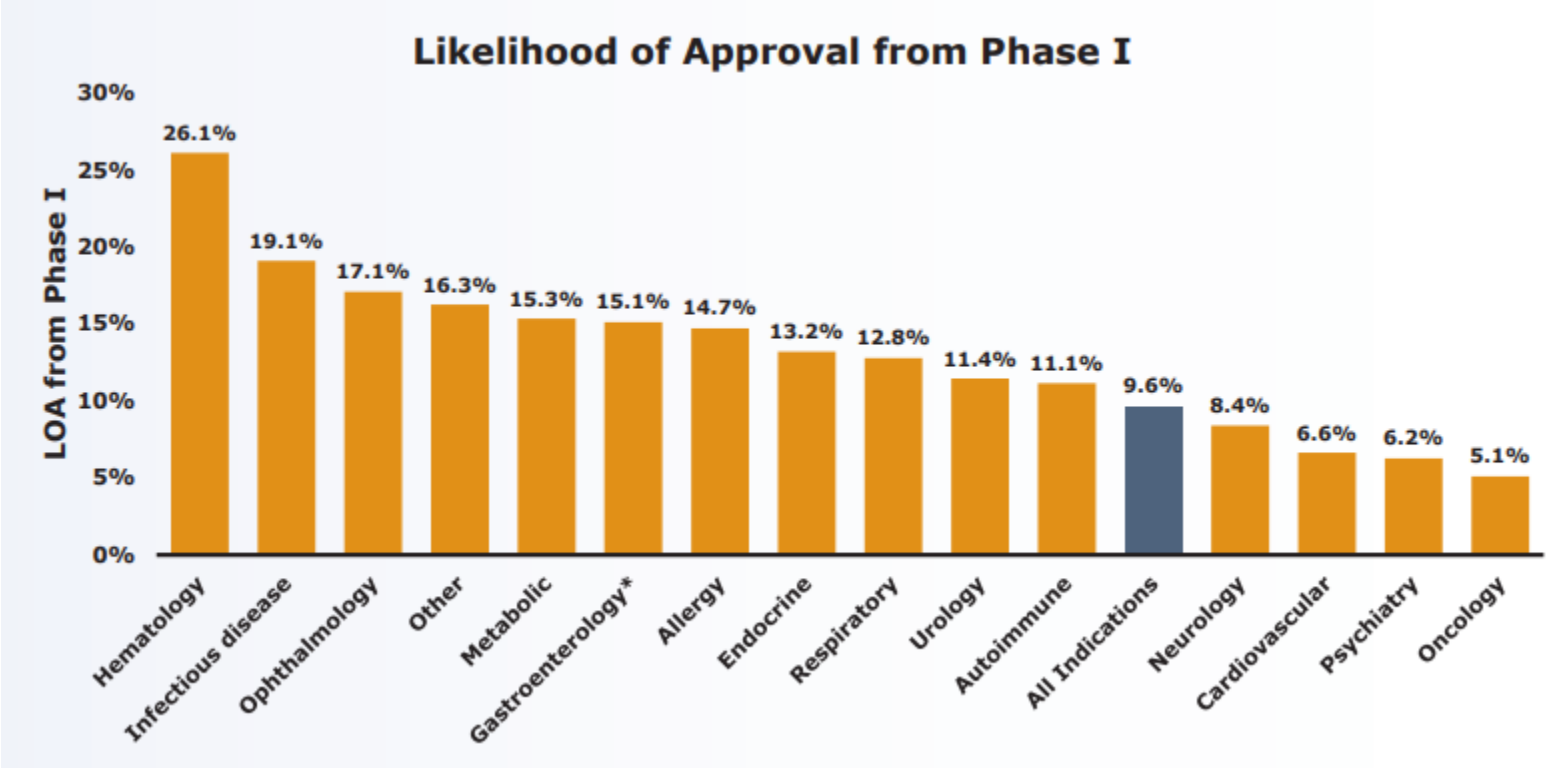
November 14, 2018

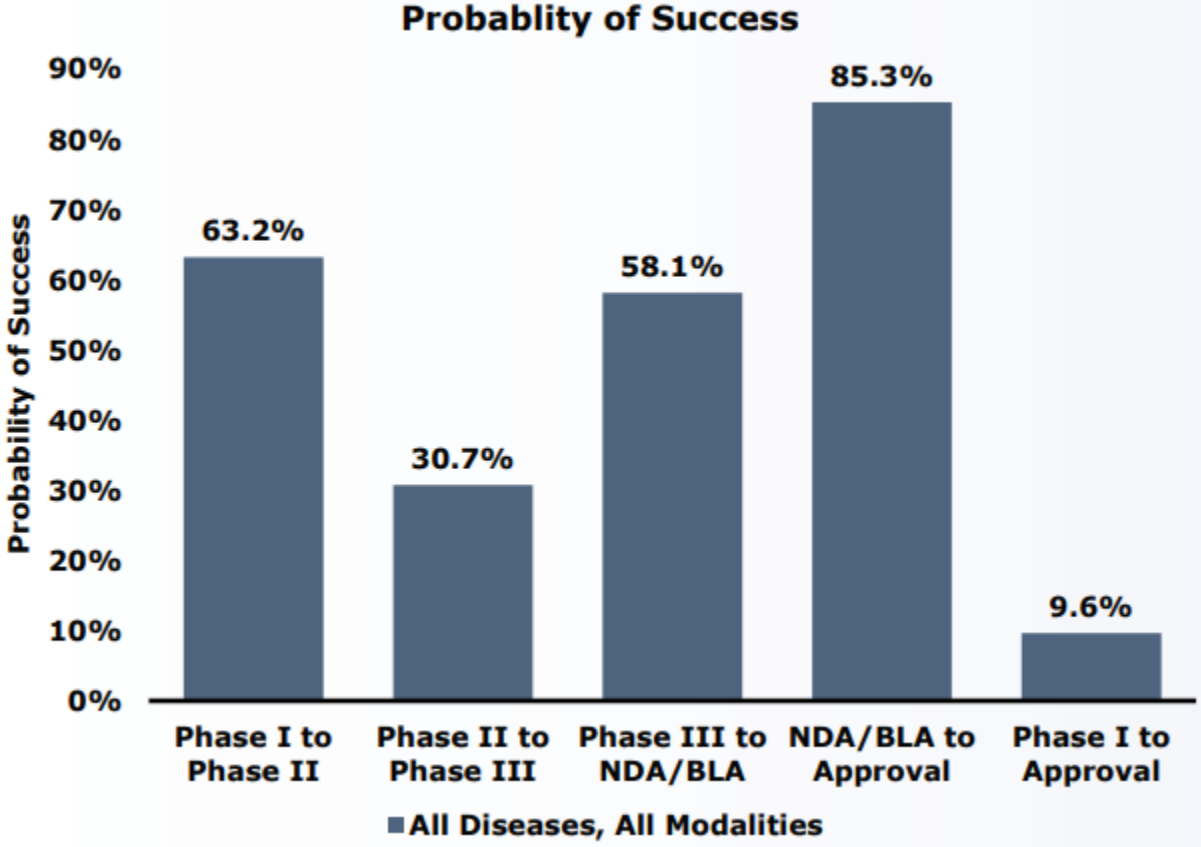
# Creating new medicines is not efficient

| | |
|---|---|
| **10-14%** | Probability of approval |
| **$1.4 billion** | Total cost to bring a drug to market |
| **10 years** | Total development time |

# Failure rates vary by indication



# Many drugs are failing even in Phase 2 & 3



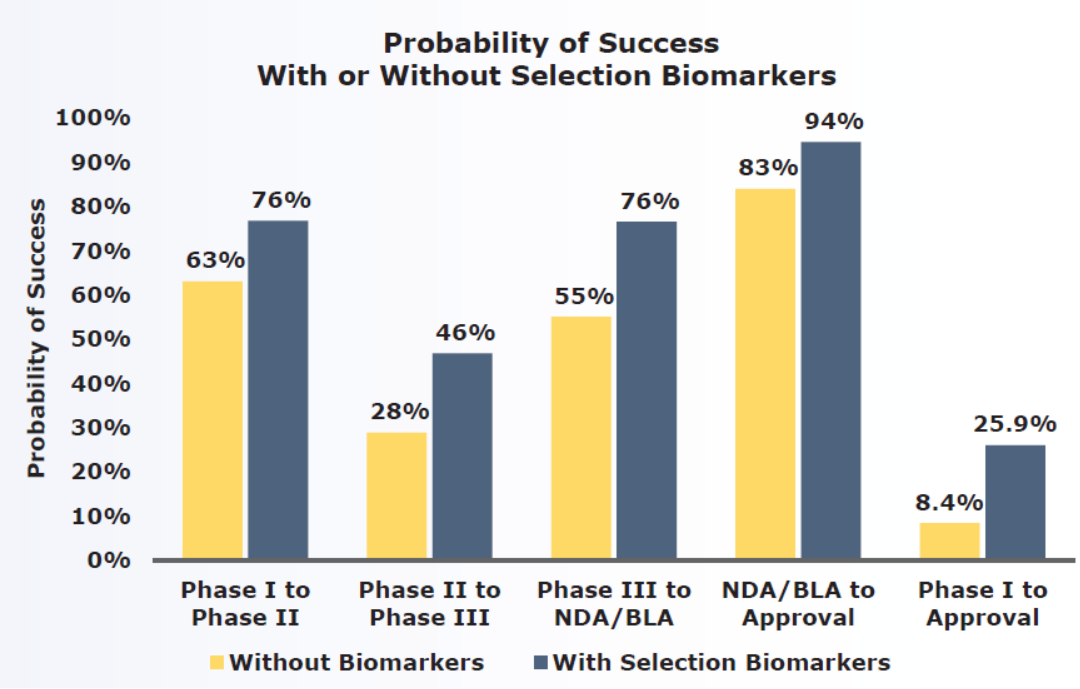
# Why do so many drugs fail?

**Biology, Biology, Biology**

Lack understanding of biology

Failure to demonstrate efficacy

# Patient stratification biomarkers improve the POS throughout development

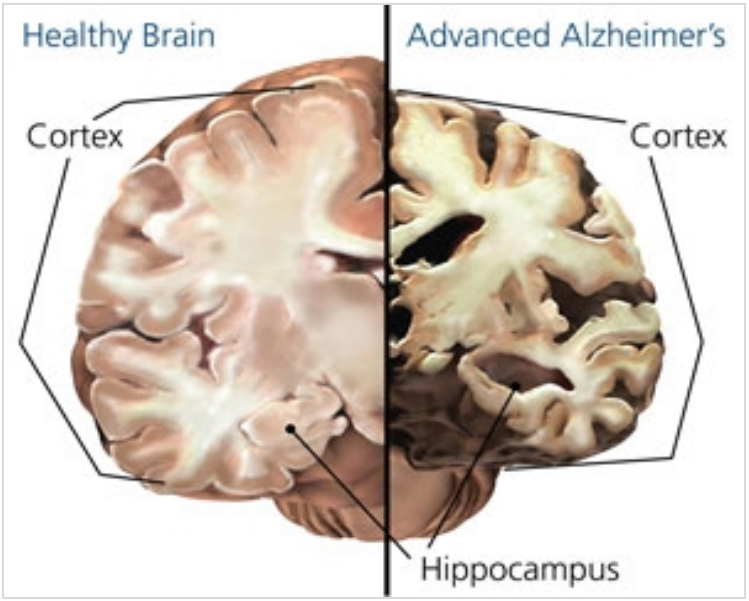


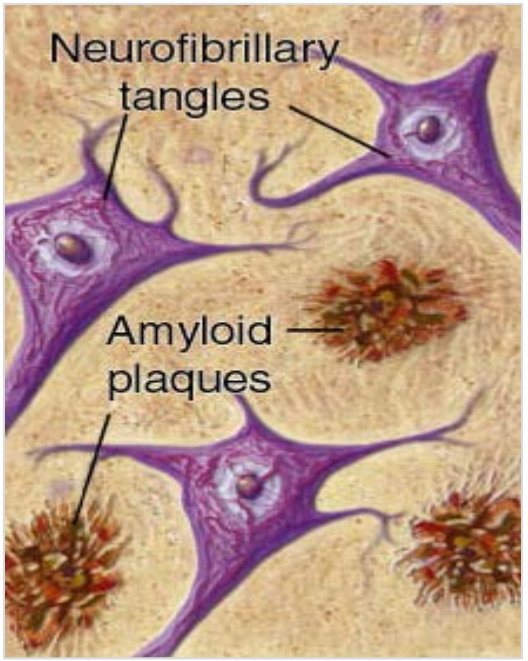

- POS was lower in chronic, high prevalence diseases, where the clinical trials are complex and involve large, heterogeneous patient populations

# The influence of biomarkers is complex

- Trials using biomarkers for patients stratification more than double the overall probability of success
  - Most significant in Phase 1 and Phase 2
- No significant difference in POS for trials whose objectives include evaluating or identifying novel biomarkers of efficacy or toxicity

# The beta-amyloid story reflects the importance of the RIGHT biomarkers

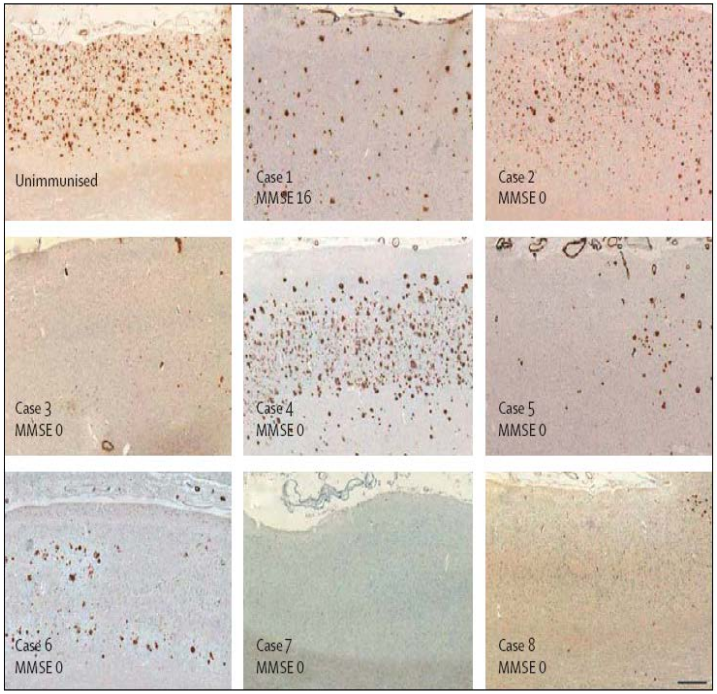


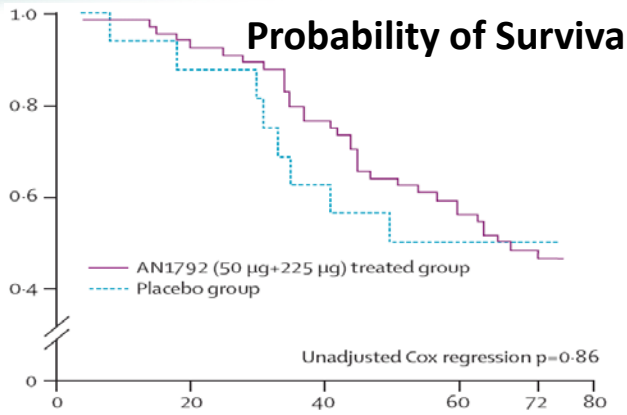



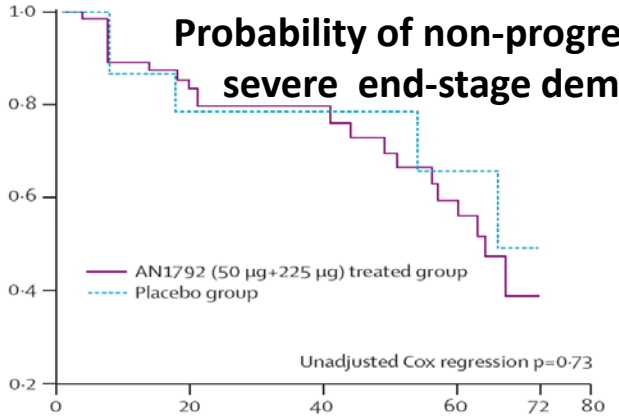

- Inherited AD is caused by mutations in APP
- No tau mutations identified in AD
- Tau events are downstream of Aβ

**Genetic data led to an Aβ-centric view of AD**

# The beta-amyloid story reflects the importance of the RIGHT biomarkers




**Even nearly complete plaque removal did not increase survival or delay dementia in Alzheimer's patients**

Holmes et al. Lancet. 2008

# The beta-amyloid story reflects the importance of the RIGHT biomarkers

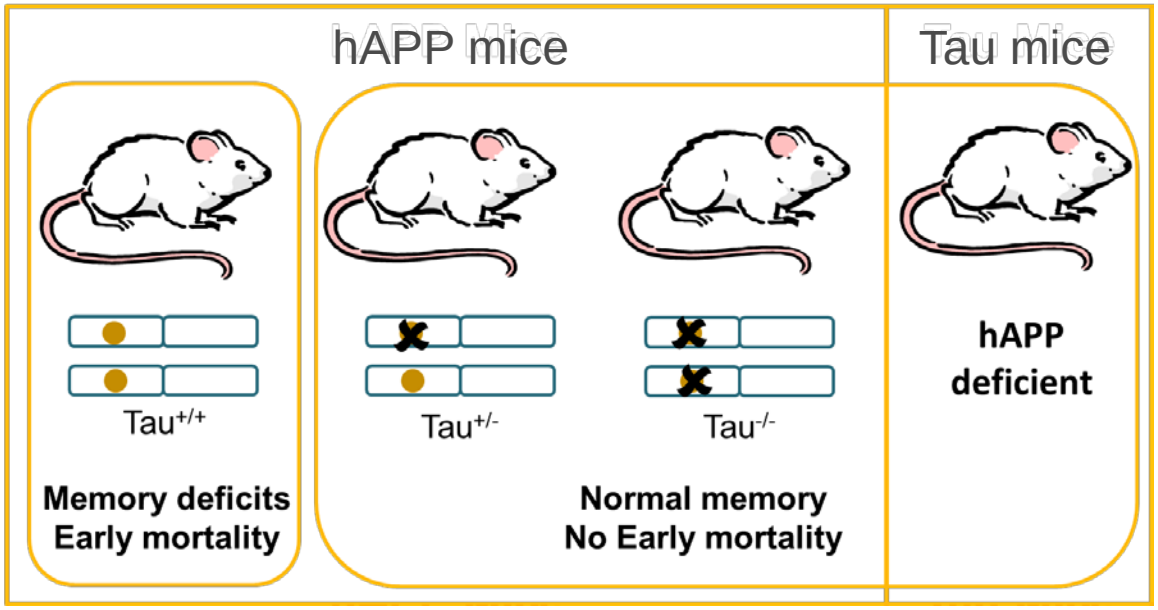
- Bapineuzumab: reduces plaque formation

| Phase 2 | | Phase 3 |
|---|---|---|
| Significant improvement in biomarkers | ≠ | No significant difference in ADAS-Cog or DAD |

- BACE inhibitors also failed to demonstrate efficacy despite positive results for biomarkers

# Beta-amyloid may be the wrong target

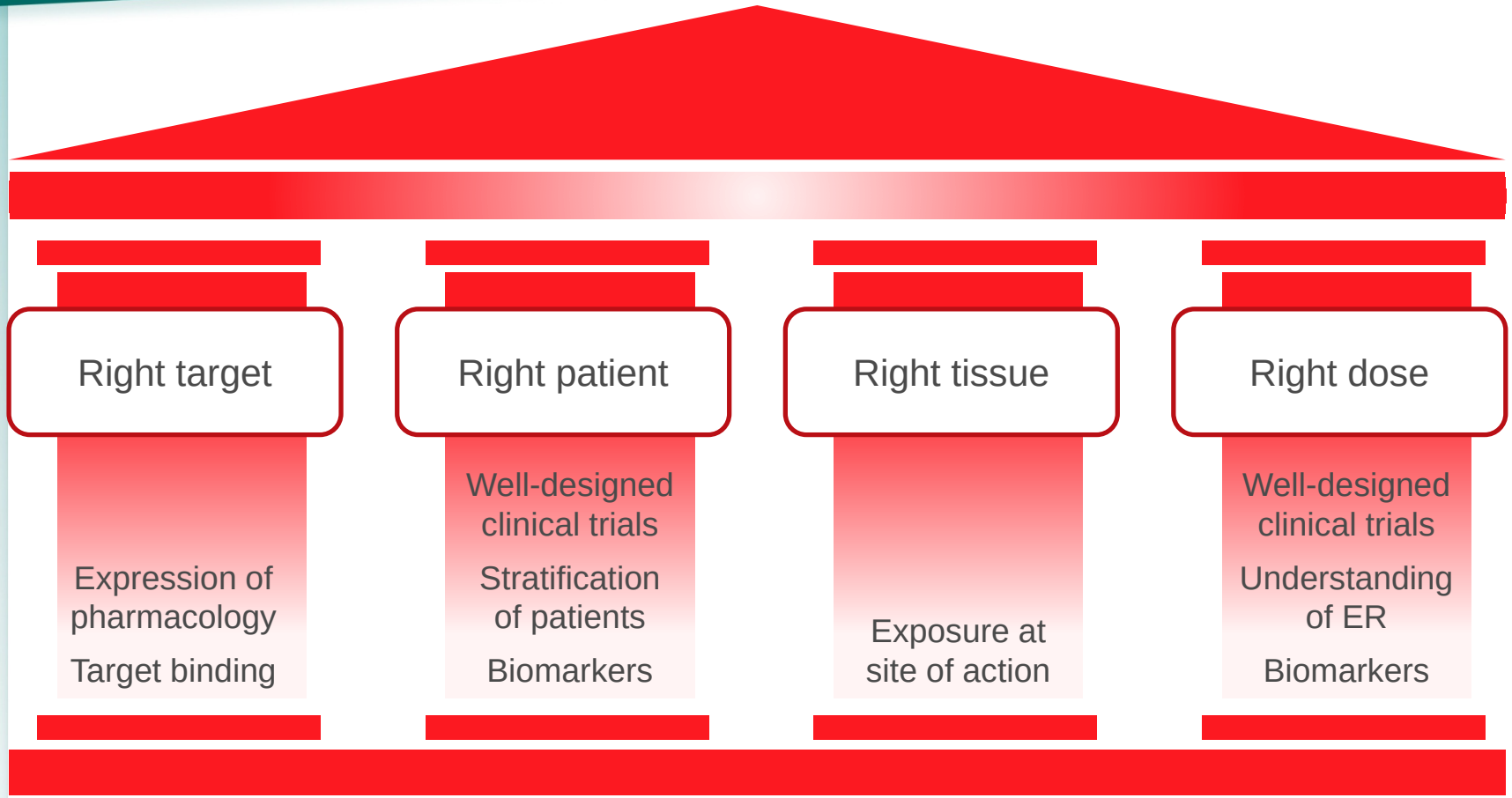
- Severity of dementia is well-correlated with the density of NFT's (but not plaques) in AD patients
- Neurons expressing tau degenerate in the presence of Aβ, but tau-depleted neurons did not degenerate
- (wt) tau reduction protects against Aβ-induced cognitive impairment in mice expressing hAPP



# Why do so many drugs fail?

- Wrong target/wrong population
  - Lack of predictive translational efficacy models in early development
  - Insufficient knowledge of therapeutic pathways in diseases with complex etiologies
- Suboptimal selection of dose, schedule, or regimen
  - Inadequate characterization of dose/exposure-response relationship in Phase 2
  - Non-stratified patient population that dilutes Ph 3 results
  - Reliance on non-validated surrogate or biomarker endpoints that are not predictive of clinical endpoints in Phase 3
- Suboptimal Ph2 study with inadequate controls leading to a false positive result
  - Small sample size
  - Subjective endpoints
  - Large placebo response
- Safety concerns

# Success requires the right target, right tissue right dose, and right patient

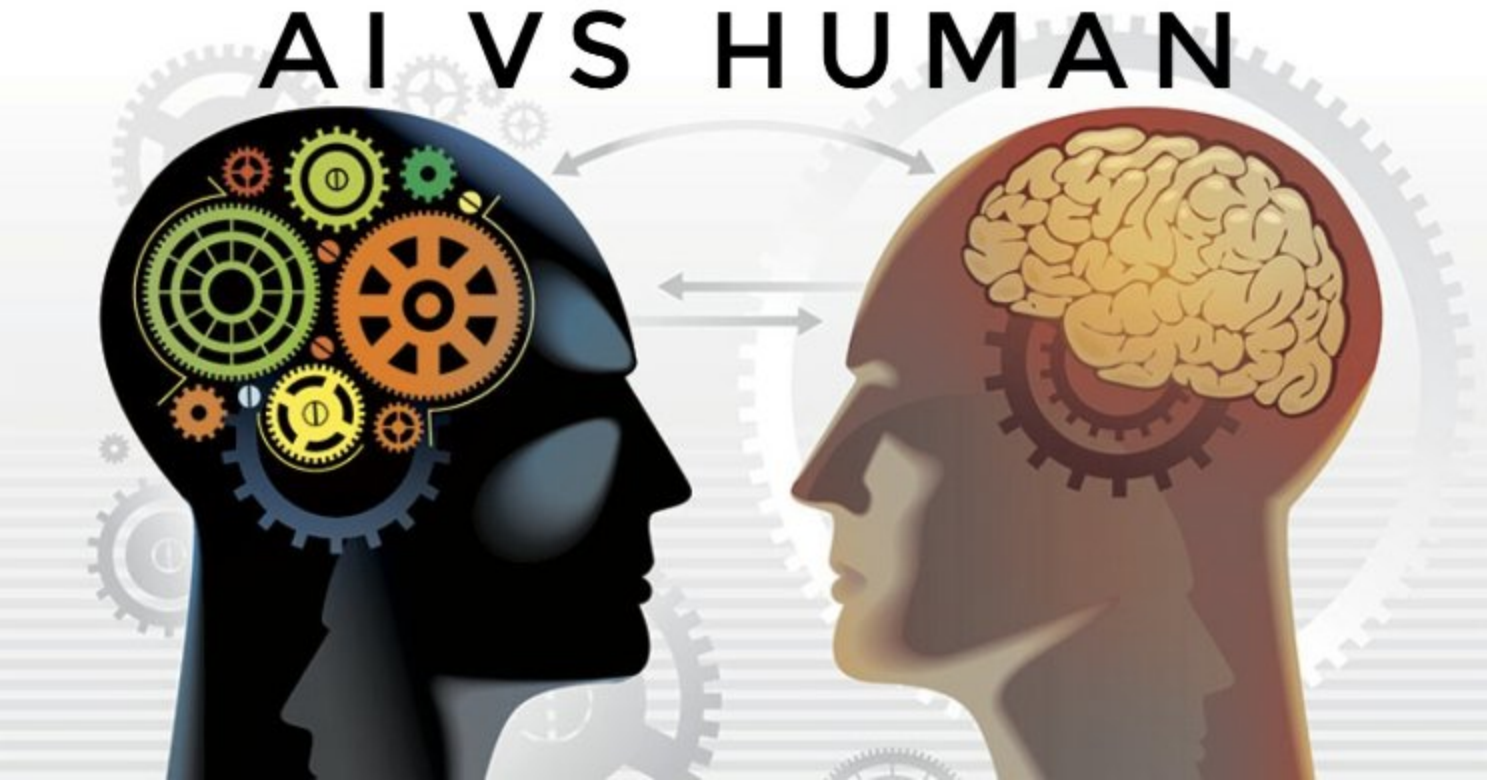


# Quantitative pharmacology toolbox informs critical success factors for development

- NCA
- Population PK modeling
- Population PKPD / ER modeling
- Physiologically-based pharmacokinetic modeling
- Disease progression modeling
- Model-based meta-analysis
- Clinical trial simulation
- Quantitative systems pharmacology
  - Fit-for-purpose
  - Not necessarily large models
  - Defined by their mechanistic nature

# Computers don’t think

- You have to come up with the biological hypothesis



# QSP isn't the answer to everything

Bursting the Genomics Bubble

A Decade Later, Genetic Map Yields Few New Cures

Deflating the Genomics Bubble

The human genome project, 10 years in: Did they oversell the revolution?

Human genome 10th anniversary: Waiting fot the revolution

The Human Genome Project Wasn't Overhyped. The Payoff Just Took Time

# QSP usually isn't the best tool to select an FIH starting dose or a Phase 3 dose

- Not usually resource effective for FIH starting dose
  - Parameters + characterization of species differences in parameters and even the underlying biology (model structure)
- Can't (usually) address key questions as effectively as population PK and ER modeling for Phase 3 and marketed dose

# QSP adds value across development


Understanding of disease pathophysiology

Target selection

Modality choice

Experimental design

Selecting combinations

Bridging between HV and patients

POC dose selection

Bridging between RO and biomarkers

Patient stratification

Understanding failures and informing back-up programs

Bridging across indications

Scaling to pediatrics

~~Target site concentration~~

~~FIH starting dose~~

~~Phase 3 / marketed dose~~

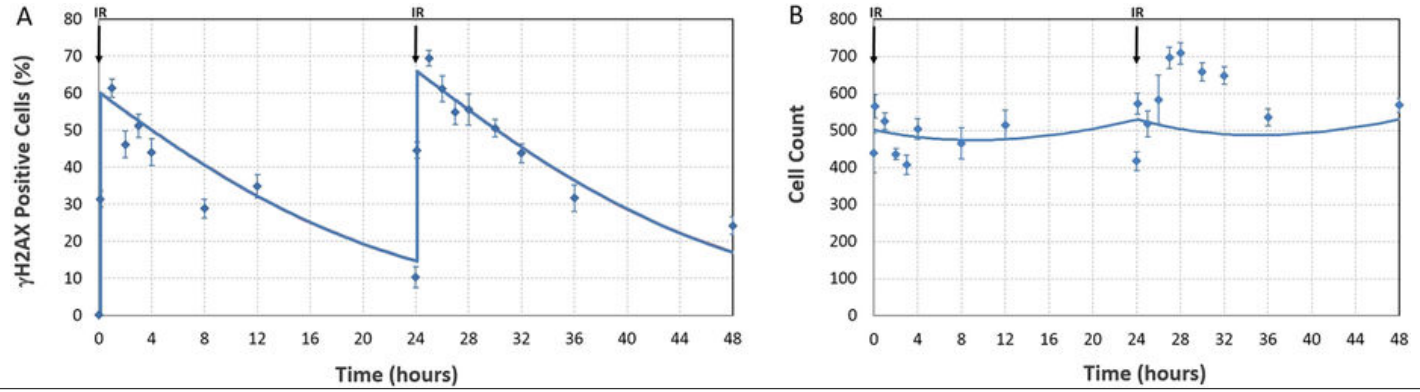
~~Clinical trial simulation~~

~~DDI, bioequivalence, intrinsic/extrinsic factors~~

# Sometimes QSP makes sense for FIH dose selection – be parsimonious!

- ATR inhibitor AZD6738 + ionizing radiation
- Model of the cell cycle, incorporating DNA damage (from replication stress and IR) and repair, and effect of AZD6738

Fitted Data (in vitro)

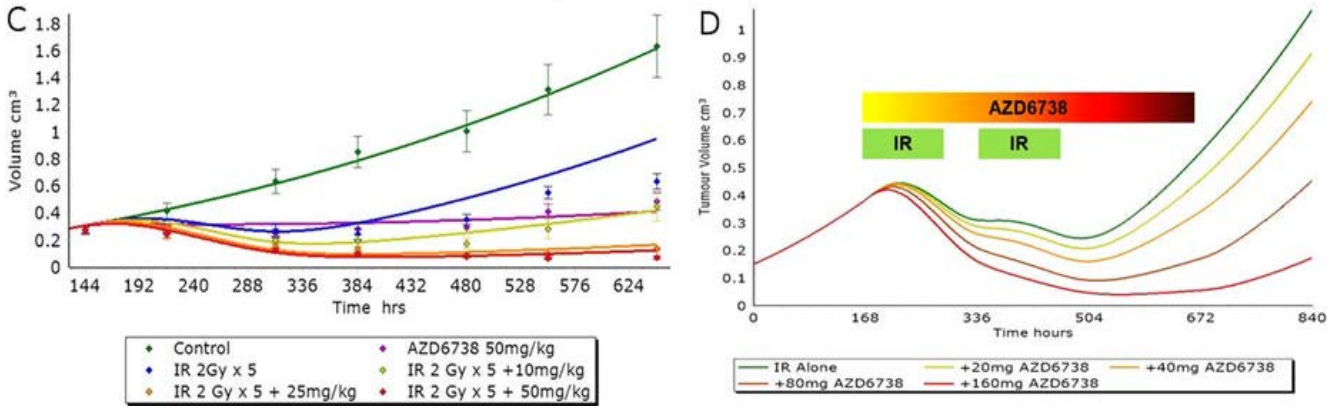



Checkley S, MacCallum L, Yates J, et al. *Scientific Reports*. 2015;5:13545. doi:10.1038/srep13545.

# Although it usually isn't, QSP was the best tool for Phase 1 dose selection in this case

- ATR inhibitor AZD6738 + ionizing radiation
- Model of the cell cycle, incorporating DNA damage (from replication stress and IR) and repair, and effect of AZD6738

Calibration data (C) (xenograft) Human predictions (D)




Checkley S, MacCallum L, Yates J, et al. *Scientific Reports*. 2015;5:13545. doi:10.1038/srep13545.

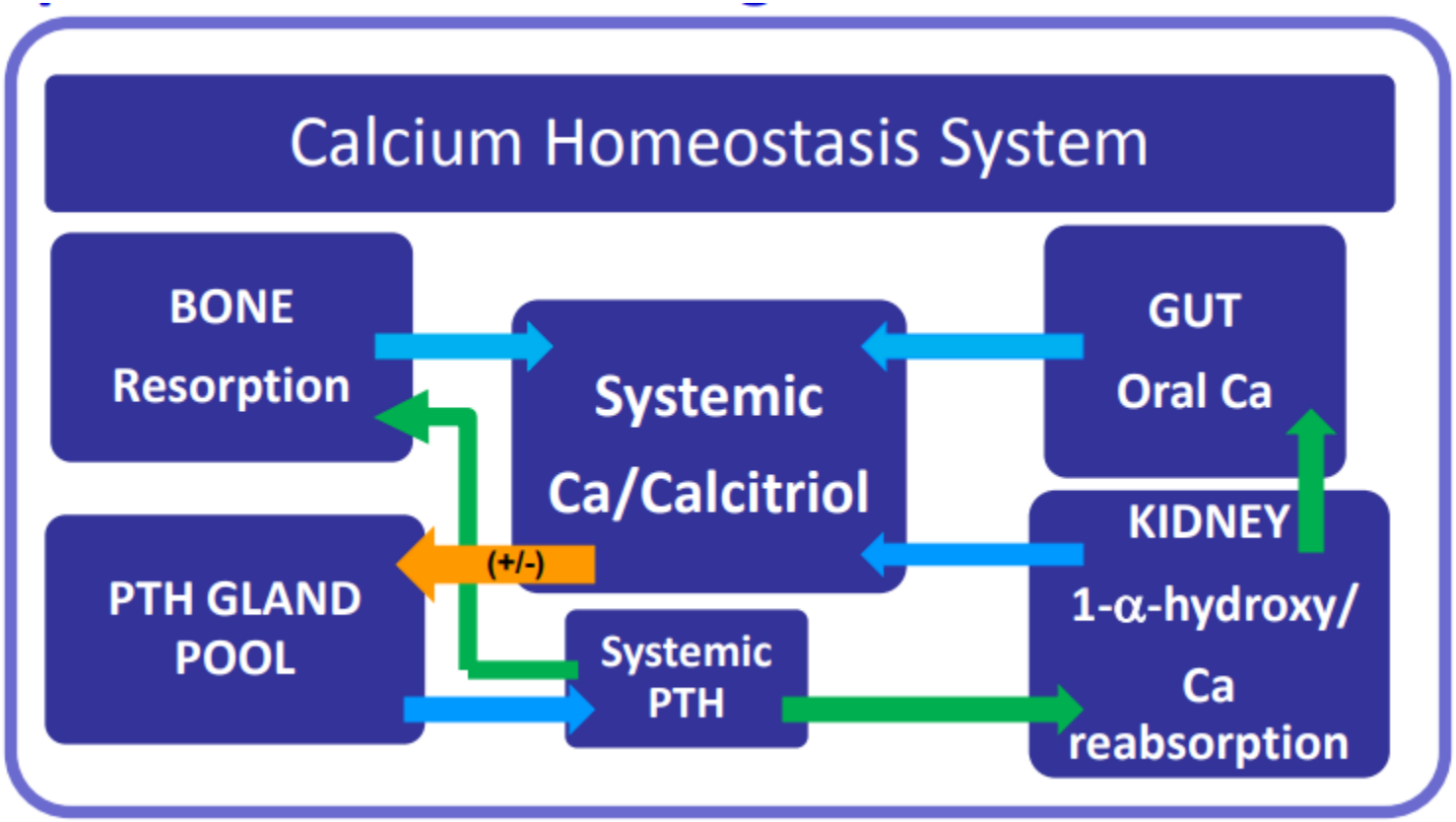
- Used to inform dose selection for Phase I

# QSP informs big decisions and has regulatory acceptance: the denosumab story

- Could not address key questions with clinical studies due to dosing interval (q6M) and required trial duration
  - Effects of drug regimen changes
  - Treatment discontinuation
  - Prior treatments
  - Sampling schemes
- Uncertainty in the scientific community regarding the physiologic links between clinical markers and clinical endpoints

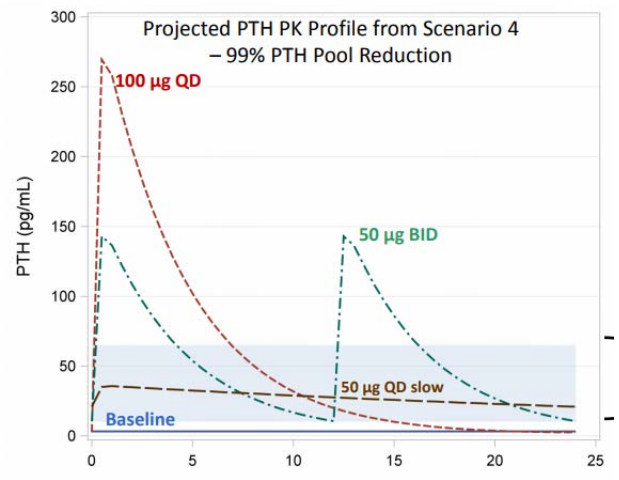
**QSP is the perfect tool to address these issues**

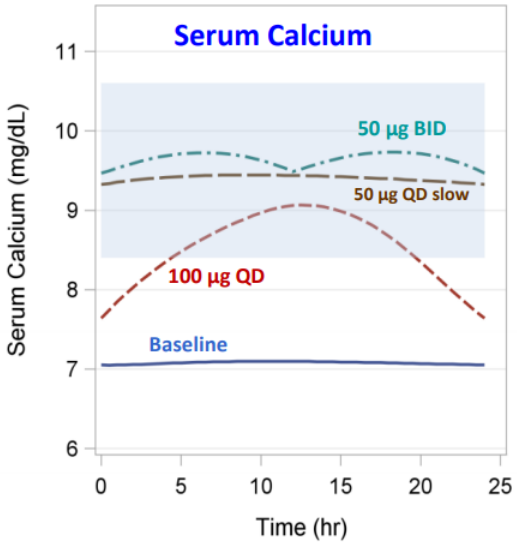
# Model incorporated bone physiology and calcium homeostatic mechanisms

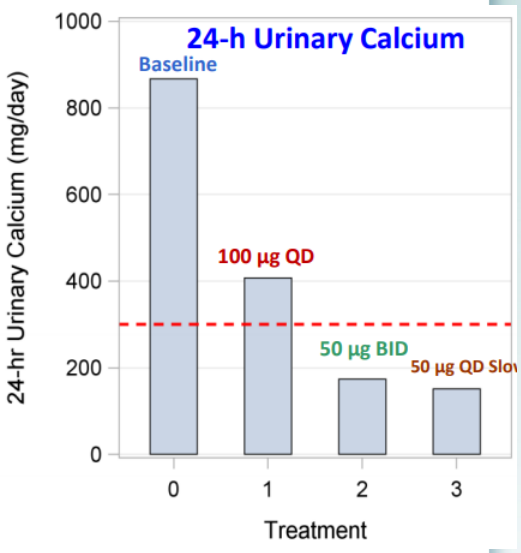


# Model improved disease understanding and supported regulatory interactions

- FDA recommended “the dose regimen (for NATPARA (Recombinant Human Parathyroid Hormone (rDNA)) should be further optimized to address the safety concerns for hypercalciuria” based on QSP modeling
- Control on hypercalciuria is feasible with more frequent regimen or a slow release PTH profile at lower systemic exposure than 100 µg QD



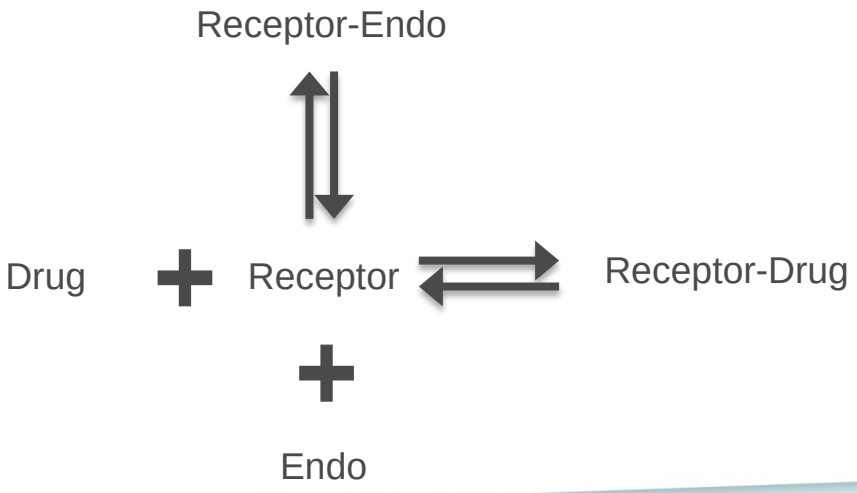
# Why QSP was so successful in this case

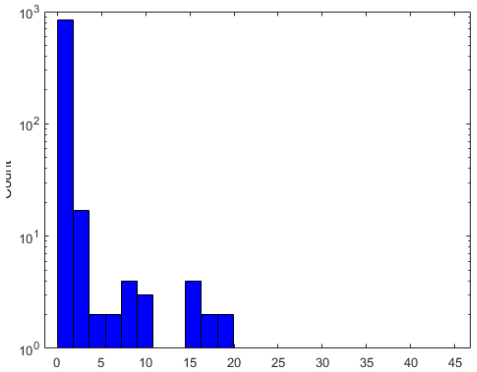
# Don’t expect QSP to support regulatory interactions as a rule yet

- Complexity and “fit-for-purpose” status of these models
- Clinical study and traditional modeling and simulation will continue to provide sufficient data and understanding to support the majority of regulatory discussions/decisions.
- No regulatory guidance
- Regulatory acceptance of a QSPM will require comfort by users and consumers with the underlying physiology, mathematics, and mechanistic assumptions supporting the application

# QSP informs small decisions

- Objective: determine suitable equilibration time for in vitro experiment
- Method: simulate competitive binding of drug and endogenous ligand to target receptor, for different concentrations of drug and ligand, with or without pre-incubation of ligand and receptor
- Data: $k_{on}$ and $k_{off}$ for drug and endogenous protein was available, but ranged across several orders of magnitude




Time to Equilibrium

# QSP models are challenging to implement

## #1 Scope – what's the right level of detail?

Parsimony guides PK/PD modeling, but not easily applicable to QSP

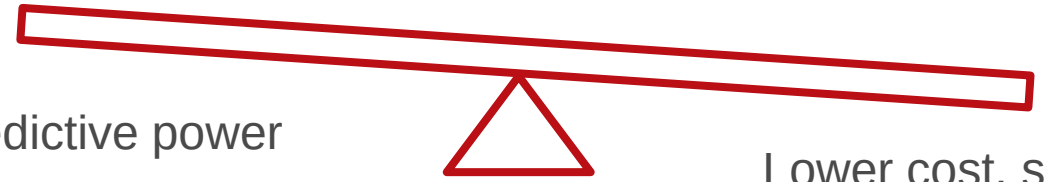
**More granular and complex**

Greater predictive power

Higher cost, longer timelines

May be difficult to interpret

Requires lots of data



**Less granular and complex**

Lower cost, shorter timelines

Easier to develop and maintain

Requires less data

**Assess need for QSP, predefine objectives, assess amount of biological and pharmacological data, consider extent of cross-functional support**

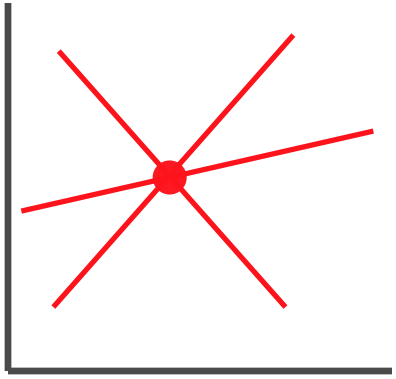
# QSP models are challenging to implement

## #2 Identifiability

Increasing complexity increases the difficulty of estimating parameters

*Structural identifiability*: can I identify the model if I have sufficient data?
*Practical identifiability:* can I identify the parameters given the data I have?

**The identifiability problem**

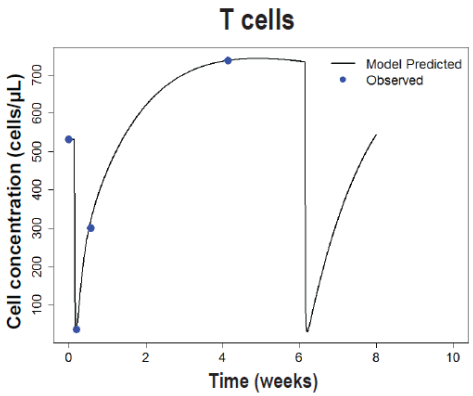


- Non-identifiable models may result in misleading conclusions
- Identifying parameters requires large amount of data
- Need to leverage *in vitro* data, data from animal models, and clinical data

# Leverage literature data, internal data, in vitro, animal, and clinical data to determine parameters

- Before you start parameterizing, reduce the model – “fit-for-purpose”
  - Lump terms
  - Sensitivity analysis
  - Exploit time-scales

- Directly from experimental data (e.g, tumor doubling time)
- Estimate other parameters from observed data
  - Modular approach, common to estimate just a few parameters at a time
- Local and global sensitivity analyses (which parameters really matter?)

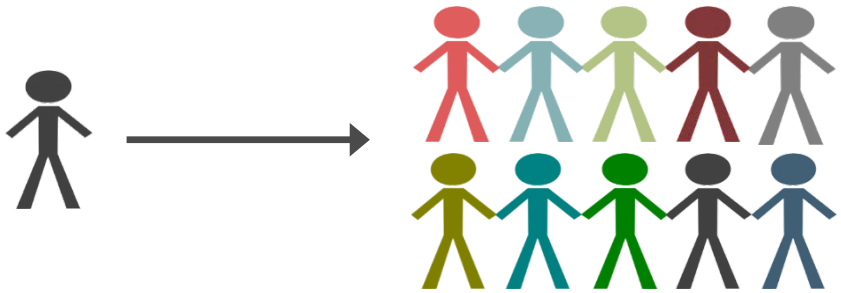



Singh, I., et al. Poster presented at the ASCPT annual meeting. Atlanta, GA (March 2014)

# QSP models are challenging to implement

## #3 Inter-individual variability

Typically, little is known about parameter distributions
(we might know thetas, but we don't know omegas)



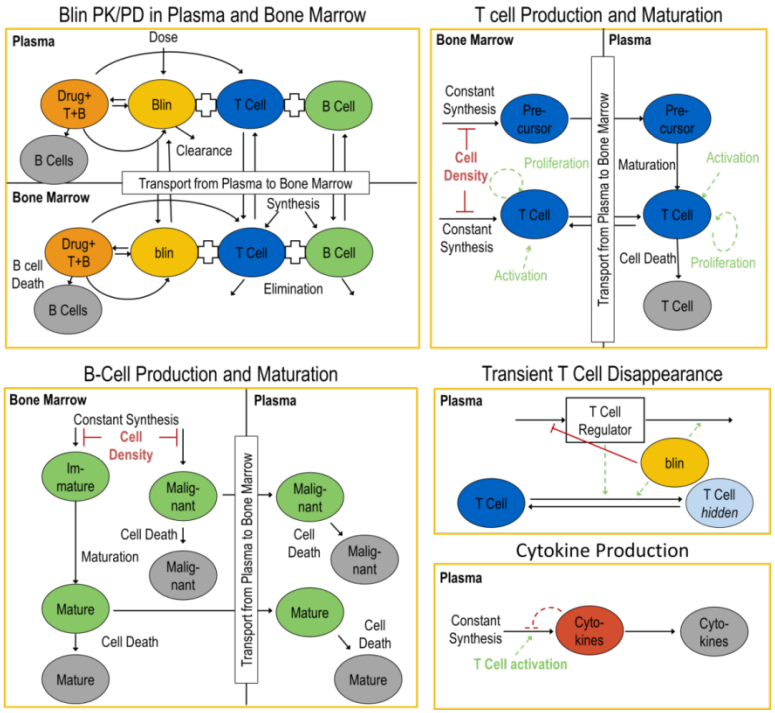
How do we go from one virtual patient to a population of virtual patients without enough data to determine the parameter distributions?
(equivalent to simulating across covariates)

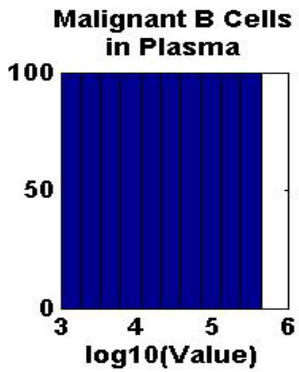
# How do we create a virtual population?

- Inform parameter distributions with data
  - Ideal, but very difficult in practice to obtain such data
- Assume distribution for parameters
  - e.g., uniform distribution from 5-fold below to 5-fold above the nominal value
  - e.g., normal distribution, mean = nominal value, SD - assume X% variability
- Use standard error of fitted estimates to create populations (not recommended)
- Monte Carlo approach to fitting non-identifiable model
  - Fit the model repeatedly and use the distribution of fitted parameters
- Check that simulated virtual patients are reasonable
  - Necessary because correlation between parameters isn't known, but likely exists
- Consider adding variability only to sensitive parameters

# Putting it into practice: Case Study #1

## PhysioPD® Model




**Cohort of patients**

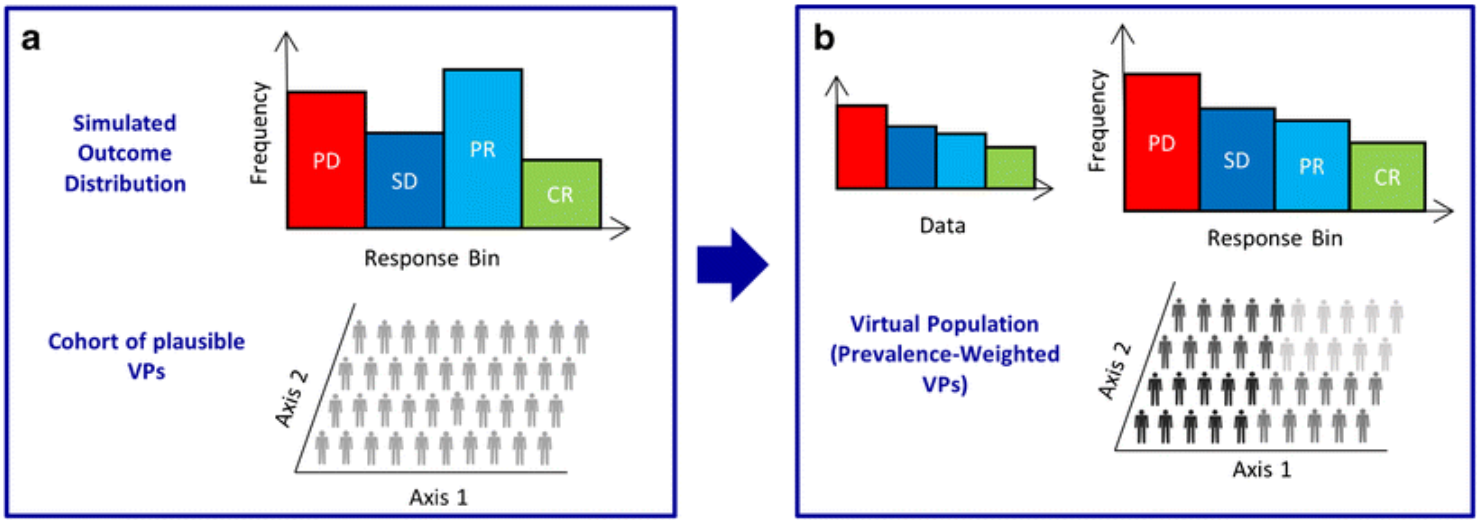
**Valid VP**
Responder
Relapser
Non-responder

**Invalid VP**

Singh, I., et al. Poster presented at the ASCPT annual meeting. Atlanta, GA (March 2014)
Yuraszeck, T., et al. Poster presented at the ASCPT annual meeting, San Diego, CA (March 2016)

# Putting it into practice: Case Study #2

…when you have more data on the outcomes

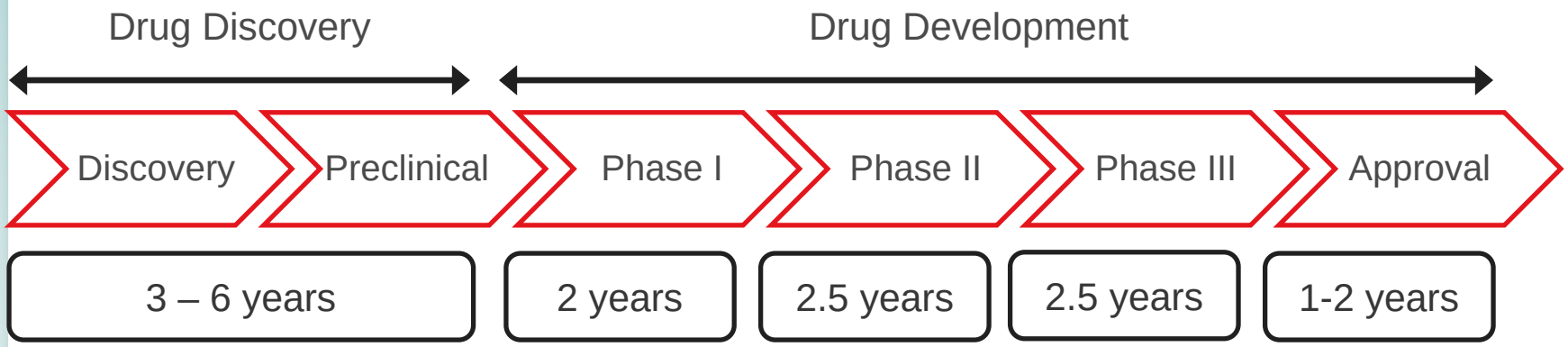



Cheng, Y., et al. (2017). The AAPS Journal **19**(4): 1002-1016.

- Create a cohort of plausible virtual patients
- Weight each virtual patient such that the calculated statistics match the trial or experimental data to create a population of virtual patients (equivalent to clinical trial simulation)

# QSP models are challenging to implement

## #4 Timelines

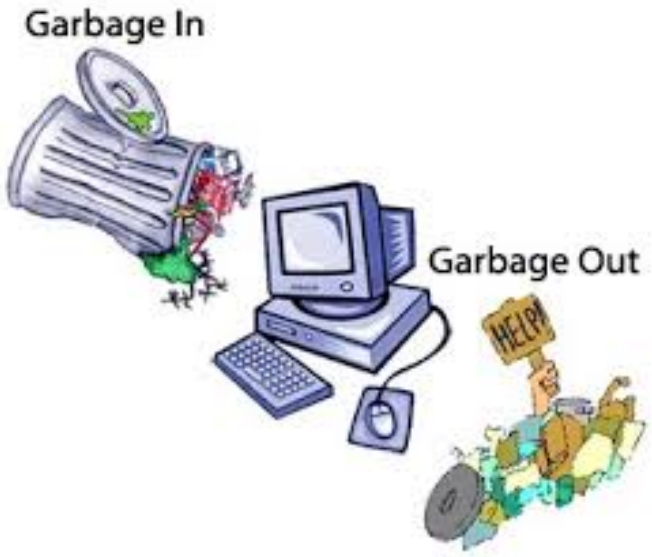



- Efforts to accelerate clinical development (rise in large, seamless Phase I trials)
  - Ipilimumab + nivolumab went from Phase I to Phase III in 2 years
- Development of QSP models requires 6 mo – 2 years

**Consider development strategy and utility of QSP early!**

# Best practices for QSP: Overcoming the Roadblocks to Implementation

- Remember QSP isn't always the answer – use it for the right questions
- Consider regulatory risk associated with using QSP
- Evaluate need for QSP early in development (pre-FIH)
- Ask the right questions and pre-define objectives
- Choose appropriate scope
- Assess identifiability
- Consider uncertainty and inter-individual variability
- Get cross-functional buy-in



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