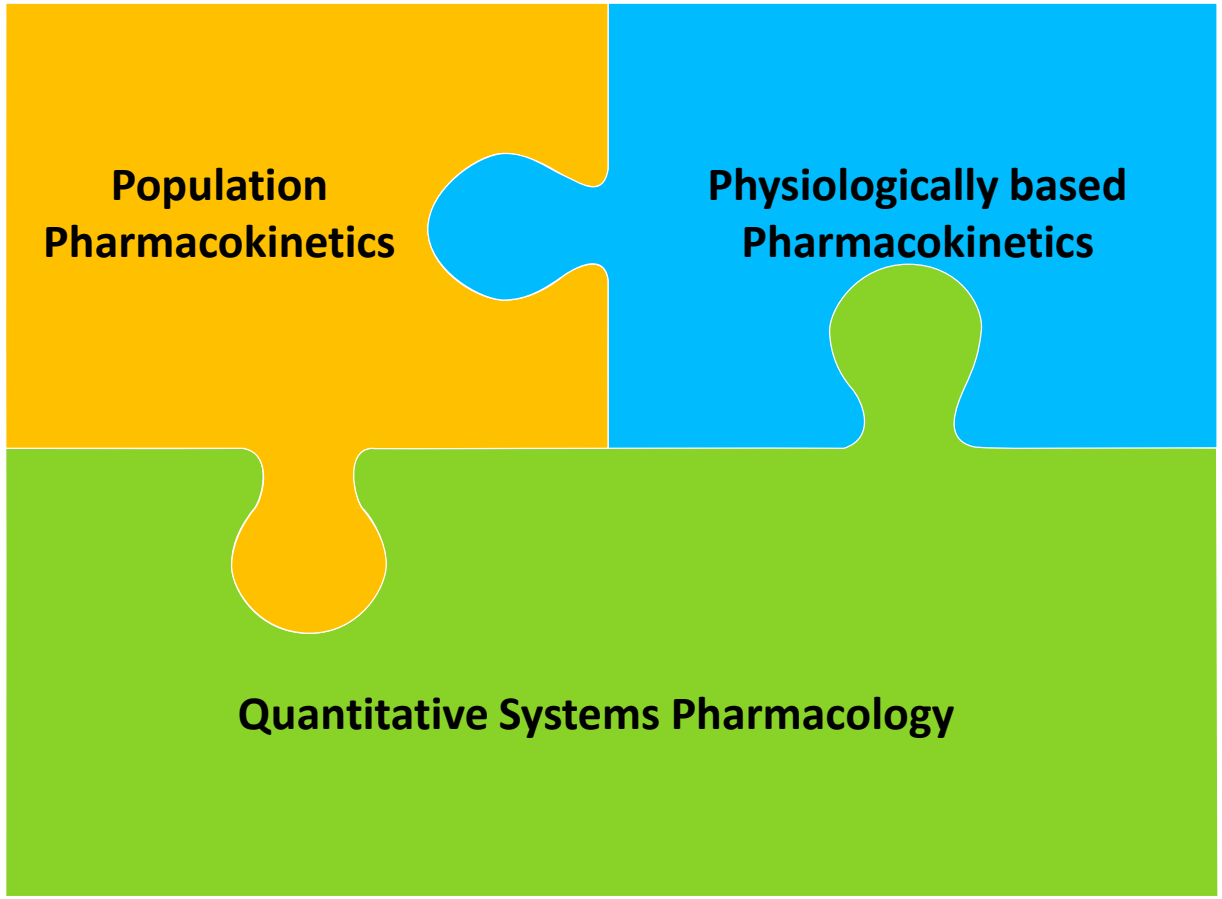
Geriatric Clinical Pharmacology:
State of the Art in a Neglected Majority

Pharmacometric Approaches to Streamline Pharmacotherapy in Older Adults

ASCPT 2019 Annual Meeting

March 15, 2019 / Jan F. Schlender


Population
Pharmacokinetics
Physiologically based
Pharmacokinetics
Quantitative Systems Pharmacology

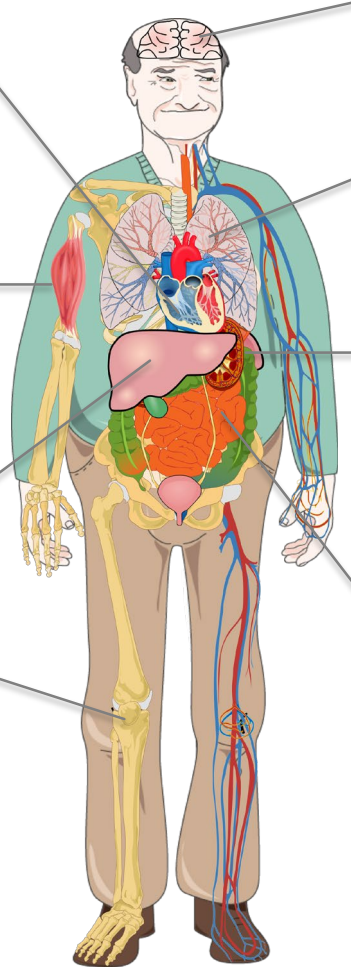
Physiology of aging

Cardiovascular System
Reduction of myocytes and capacity

Skeletal muscles
Decline of mass, function and strength

Liver
Altered metabolic capacity

Body composition
Shift of fat to muscle mass ratio and body water distribution

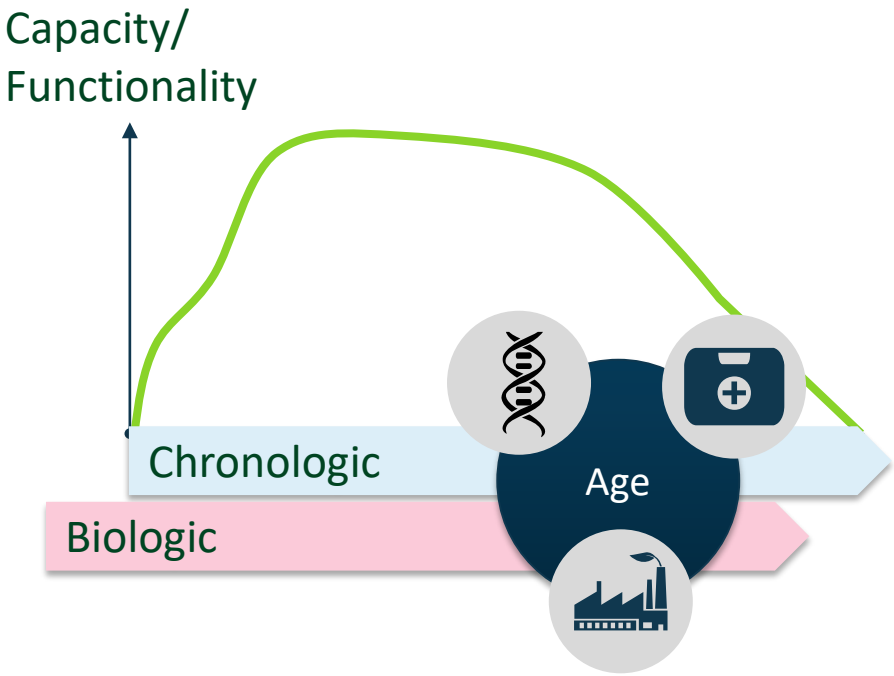


Brain
Altered blood-brain barrier permeation

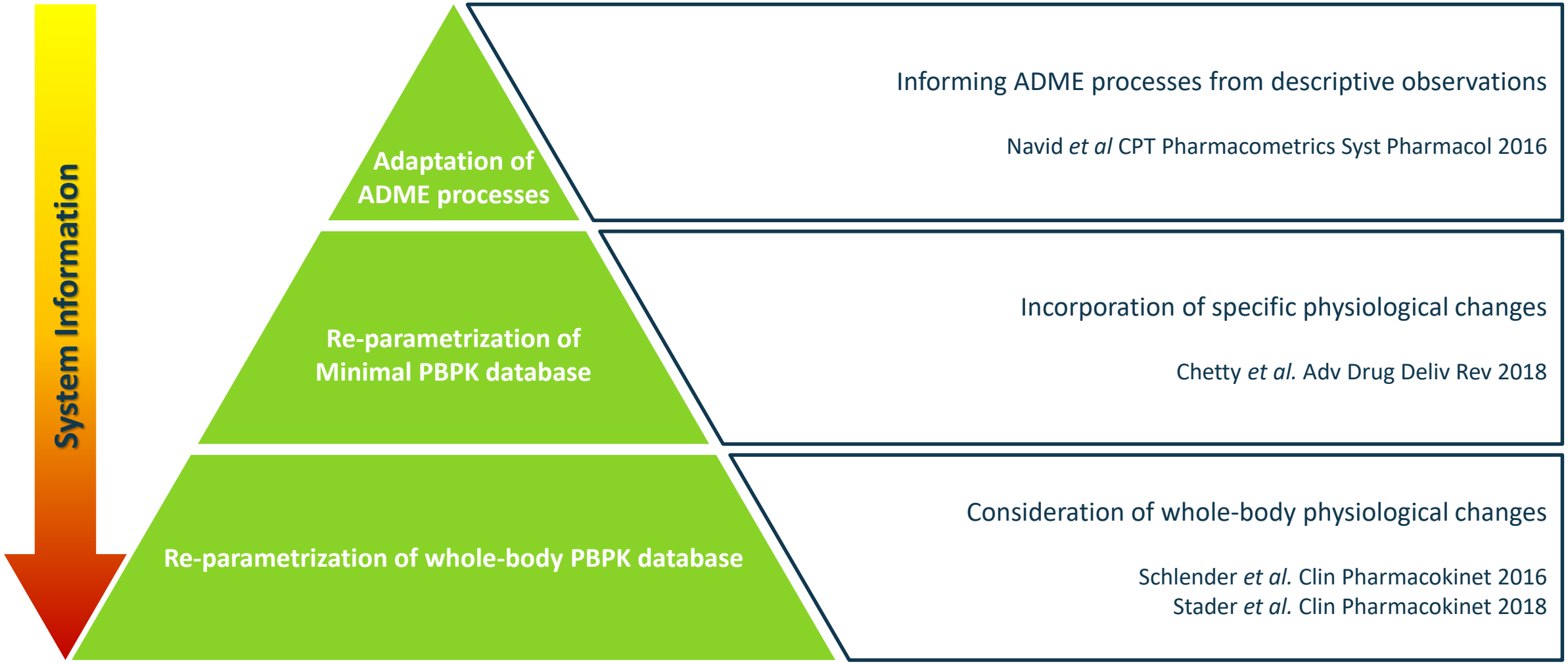
Respiratory tract
Reduced functional capability

Kidney
Sclerotization of functional mass and filtration rate

Gastrointestinal tract
Reduced digestion and altered pH-regulation

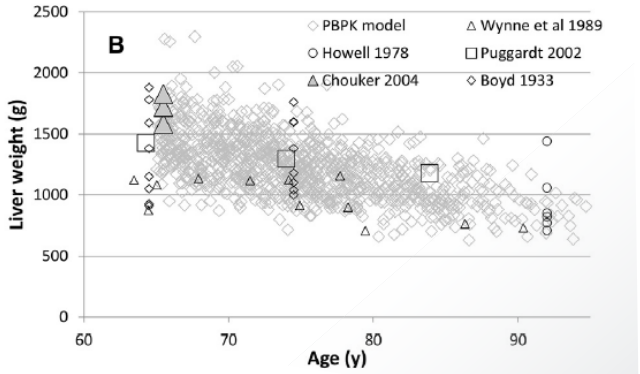


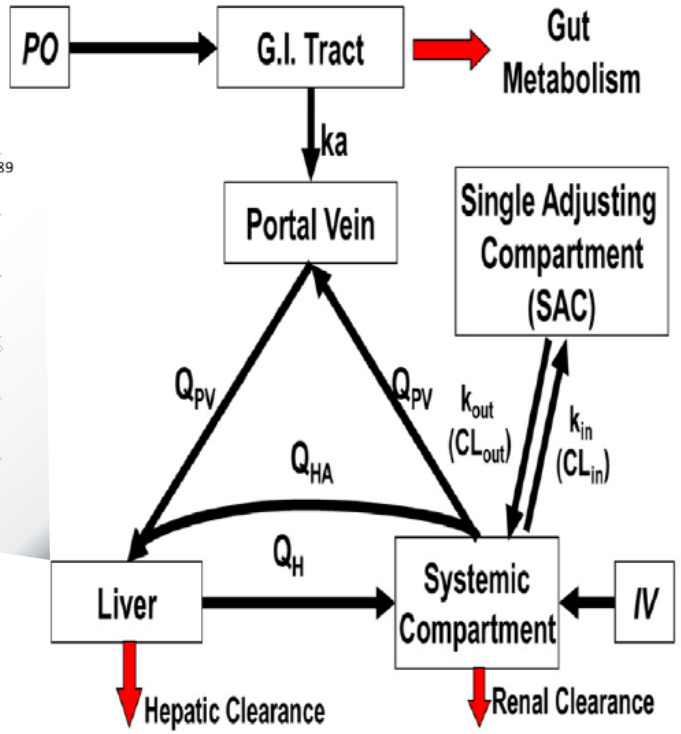
Physiologically based Pharmacokinetics (PBPK) approaches to describe an aging population

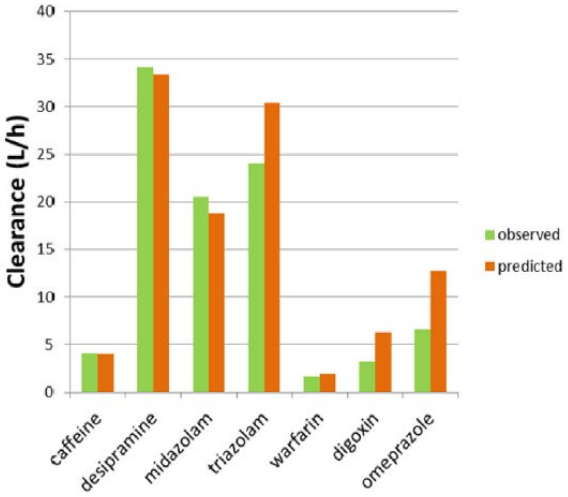


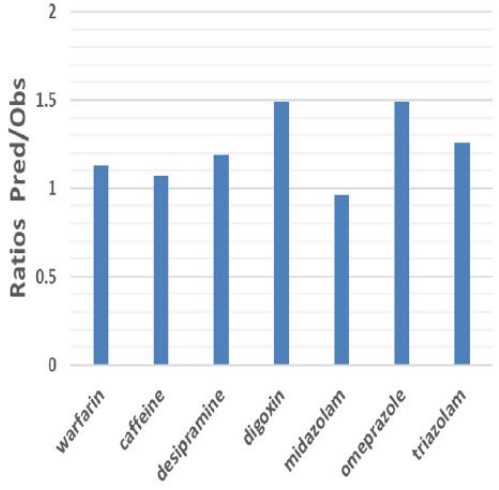
PBPK approaches to describe an aging population

Re-parametrization of Minimal PBPK physiological database









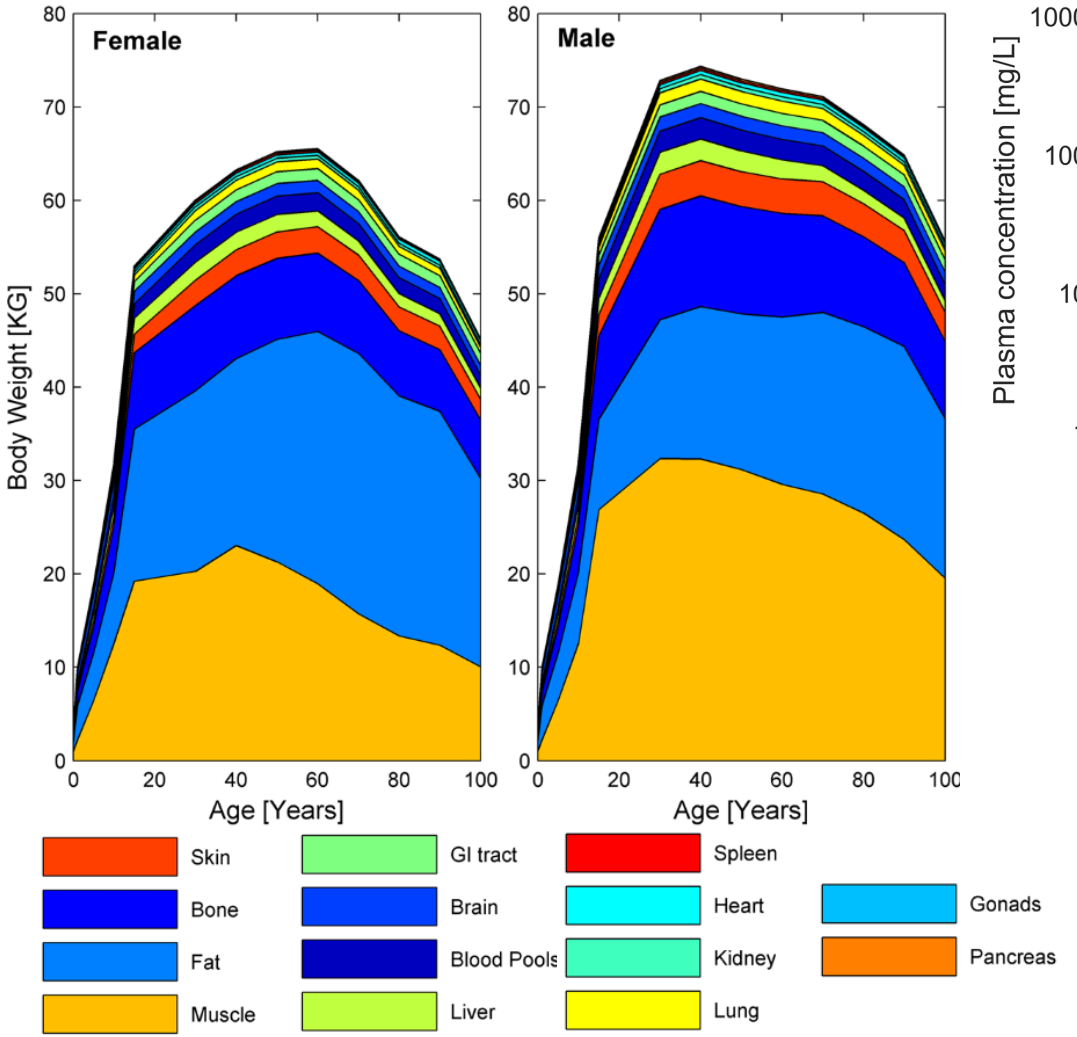
// Heterogeneous physiological aging progress is not characterize and my lead to miss-predictions of distribution

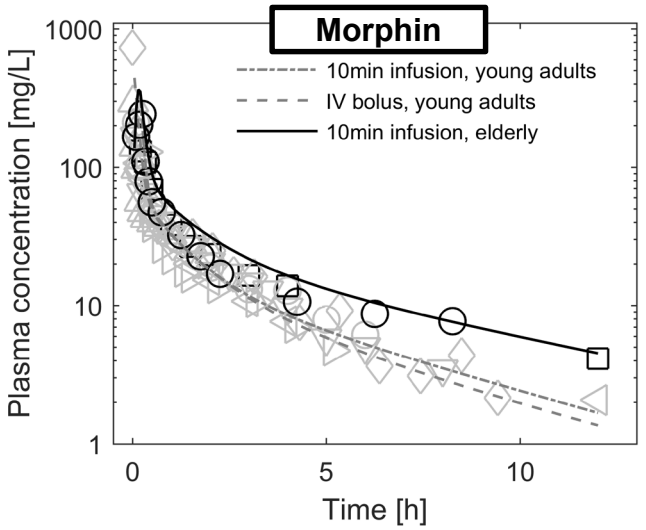
// Depending on the application, a more simple structure of a PBPK model might be sufficient

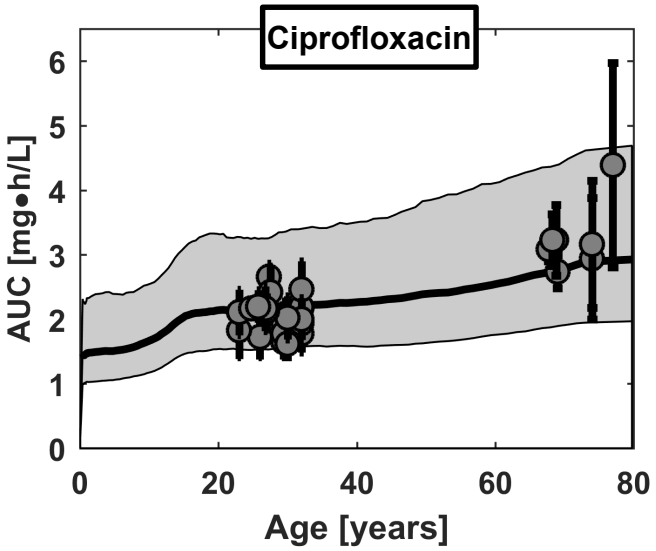
Chetty et al. Adv Drug Deliv Rev 2018

PBPK approaches to describe an aging population

Re-parametrization of whole-body physiological database







- // Complexity
- // Confidence in sparse data base for certain parameters

- // Distinguish between disease and age-related changes
- // Supportive for mechanistic PD modeling

Schlender *et al.* Clin Pharmacokinet 2016
Schlender *et al.* Clin Pharmacokinet 2018

Availability of Information in aging adults

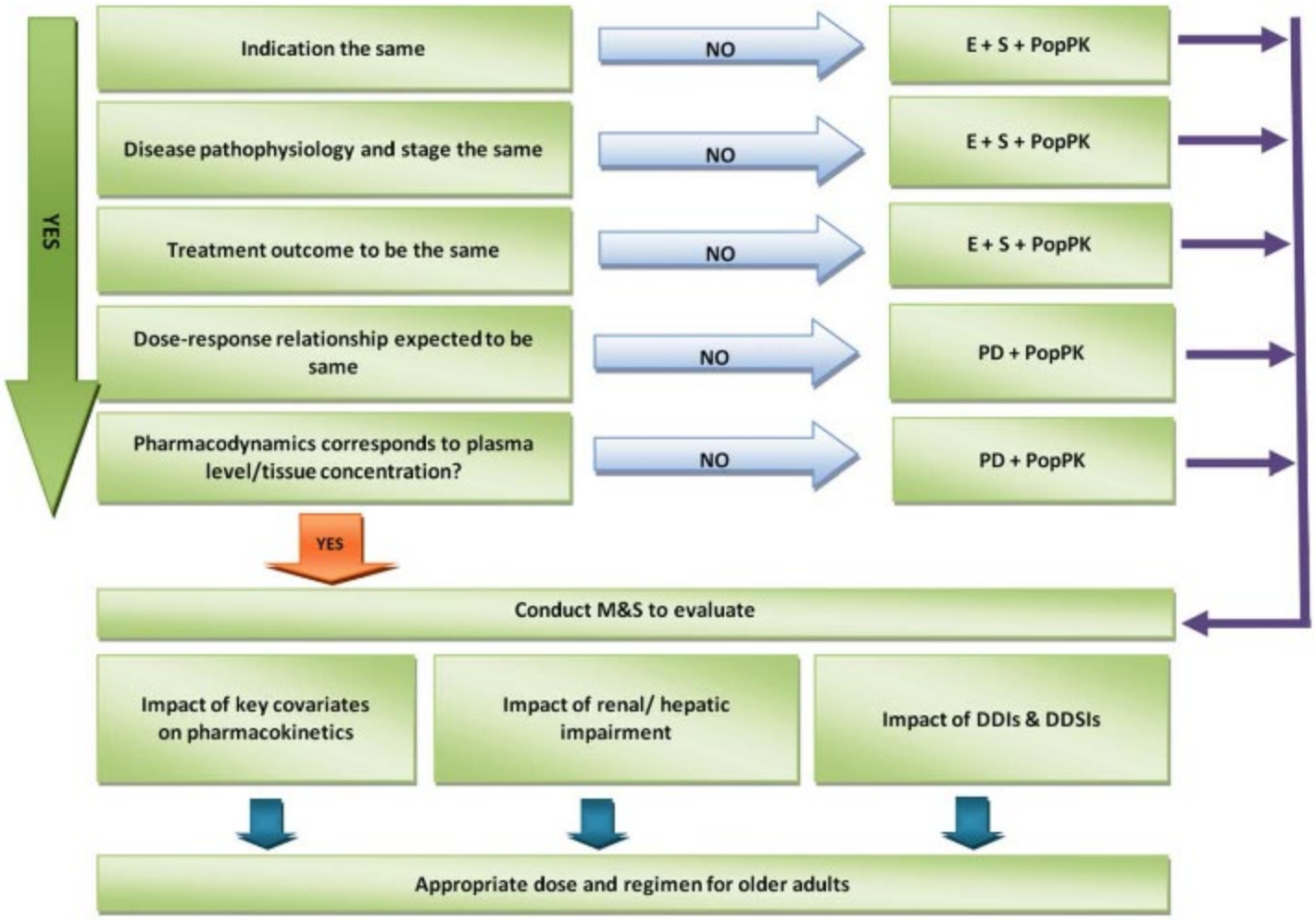
Knowledge gaps

	Populations			
	Young Adults	Midlifers	Young Old	Oldest Old
Anatomy	✓	✓	✓	✗
Physiology	✓	✓	✓	✗
Blood flow rates	✓	✓	✗	✗
Protein abundance/activity	✓	✓	✓	✗
GI-Tract	✓	✗	✗	✗
PK Data	✓	✗	✓	✗

✓ Data available (quantitative, human) ✗ Limited or conflicting data

Consideration of aging in Population Pharmacokinetics/Pharmacodynamics

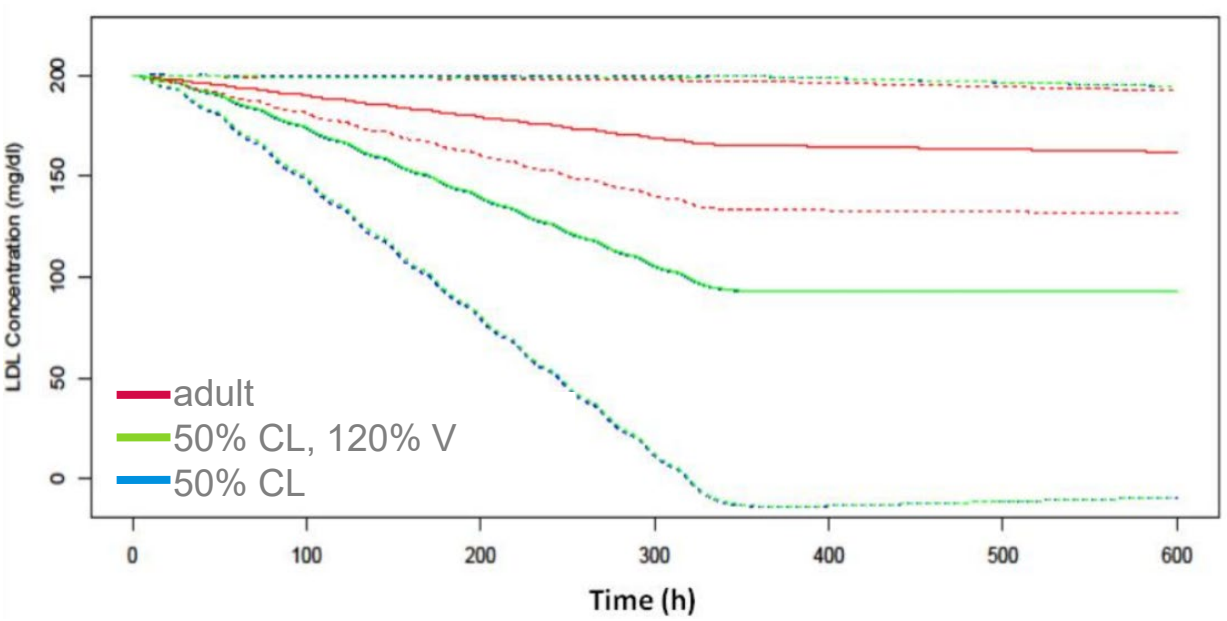
- M&S can be employed to “synthesize” the available evidence on PKPD, safety, and efficacy
- Model predictions can then be “confirmed” by conducting small observational or prospective (exploratory) bridging studies in the target patient population, if deemed appropriate
- Therefore, a decision tree is proposed that delineates a strategy for bridging the evidence gap for safe/effective use of medicines in elderly

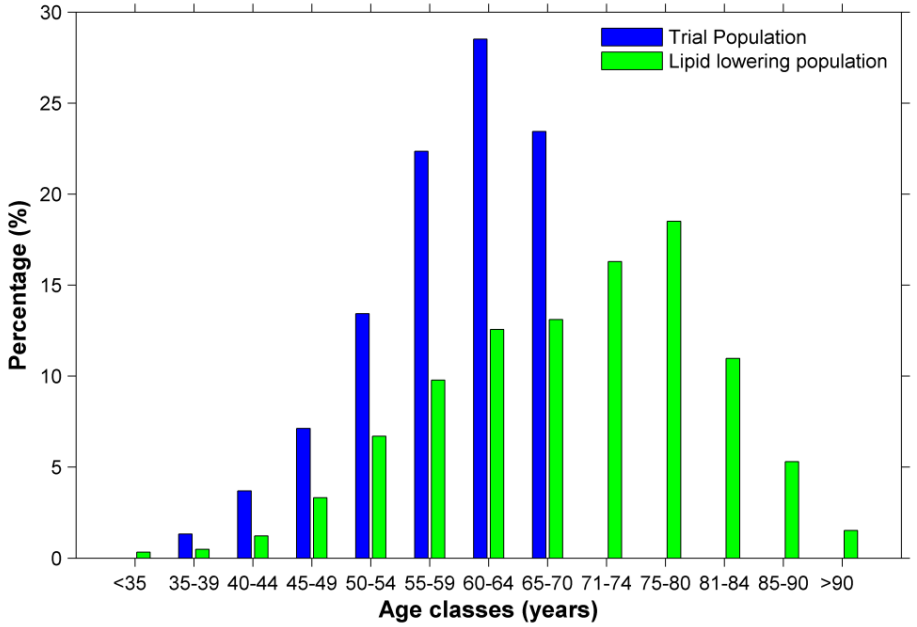


Saeed *et al* Clin Pharmacol Ther 2015

Consideration of aging in Population PK/PD

- Simvastatin has a well-characterized PKPD relationships
- Known PK-changes in the older adults population considered for simulation of pharmacodynamic alterations
- Exposure of simvastatin and simvastatin acid in each scenario are elevated causing an amplification of the PD effect





Schlender *et al.* Eur J Pharm Sci. 2018
Saeed *et al* Clin Pharmacol Ther 2015

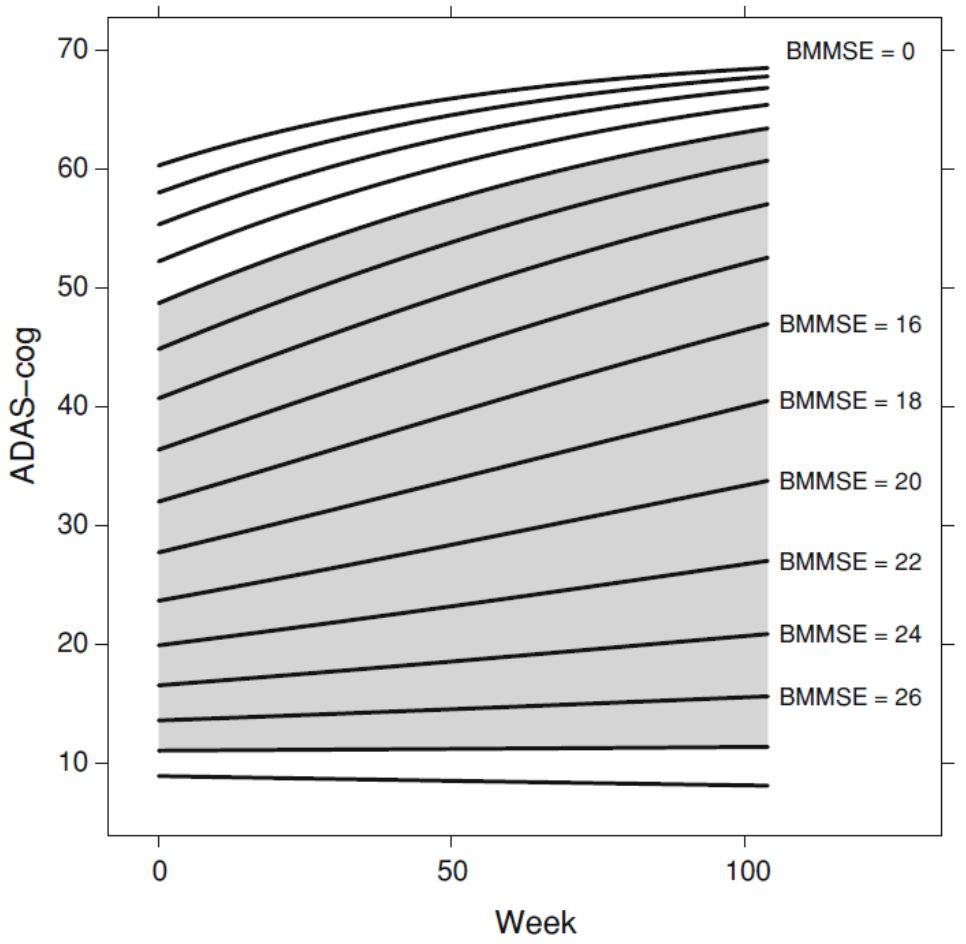
Consideration of aging in Population PK/PD

Disease Progression

- Beta regression model to describe the longitudinal progression of the 11 item Alzheimer's disease assessment scale cognitive subscale (ADAS-cog) in Alzheimer's disease patients in both natural history and randomized clinical trial settings
- Disease progression was dependent on **time**, **ApoE4 status**, **age**, and **gender**

Table 5 Model predicted expected mean change in ADAS-cog score over one year in the absence of a placebo or drug effect, by baseline age

Age	Median	5% LB	95% UB
69	4.92	3.71	6.13
75	4.39	3.51	5.39
80	4.00	2.97	5.17

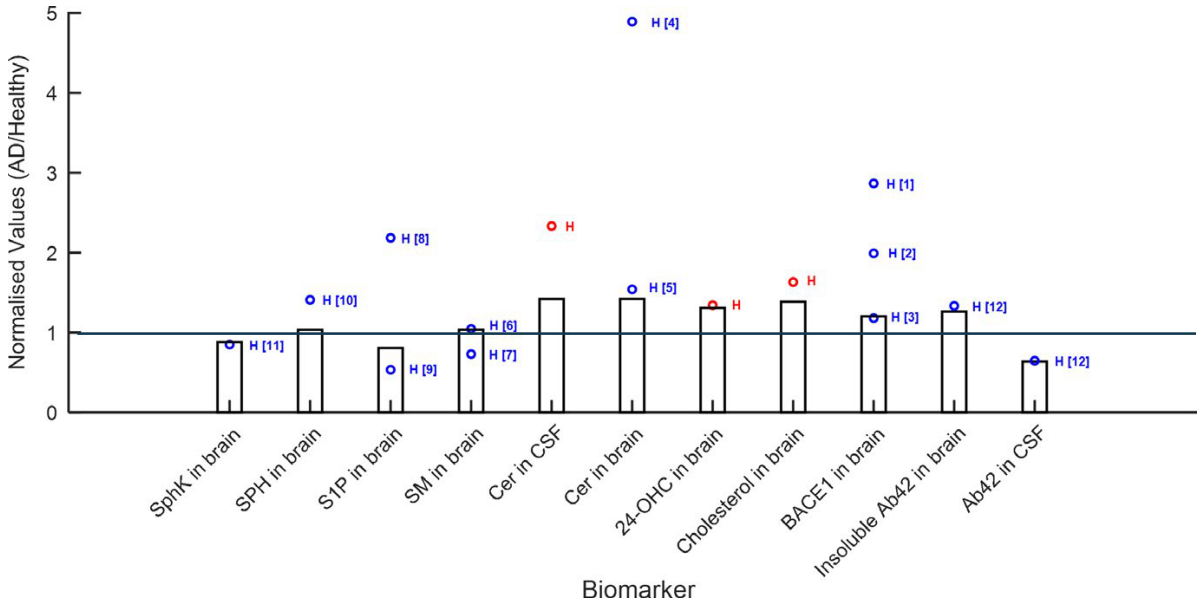


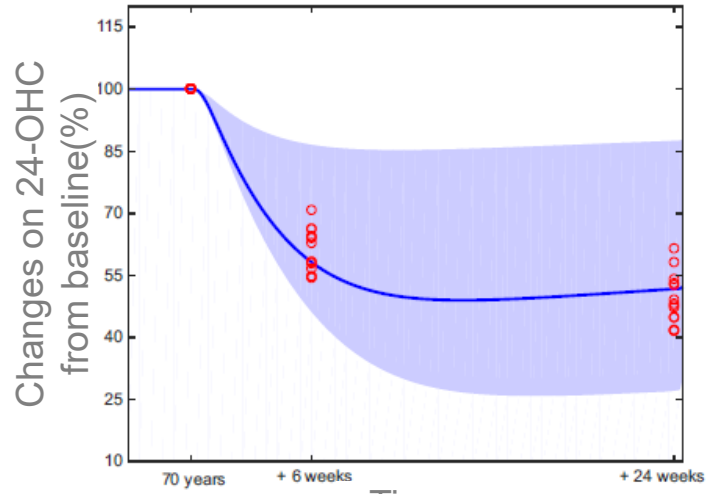
Rogers *et al.* J Pharmacokinet Pharmacodyn 2012

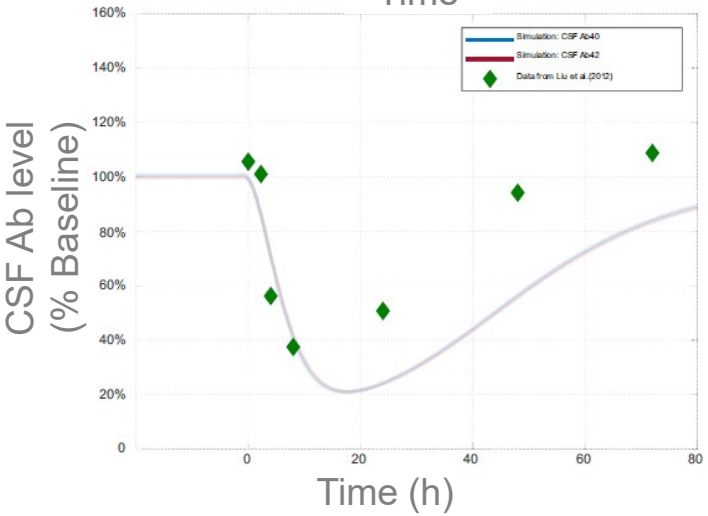
Quantitative Systems Pharmacology

Alzheimer disease (AD) – Discover Treatment Options

- QSP model for AD with a particular focus on investigating the relevance of dysregulation of cholesterol and sphingolipids
- Model captures the modulation of several biomarkers in subjects with AD and age, as well as the response to pharmacological interventions
  - Targeting the **sphingosine-1-phosphate 5 receptor (S1PR5)** as a potential novel treatment option





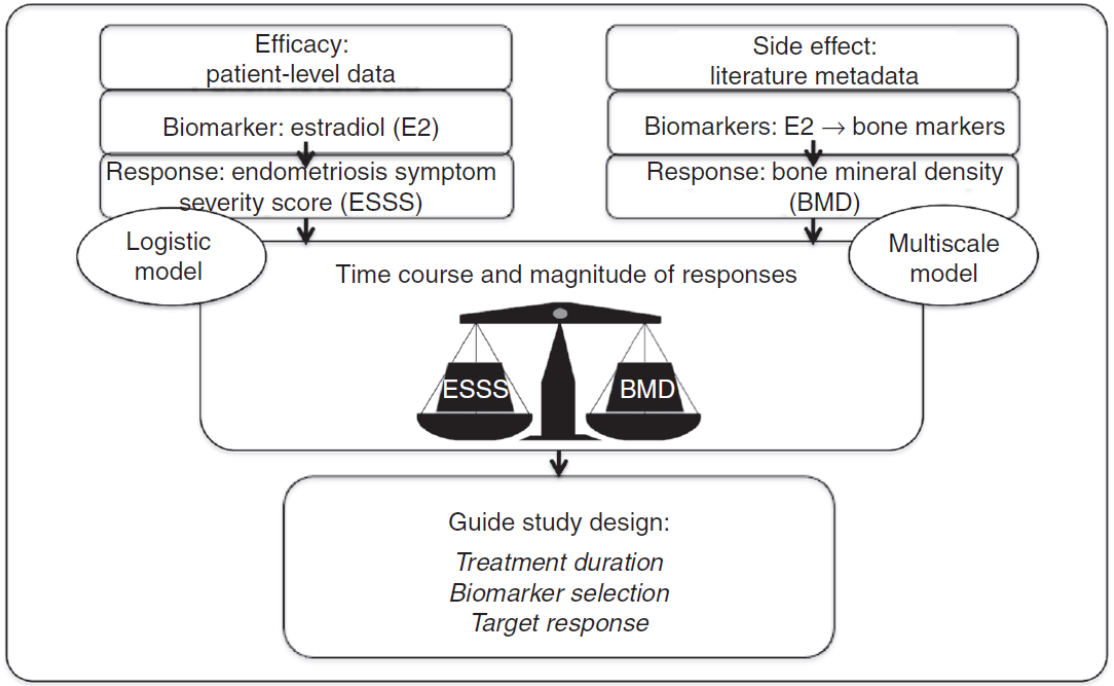


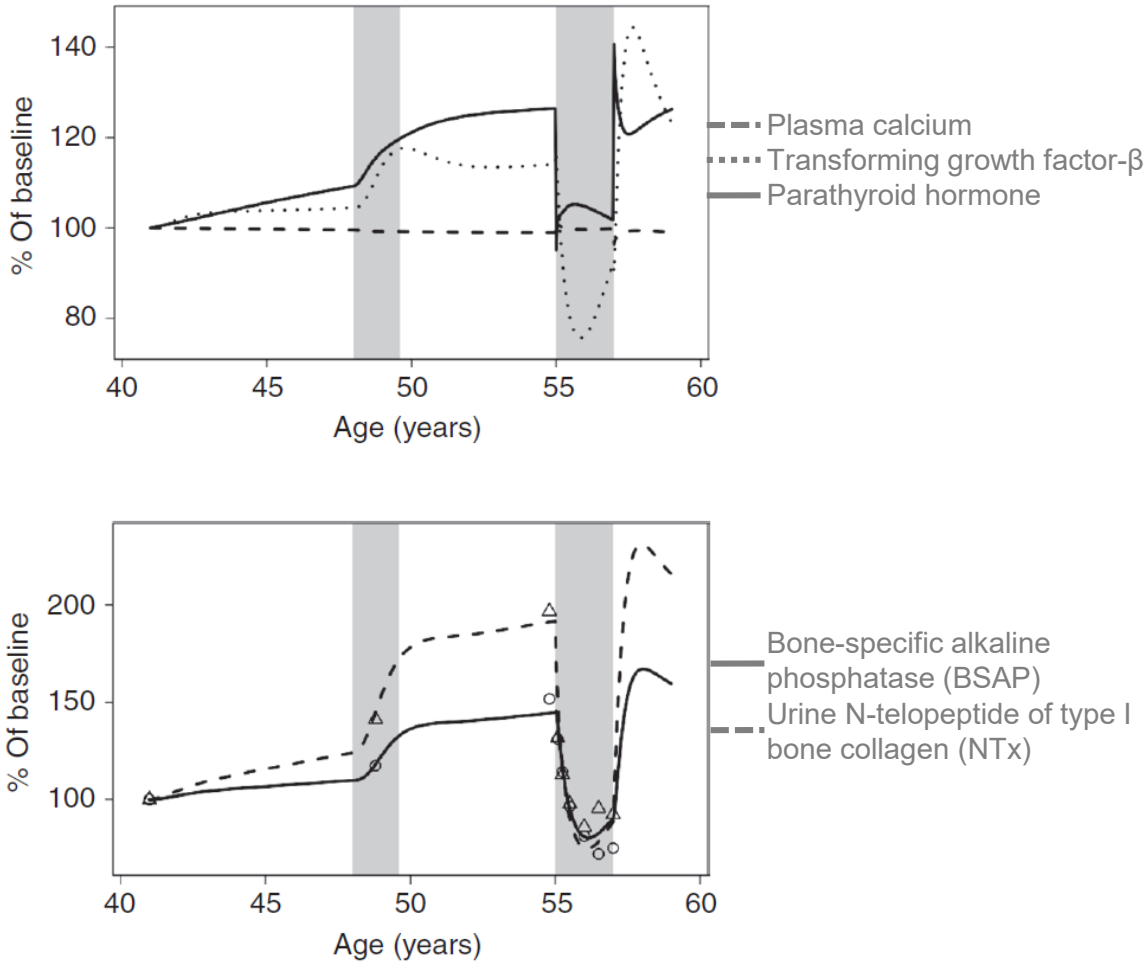
Clausznitzer *et al.* CPT Pharmacometrics Syst Pharmacol. 2018

Quantitative Systems Pharmacology

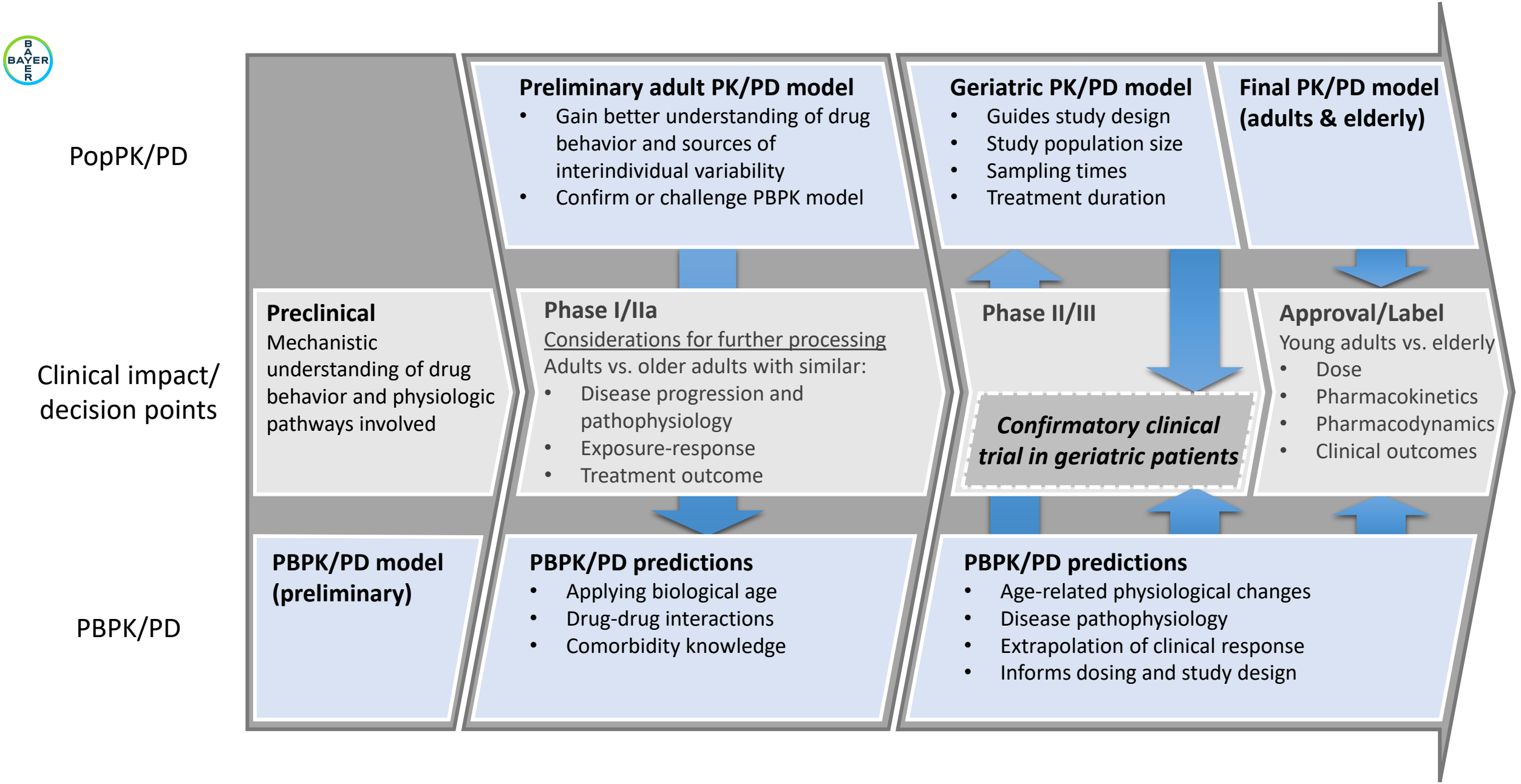
Endometriosis – Understanding target response

- Model-based guidance for GnRH-modulating clinical programs intended for endometriosis management
- Targeting **estradiol** between **20** and **40 pg/ml** was predicted to provide efficacious endometrial pain response while minimizing BMD effects





Riggs *et al.* CPT Pharmacometrics Syst Pharmacol. 2012

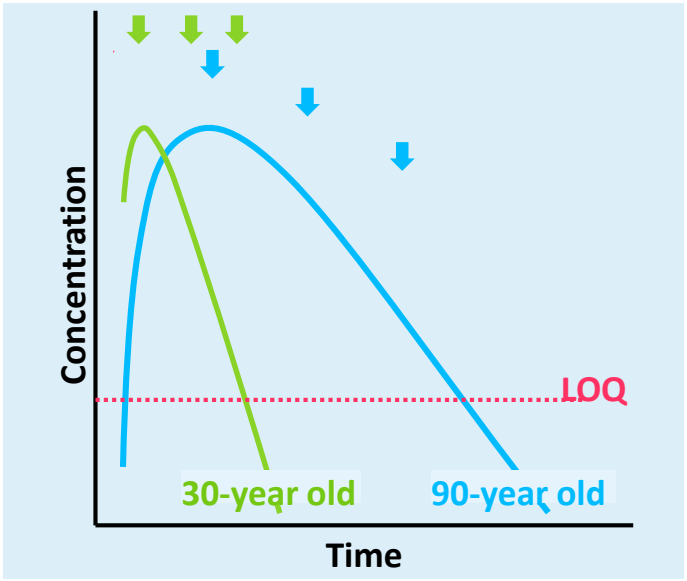


Schlender *et al.* Eur J Pharm Sci. 2018.

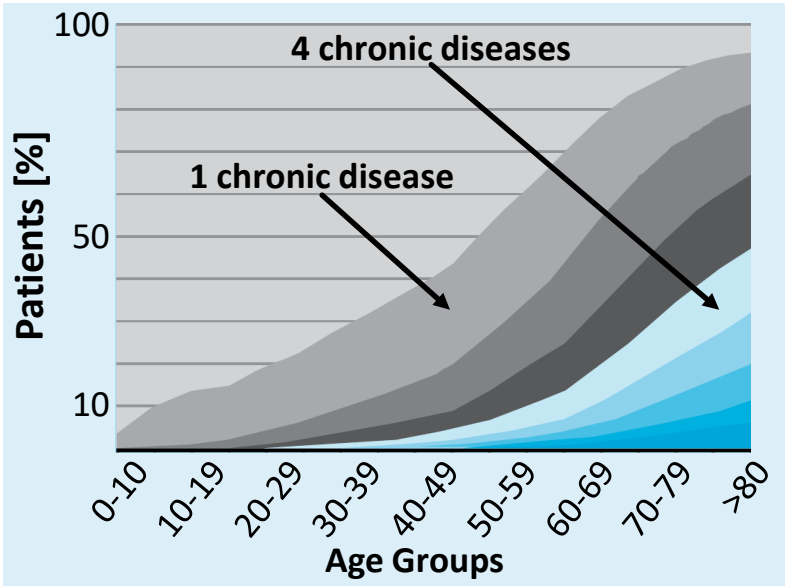
Quantitative approaches to describe an aging population

Proliferation

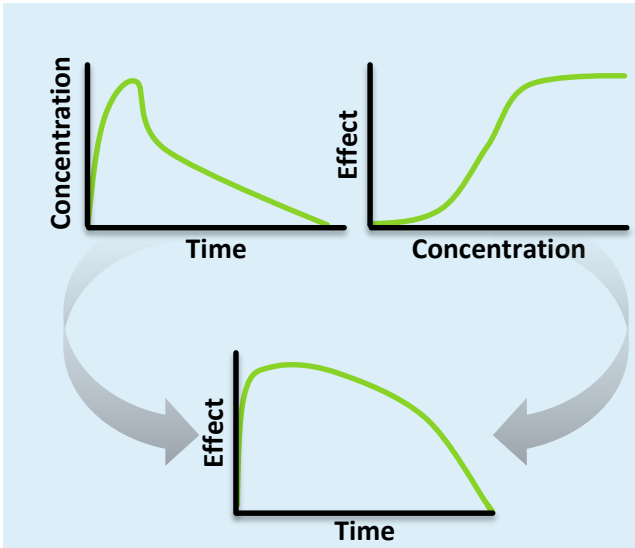
Study- and Therapy-optimization



Disease understanding



Pharmacokinetics/Pharmacodynamics



! OPEN ACCESS OSP OPEN SYSTEMS PHARMACOLOGY PK-Sim®

Continues Development

Modified from:
Barnett *et al.* The Lancet. 2012

Conclusion

Challenges

- Complex dosing regimes
- Narrow therapeutic index drugs
- Poly-medication
- Multimorbidity
- Lack of information
- Utilization of postapproval data

Opportunities

- Confidence in Dose Selection
- Understanding physiologic linkages
- Conversion of theoretical into quantitative predictions
- Development of deep expertise and system knowledge
- Efficient trial and therapy designs
- Halting/accelerating programs

Table 1. Proportion of 2013 and 2014 Approvals Without Explicit Dosing Recommendations at the Initial Approval

		Proportion[a]	
Section	Population	2013 (n = 27)	2014 (n = 32)
8.1	Pregnancy	70%	100%
8.2	Labor and delivery	100%	100%
8.3	Nursing mothers	92.5%	100%
8.4	Pediatrics	88.8%	97%
8.5	Geriatrics	22.2%	25%
Not explicitly defined but appears several times in labeling guidance	Female and male reproductive potential	63%	84%

Jadhav *et al.* J Clin Pharmacol. 2015

Thank you!

Bye-Bye