Covariate clinical relevance determination in population pharmacokinetic analyses: comparison using full model, FREM, SCM+, LASSO & GA approaches

Team BIPID - IAME laboratory, UMR 1137, INSERM and Université de Paris
Institut Roche

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20/09/2024

Introduction

Covariate analysis in population pharmacokinetics modeling

- Identify and quantify the sources of variability between individuals
- Ultimate goal
  - Dose adjustment in a subpopulation of interest to avoid risk of underexposed or overexposed subpopulation
  - Predictions (interpolation or extrapolation) under new experimental conditions

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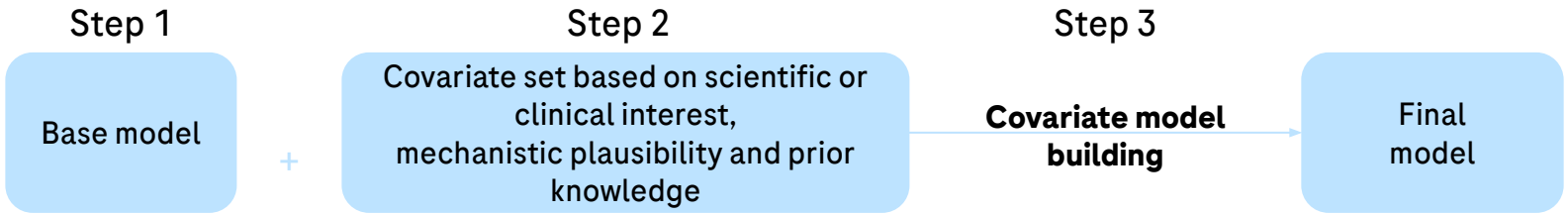

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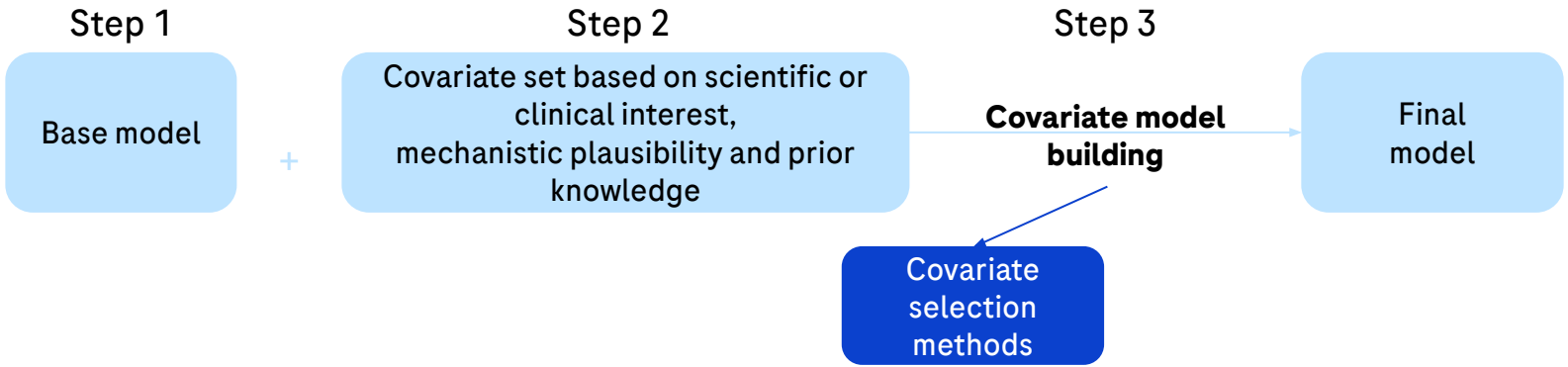

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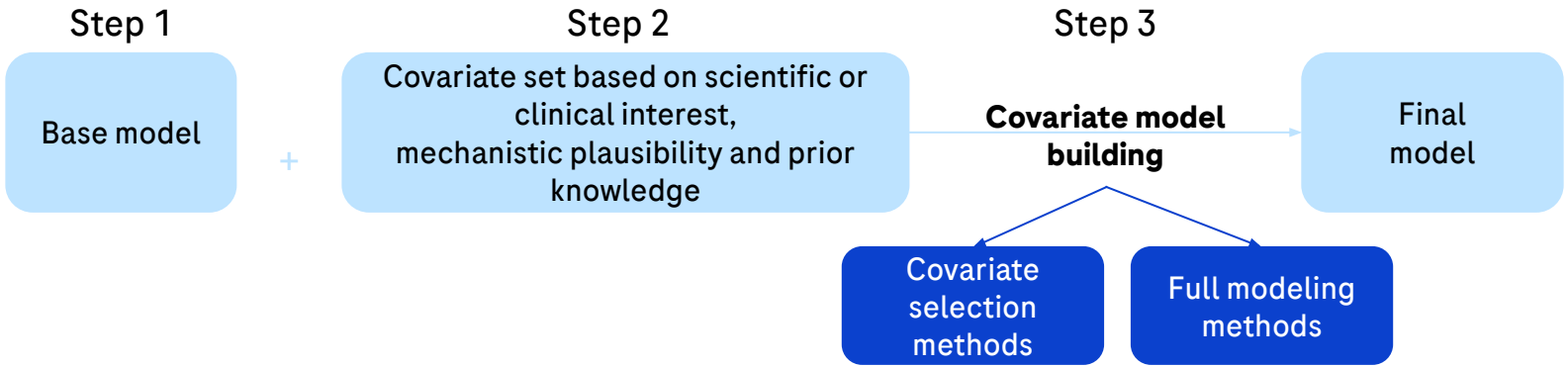

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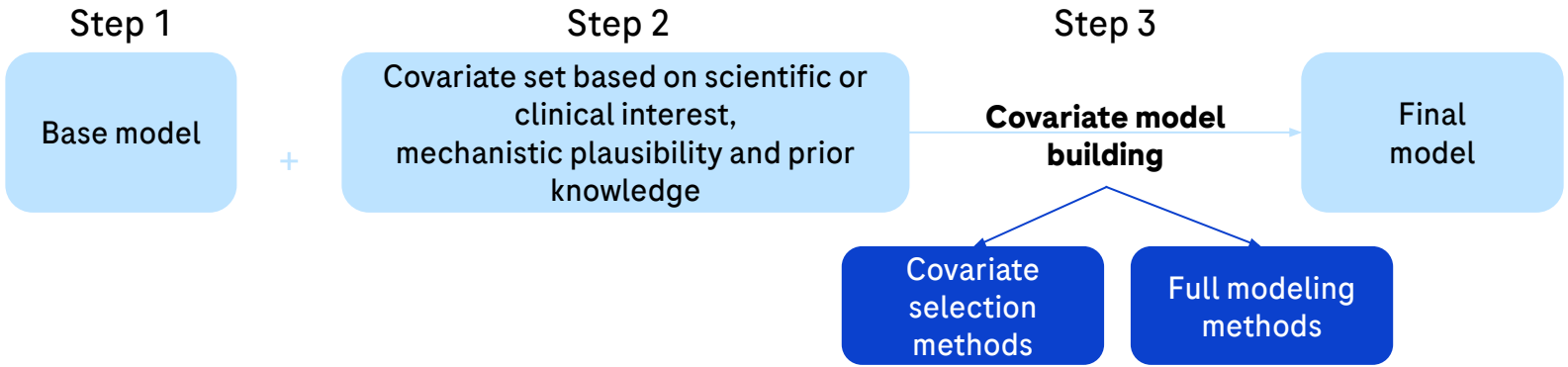
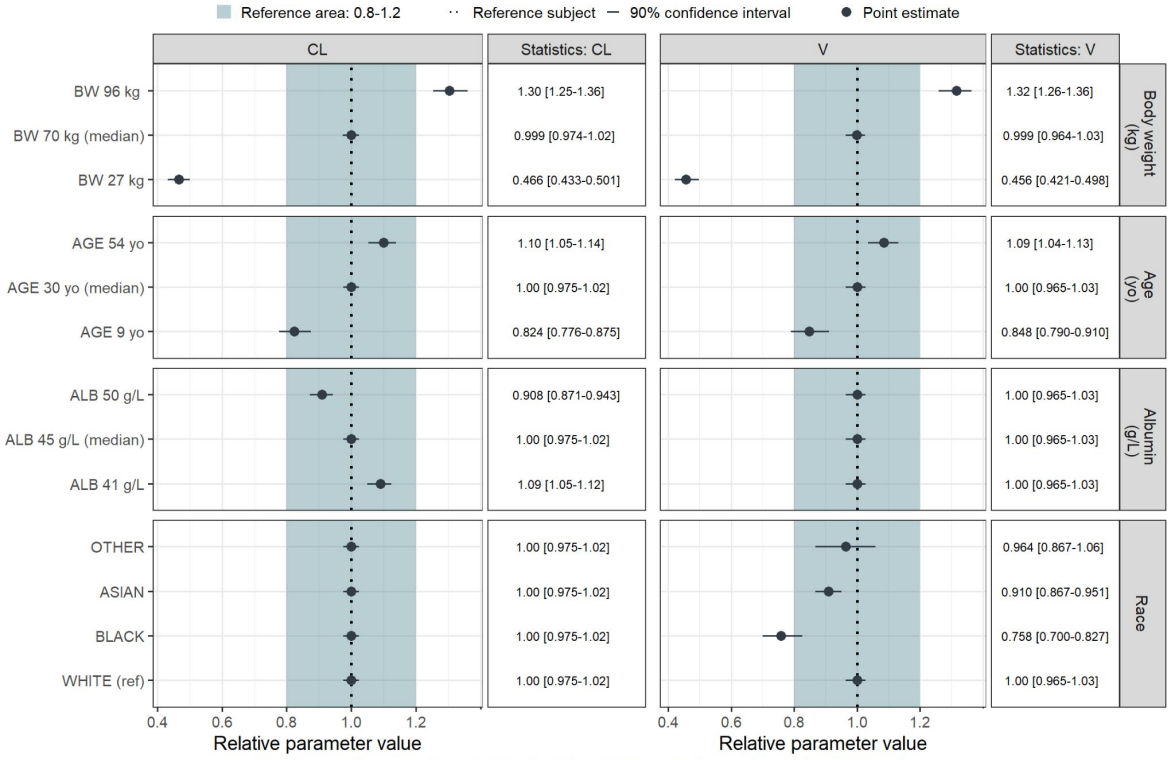


Health authority guidelines → no strong recommendations on the use of any particular covariate modeling method

U.S FDA, Population Pharmacokinetics - Guidance for Industry, 2022

"Model development issues can be addressed through several valid approaches, each with its own benefits and drawbacks. For example, **covariate analysis can be performed based on several approaches or their possible combinations (e.g., stepwise covariate analysis, full covariate model approach, the Lasso)** (Wählby, Jonsson, and Karlsson 2002; Gastonguay 2004; Ribbing et al. 2007). In such cases, sponsors should justify why a particular approach was used."

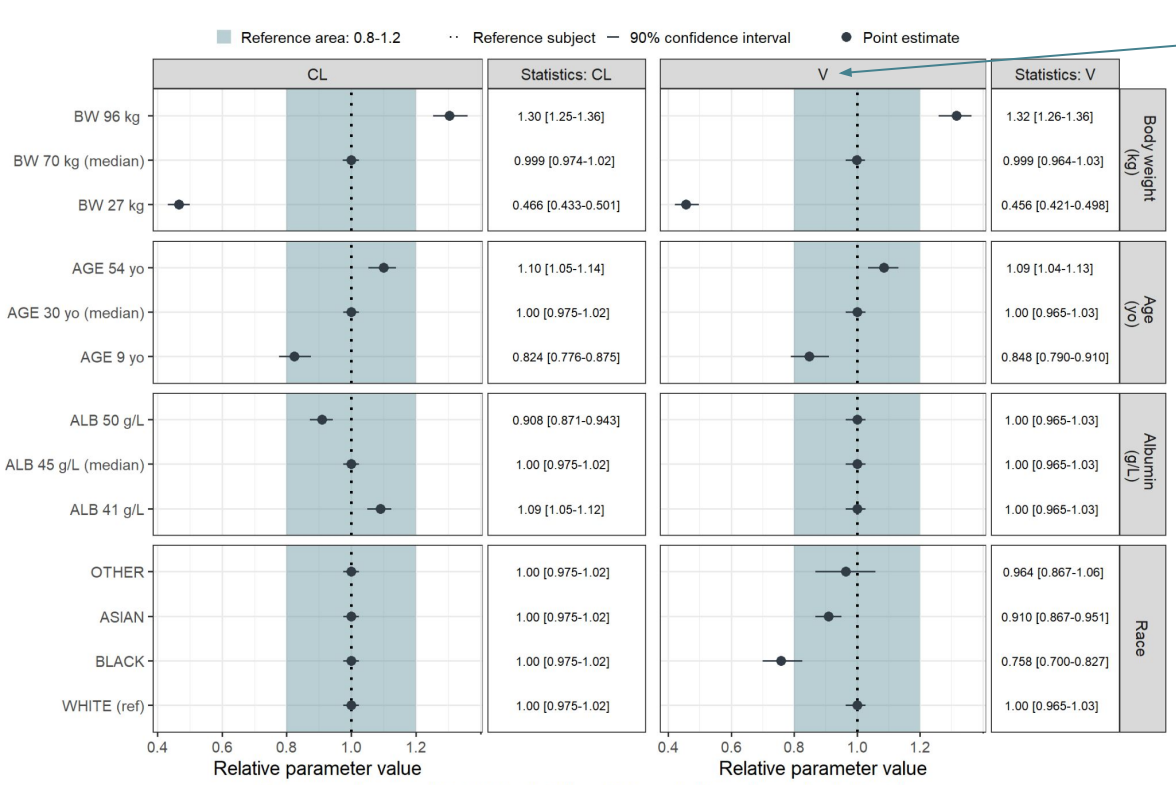
Graphics used to support the decision on the clinical relevance of covariate effects on exposure



Reference subject: a white individual of 30 yo, 70 kg and with an albumin level at 45 g/L

https://github.com/pharmetheus/PMXForest

Graphics used to support the decision on the clinical relevance of covariate effects on exposure



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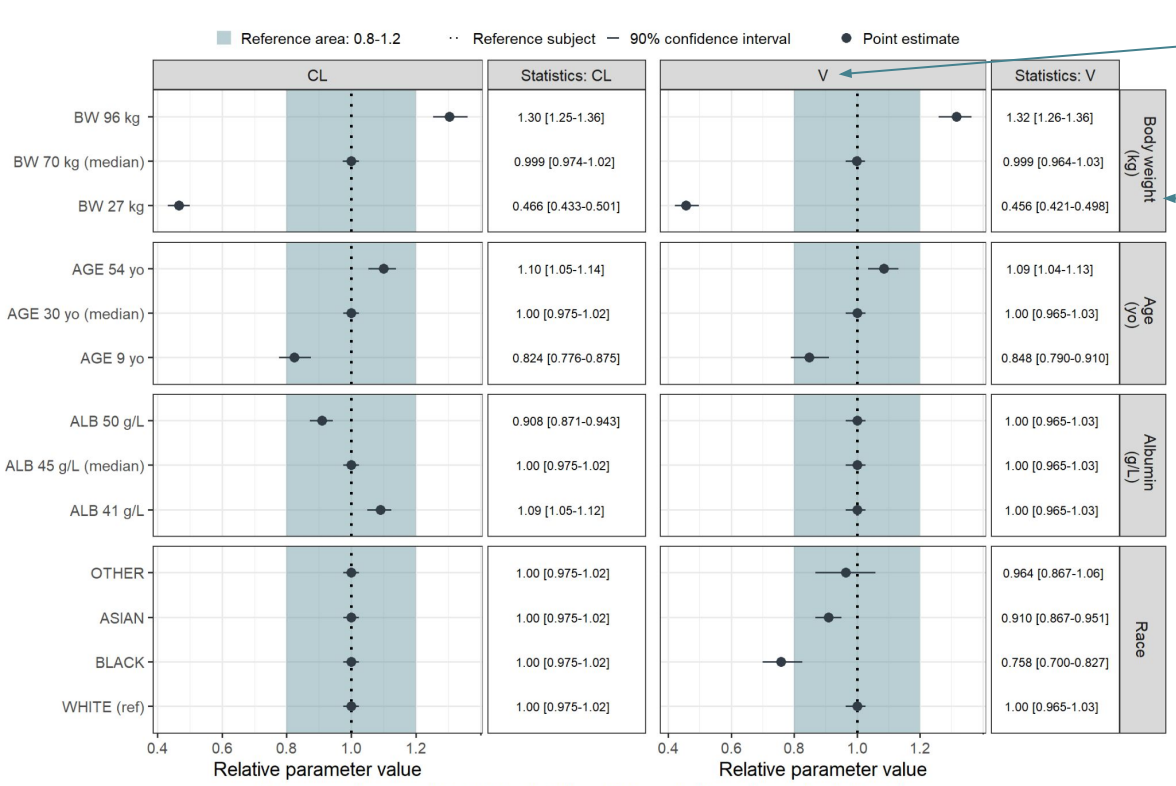

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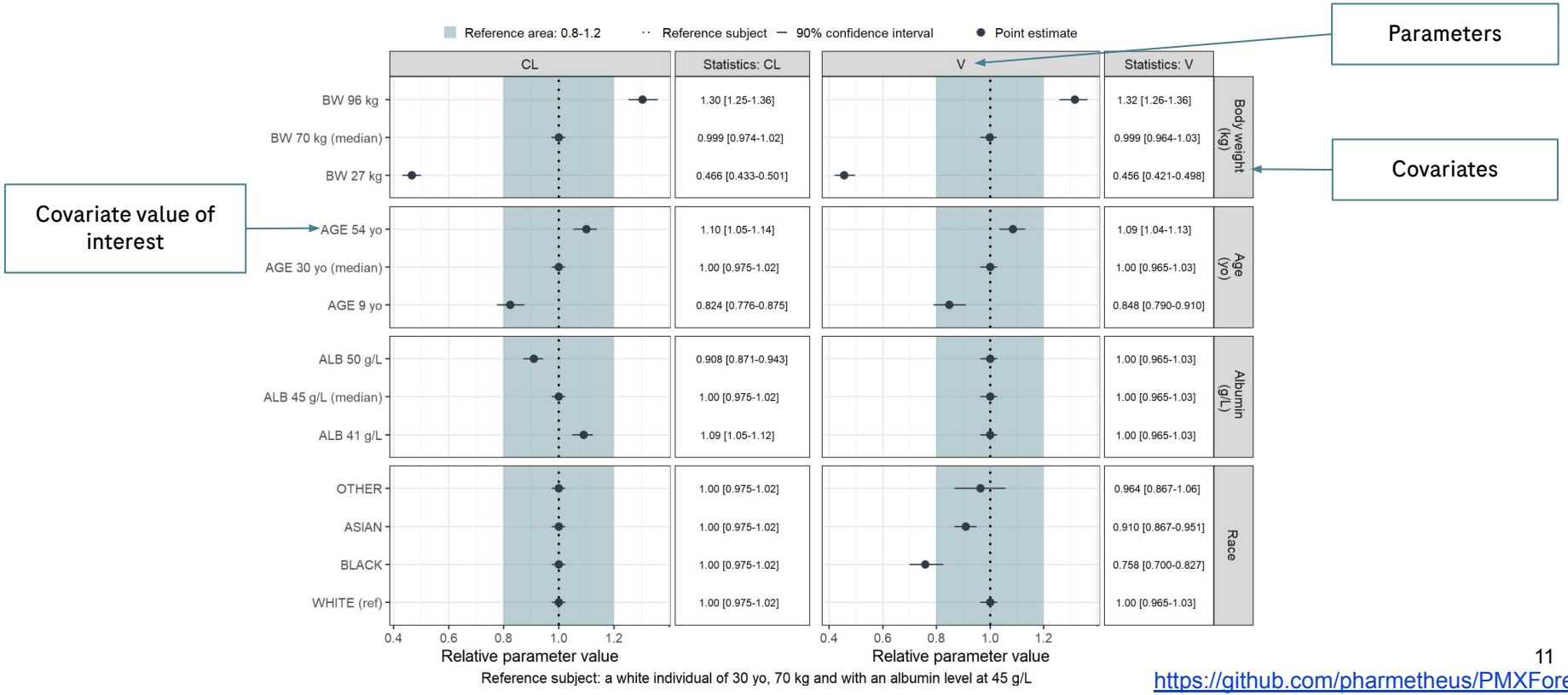

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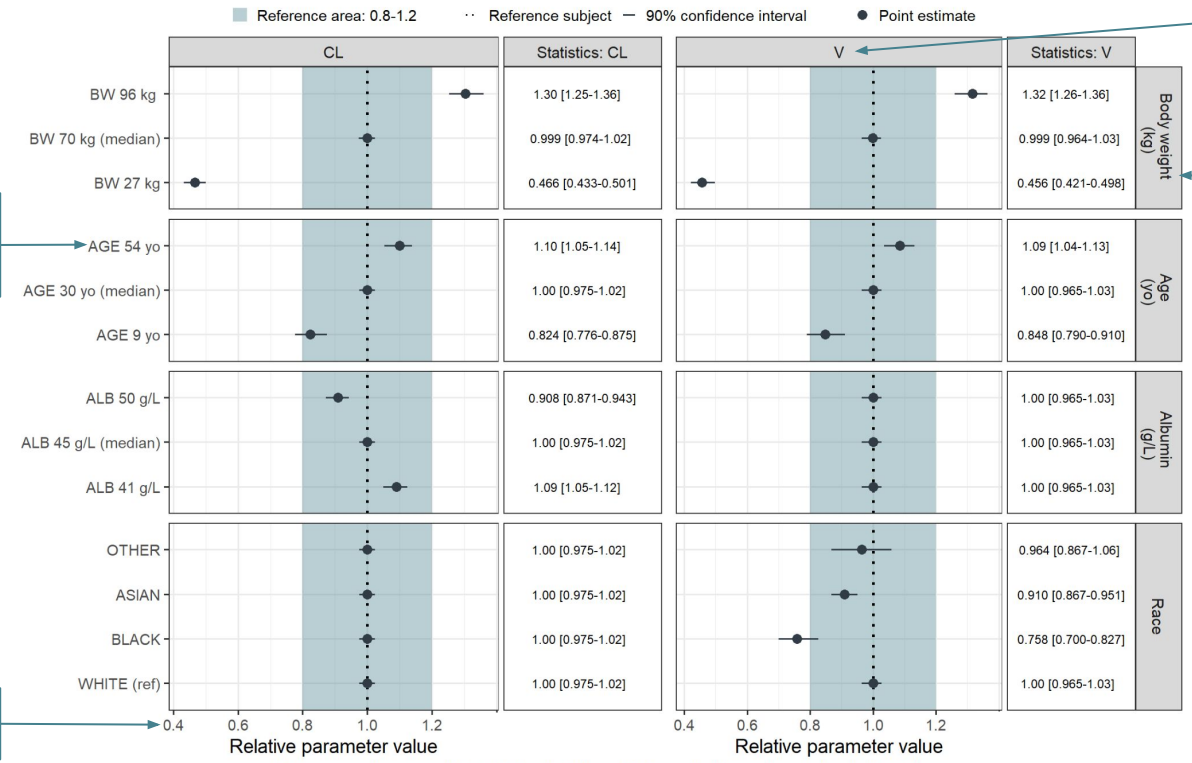

Parameters

Covariates

Covariate value of interest

Ratio

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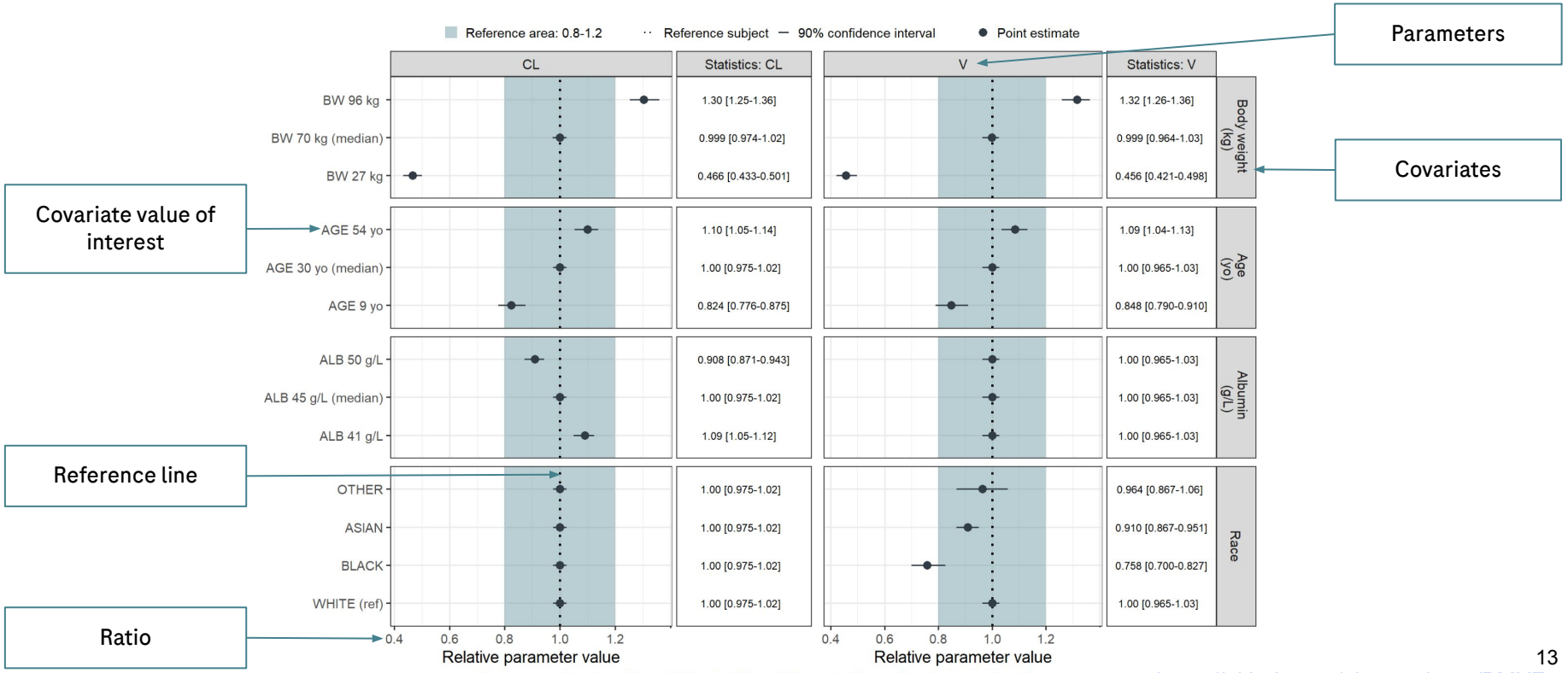

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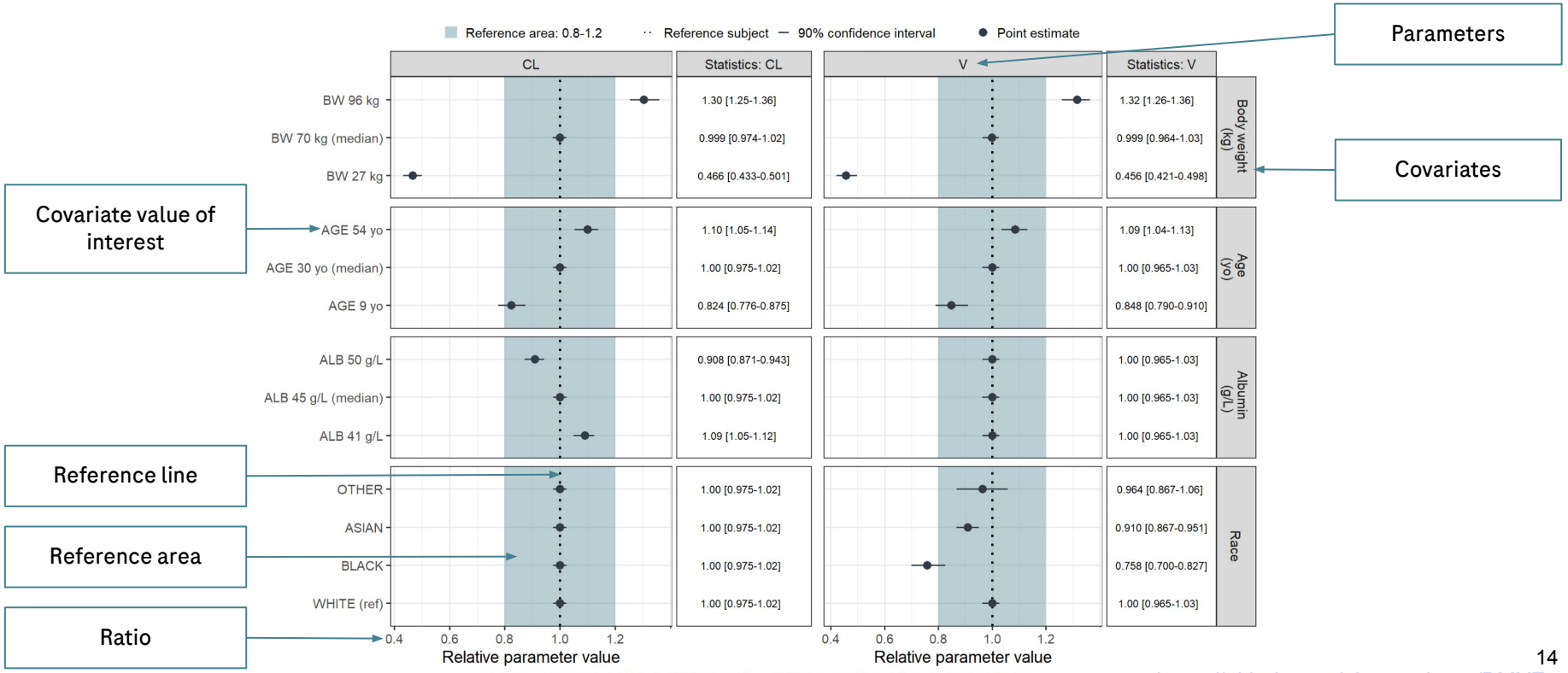

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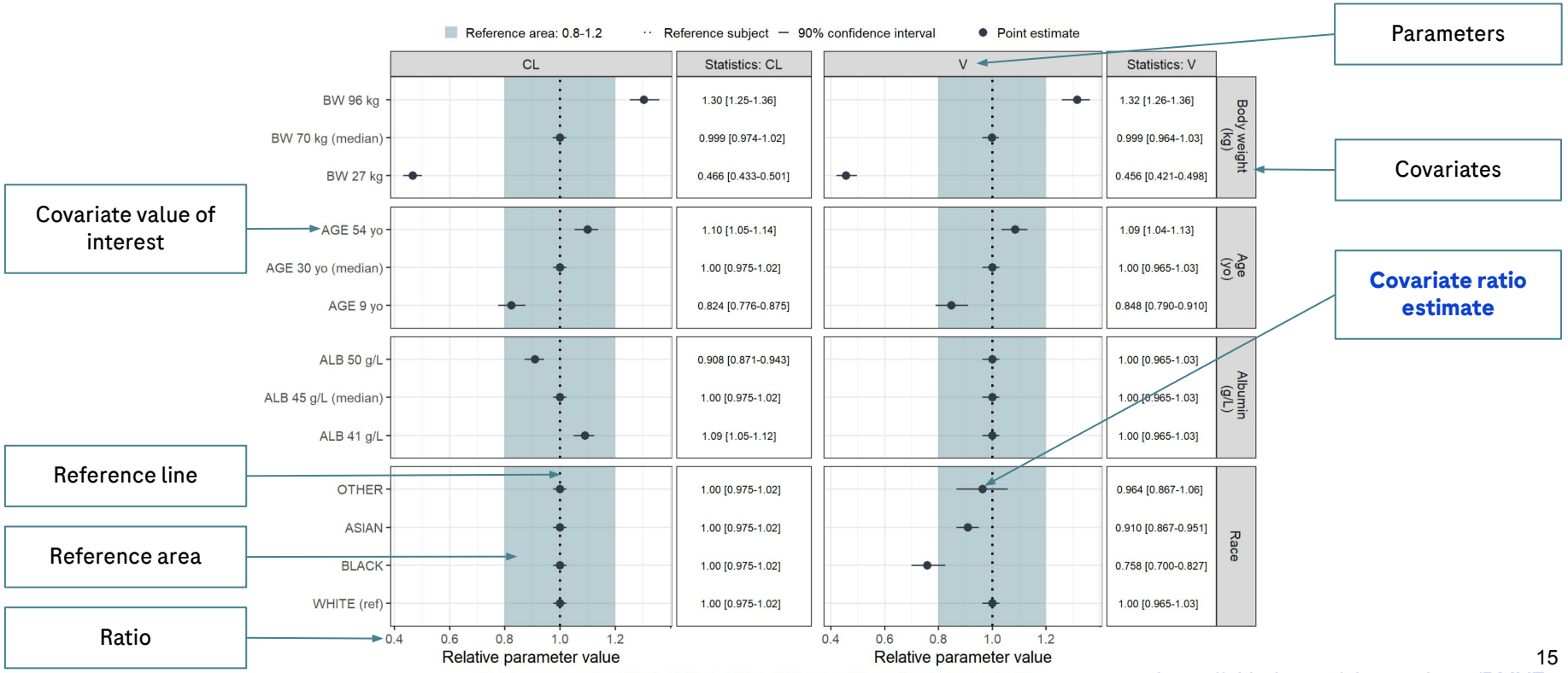

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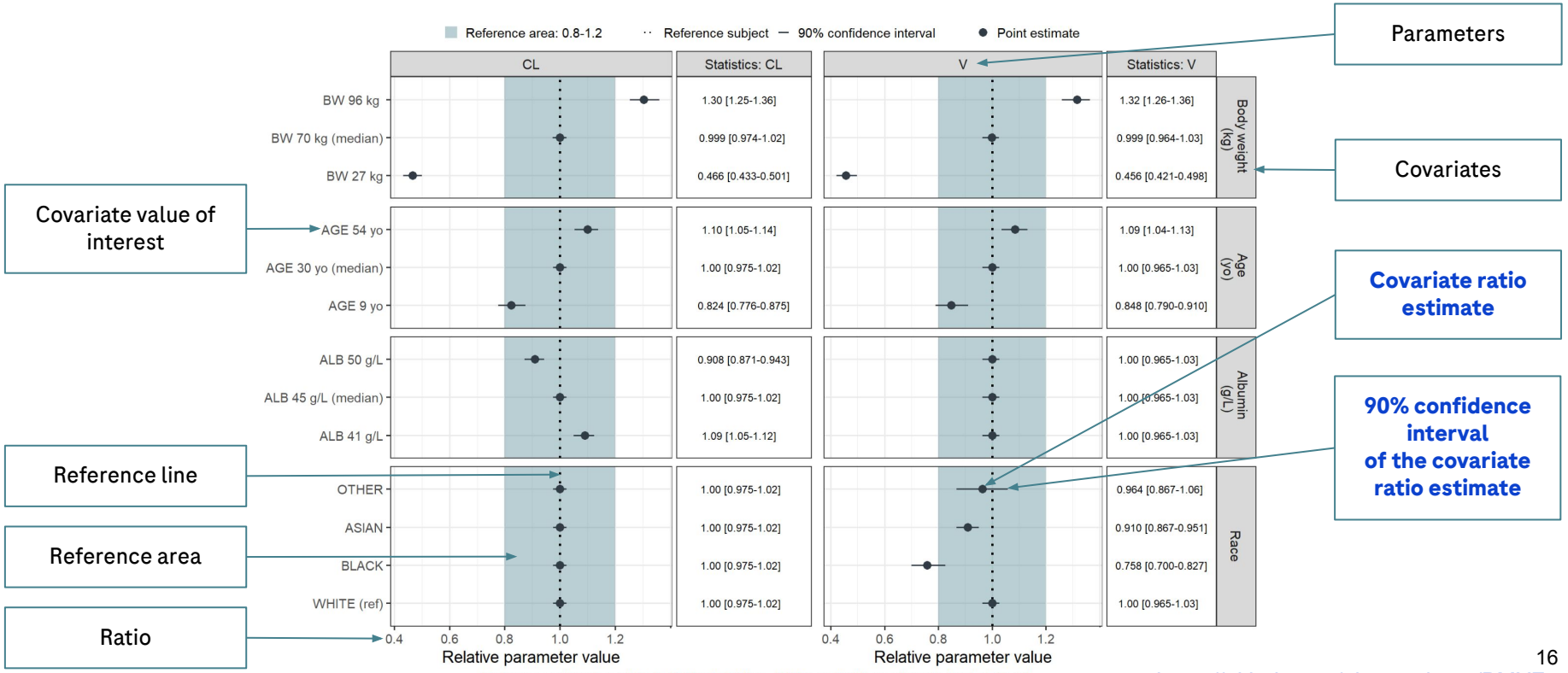

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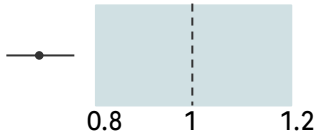
Covariate clinical relevance (CCR) evaluation

- Relevant → **R**



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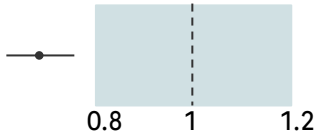
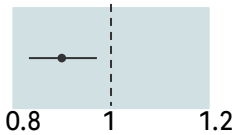
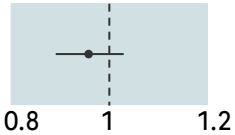


- Not relevant
  - Significant → **NRS**



  - Non-significant → **NRNS**



Covariate clinical relevance (CCR) evaluation

- Relevant → **R**
- Not relevant
  - Significant → **NRS**
  - Non-significant → **NRNS**
- Insufficient information
  - Significant → **IIS**
  - Non-significant → **IINS**

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- Not relevant
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→ Precise and accurate estimation of covariate ratios and their associated uncertainty is critical

Covariates model building approaches comparison

- Previous research focused on comparing the performance of covariate detection and the accuracy of their effect

Approaches compared	Metrics of comparison	Reference
Stepwise generalized additive models with backward elimination vs SCM	Covariate model correctness, covariate effects estimation accuracy, predictive performances and computational speed	Wählby et al. *AAPS PharmSci*. 2002
LASSO vs SCM	Predictive performances and computational speed	Ribbing et al. *J Pharmacokinet Pharmacodyn*. 2007
Simplified SCM vs FM vs Prior-Adjusted Covariate Selection	Performances (selection of the true covariate)	Chasseloup et al. *J Pharmacokinet Pharmacodyn*. 2020
Random forest vs neural network vs support vector regression vs SCM vs COSSAC vs LASSO	Performances (ROC curves, F1 scores), computational speed	Sibieude et al. *J Pharmacokinet Pharmacodyn*. 2021
COSSAC vs SCM	Covariate selection, OFV, computational speed	Aryal et al. *CPT: Pharmacomet Syst Pharmacol*. 2021
SAMBA vs COSSAC vs SCM	Covariate selection, OFV, computational speed	Prague et al. *CPT: Pharmacomet Syst Pharmacol*. 2021
FREM vs FM	Covariate effects estimation accuracy	Yngman et al. *CPT: Pharmacomet Syst Pharmacol*. 2022
SCM vs SCM+	Efficiency (number of runs and function evaluations), relevance (number of relevant covariate selected)	Svensson et al. *CPT: Pharmacomet Syst Pharmacol*. 2022
FREM vs SCM	Power to detect the true covariate, precision and accuracy of the covariate coefficient	Amann et al. *J Pharmacokinet Pharmacodyn*. 2023
GA vs SCM	Covariate selection, OFV, computational speed	Ronchi et al. *J Pharmacokinet Pharmacodyn*. 2023
GA vs Gaussian process vs random forest vs gradient boosted random tree vs particle swarm optimization vs forward addition/backward elimination	Robustness (comparison of the optimal model found with that obtained by an exhaustive search), efficiency (number of models examined before finding the optimal model), calculation speed	Xinnong Li et al. *J Pharmacokinet Pharmacodyn*. 2024

Covariates model building approaches comparison

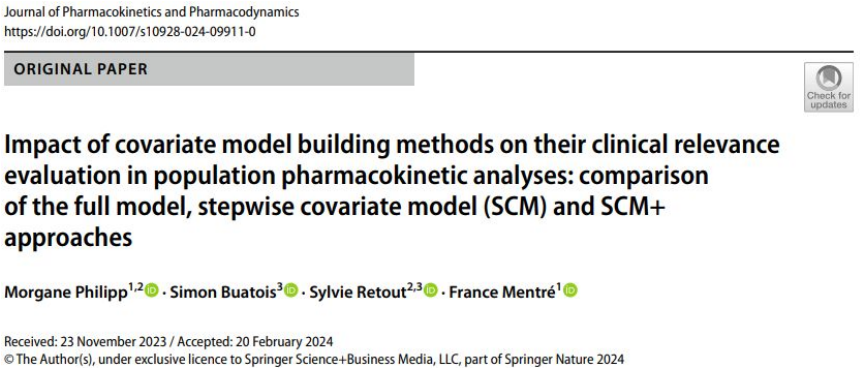
- Previous research focused on comparing the performance of covariate detection and the accuracy of their effect

Lack of assessment of:

- Accuracy of covariate ratios with their associated uncertainty
- Correctness of the CCR evaluation
- Comparison of the “stepwise covariate analysis, full covariate model approach, the Lasso” (U.S. FDA, Population Pharmacokinetics - Guidance for Industry, 2022)

Aim of this work

- Our previous investigations compared the accuracy of CCR assessment of SCM, SCM+ & Full Model
  - Simulation study with 200 simulated datasets inspired by a real population PK analysis of Emicizumab [1,2,3]
  - All approaches provided satisfactory results close to those of the reference model (i.e. the true model used to simulate the data)



Journal of Pharmacokinetics and Pharmacodynamics
https://doi.org/10.1007/s10928-024-09911-0

ORIGINAL PAPER

Check for updates

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Morgane Philipp[1,2] · Simon Buatois[3] · Sylvie Retout[2,3] · France Mentré[1]

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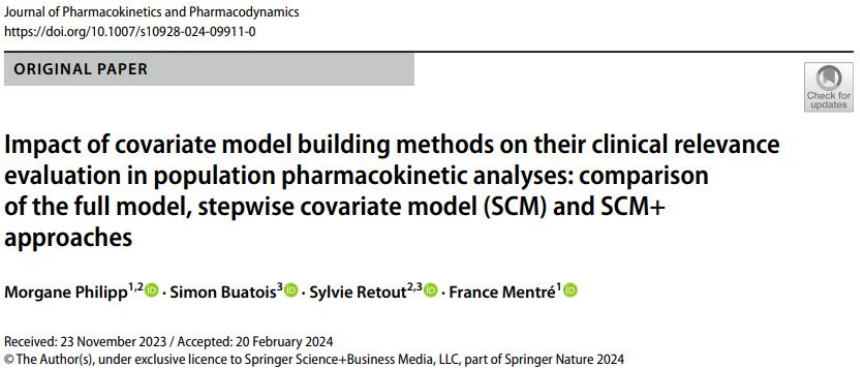

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→ Investigate 3 alternative approaches FREM [4], LASSO [5] & GA [6] and compare the CCR determination results with those obtained by FM [7,8], SCM+ [9] & the reference model in a proof of concept study using a simulated dataset from the previous work

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Methods

Data simulation

PK model [1,2]
One compartment model (V/F), first order absorption (ka), linear elimination (CL/F)

Design [1,2]
N = 383 with rich (1 phase I/II trial) or sparse (4 phase III trials with a peak and trough strategy) PK sampling scheme

Error model [1,2]
Combined (a and b)
→ with a the additive (fixed) and b the proportional term

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Covariate models [1,2]
Body weight (BW), age (AGE), albumin (ALB), black (BLK) race

Base model

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→ with μ the fixed effects and $\eta_i \sim N(0,\Omega)$ the between subject random-effects of individual i, Ω being the variance-covariance matrix,with $\beta_{par,cov}$ the effect of a covariate (cov) on a parameter (par)

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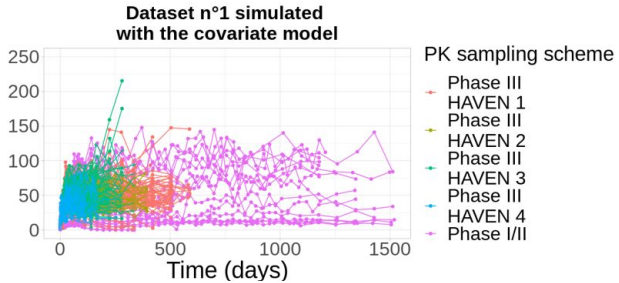
Data simulation
1 dataset simulated with the **Base model** & **Covariate model**



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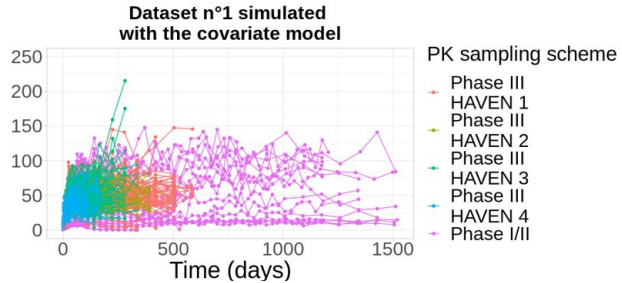

Parameter estimation
Software: NONMEM 7.4
Estimation algorithm: FOCEi
SE: derived from the covariance matrix computed as $R^{-1}SR^{-1}$ (R: hessian matrix, S: cross-product gradient matrix)

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Covariate model

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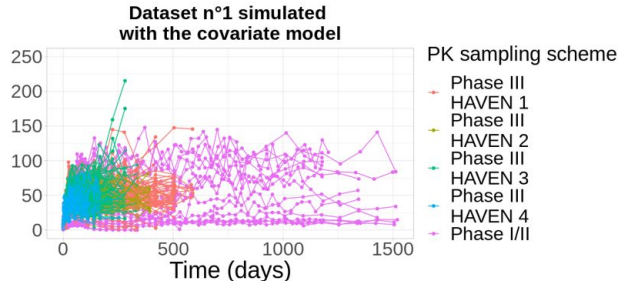
$$V/F_i = \mu_{V/F} \times \left(\frac{BW_i}{70}\right)^{\beta_{V/F,BW}} \times \left(\frac{AGE_i}{30}\right)^{\beta_{V/F,AGE}} \times (1 + \beta_{V/F,BLK} \times 1_{RACE_i=BLK}) \times e^{\eta_{V/F,i}}$$

$$KA_i = \mu_{KA} \times e^{\eta_{KA,i}}$$

→ with μ the fixed effects and $\eta_i \sim N(0,\Omega)$ the between subject random-effects of individual i, Ω being the variance-covariance matrix, with $\beta_{par,cov}$ the effect of a covariate (cov) on a parameter (par)

Data simulation
1 dataset simulated with the **Base model** & **Covariate model**



Parameter estimation
Software: NONMEM 7.4
Estimation algorithm: FOCEi
SE: derived from the covariance matrix computed as $R^{-1}SR^{-1}$ (R: hessian matrix, S: cross-product gradient matrix)

Reference model fitting
Software: PsN 5.3.2
Base model & **Covariate model**

[1] Philipp et al. *J Pharmacokinet Pharmacodyn*. 2024; [2] Retout et al. *Clin Pharmacokinet*. 2020

Covariate modeling - 2 covariate sets

Prespecified covariate set (14 relationships, 18 $\beta_{par,cov}$) & Saturated covariate set (21 relationships, 27 $\beta_{par,cov}$)

Continuous covariates, med [min - max]	CL/F	V/F	KA
Body Weight (BW, kg), 69.1 [9.50–156]	B, C	B, C	
Age (AGE, years), 30.0 [1.22 - 77.00]	C	C	
Albumine (ALB, g/L), 45.0 [33.0–56.6]	C		
Aspartate aminotransferase (AST, U/L), 23.0 [11.0–91.0]			
Bilirubin (BILI, µmol/L), 9.0 [0.33–46.0]			
Categorical covariates: category, N [%]	**CL/F**	**V/F**	**KA**
Status: Non-inhibitor, 195 [50%] / FVIII inhibitor (INH), 194 [50%]			
Race: White, 244 [63%] / Black (BLK) 31 [8%] / Asian (ASN), 89 [23%] / Other (OTH), 25 [6%]		C	

→ **B**, **C**: covariate effect simulated for the **Based** & the **Covariate model**, respectively
→ **P**, **S**: covariate effect tested on the parameter considering the **Prespecified** or the **Saturated covariate set**

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Continuous covariates, med [min - max]	**CL/F**	**V/F**	**KA**
Body Weight (BW, kg), 69.1 [9.50–156]	B, C, P	B, C, P	
Age (AGE, years), 30.0 [1.22 - 77.00]	C, P	C, P	P
Albumine (ALB, g/L), 45.0 [33.0–56.6]	C, P	P	
Aspartate aminotransferase (AST, U/L), 23.0 [11.0–91.0]	P		
Bilirubin (BILI, µmol/L), 9.0 [0.33–46.0]	P		
Categorical covariates: category, N [%]	**CL/F**	**V/F**	**KA**
Status: Non-inhibitor, 195 [50%] / FVIII inhibitor (INH), 194 [50%]	P	P	P
Race: White, 244 [63%] / Black (BLK) 31 [8%] / Asian (ASN), 89 [23%] / Other (OTH), 25 [6%]	P	C, P	

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Age (AGE, years), 30.0 [1.22 - 77.00]	**C**, **P**, **S**	**C**, **P**, **S**	**P**, **S**
Albumine (ALB, g/L), 45.0 [33.0–56.6]	**C**, **P**, **S**	**P**, **S**	**S**
Aspartate aminotransferase (AST, U/L), 23.0 [11.0–91.0]	**P**, **S**	**S**	**S**
Bilirubin (BILI, µmol/L), 9.0 [0.33–46.0]	**P**, **S**	**S**	**S**
Categorical covariates: category, N [%]	**CL/F**	**V/F**	**KA**
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Race: White, 244 [63%] / Black (BLK) 31 [8%] / Asian (ASN), 89 [23%] / Other (OTH), 25 [6%]	**P**, **S**	**C**, **P**, **S**	**S**

→ **B**, **C**: covariate effect simulated for the **Based** & the **Covariate model**, respectively
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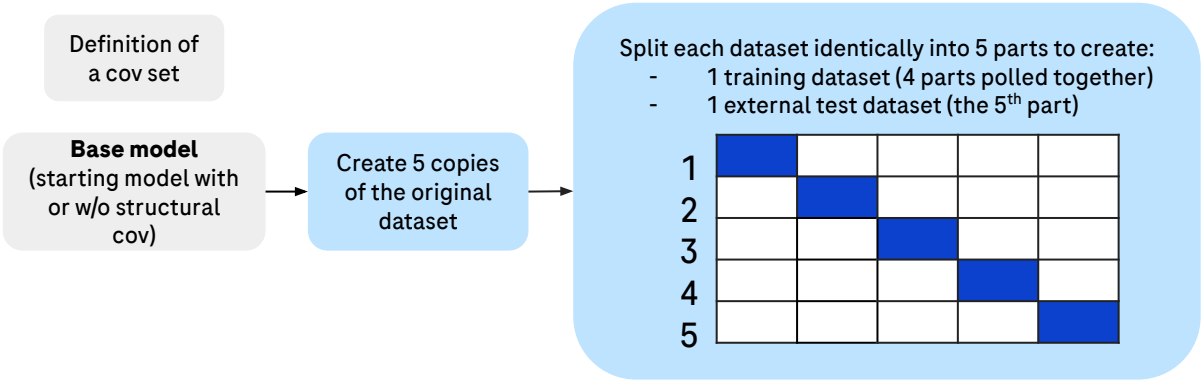
LASSO [1]

- Regression method with a constraint on the covariate effect values → $\Sigma|\beta_{par,cov}| \leq t$

LASSO PsN algorithm flowchart



[1] Ribbing et al. *J Pharmacokinet Pharmacodyn*. 2007

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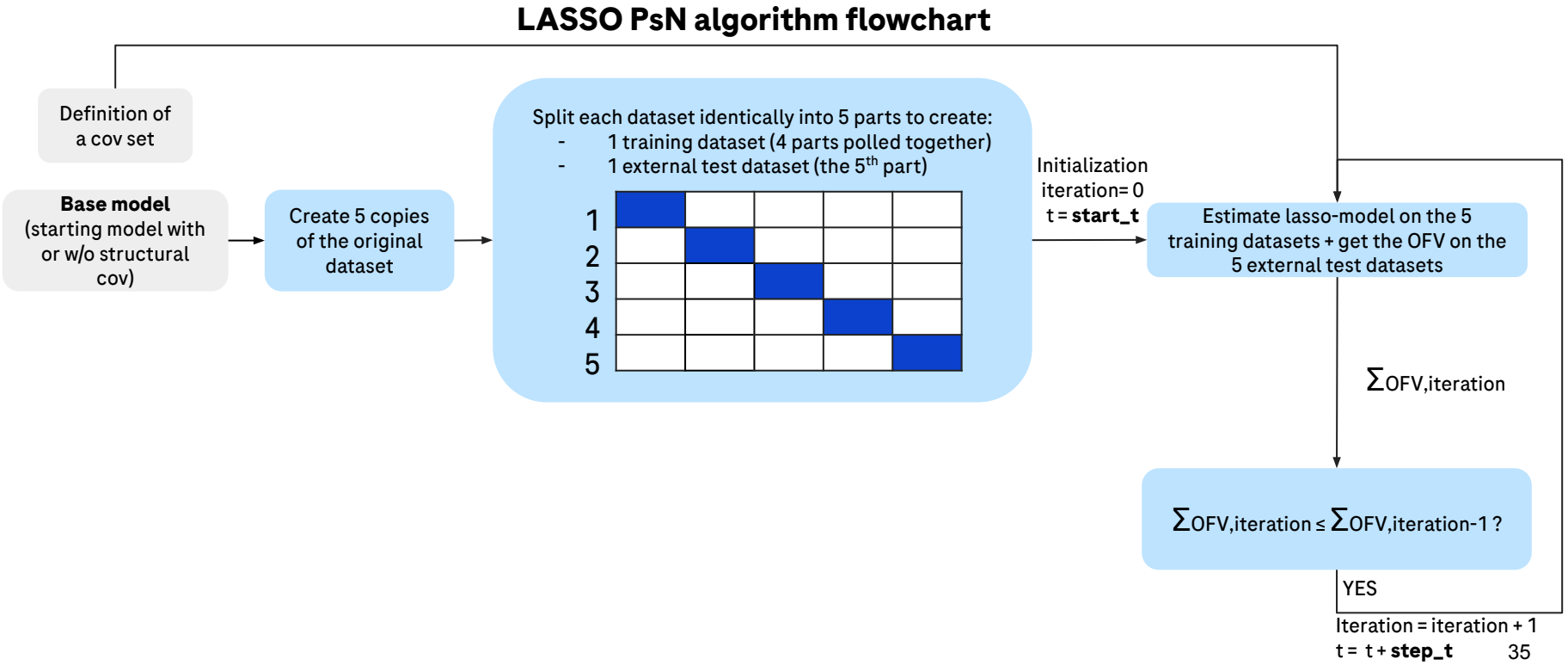

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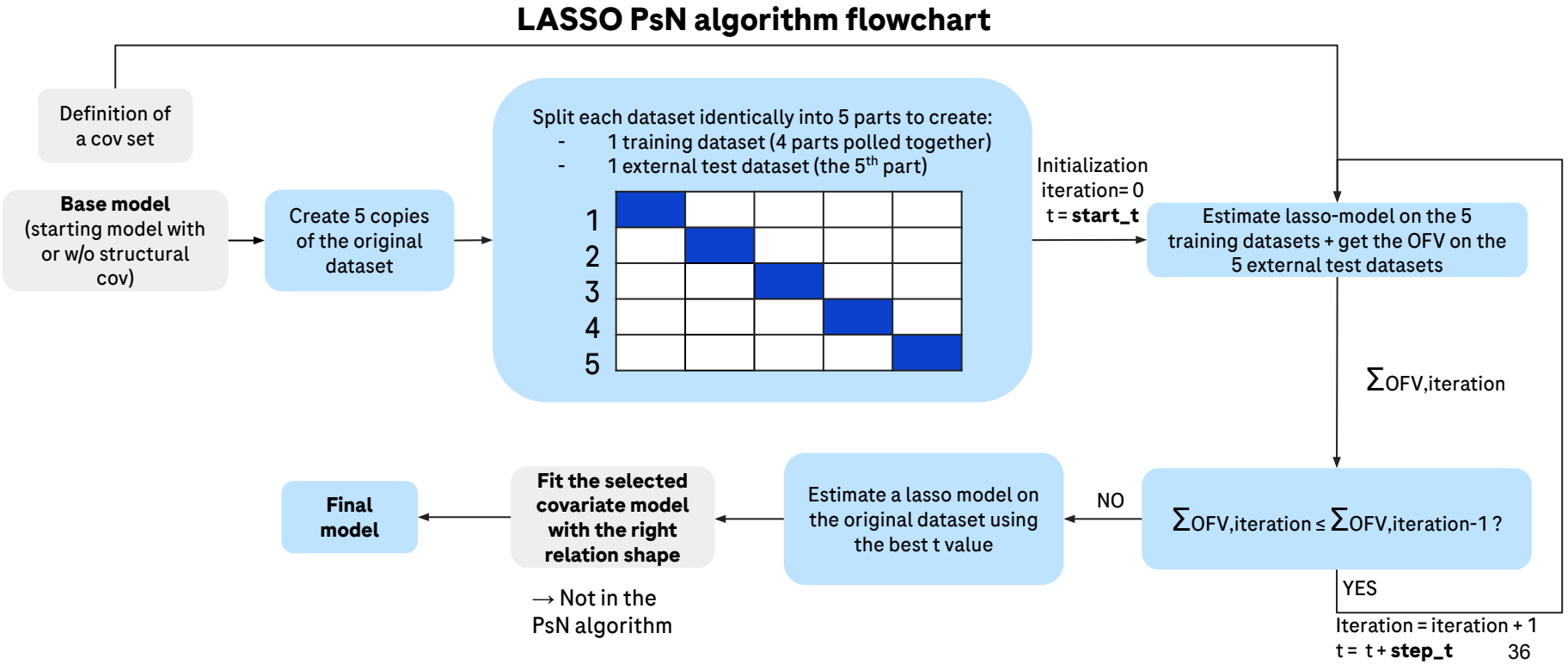
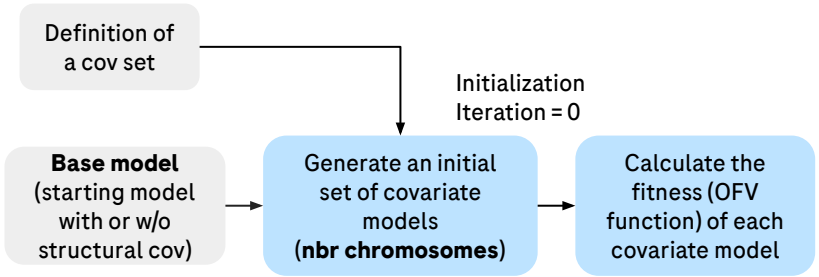


[1] Ribbing et al. *J Pharmacokinet Pharmacodyn*. 2007

GA [1]

- Heuristic search approach using principles inspired by natural selection and genetic

GA algorithm flowchart of Ronchi et al. [1]



[1] Ronchi et al. *J Pharmacokinet Pharmacodyn*. 2023

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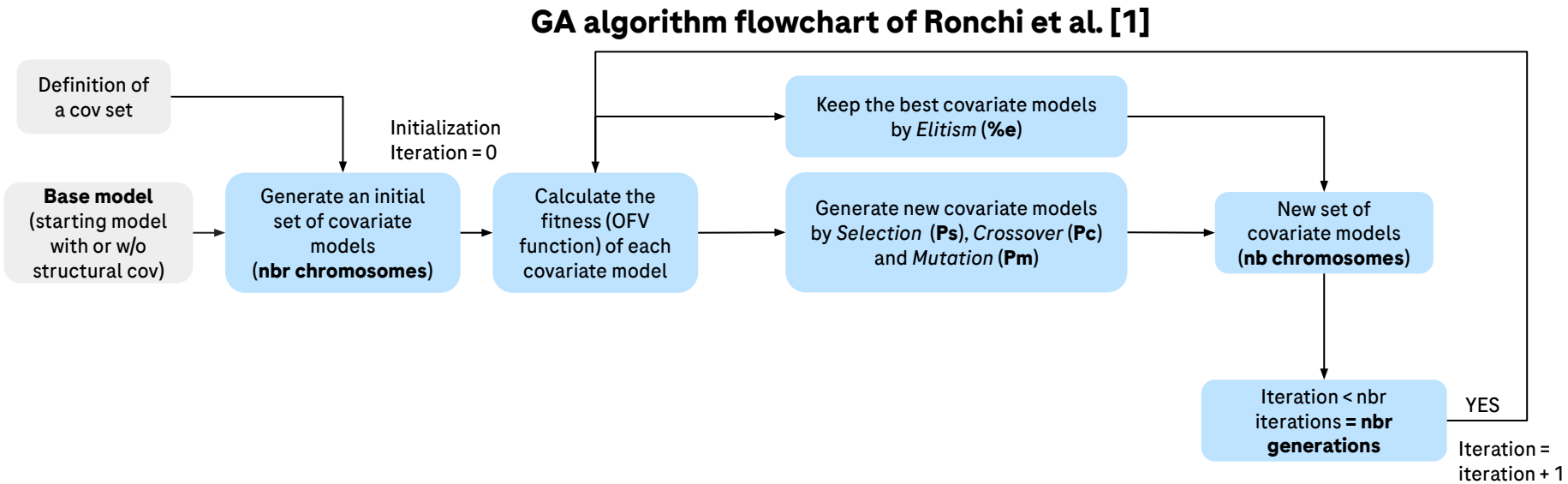

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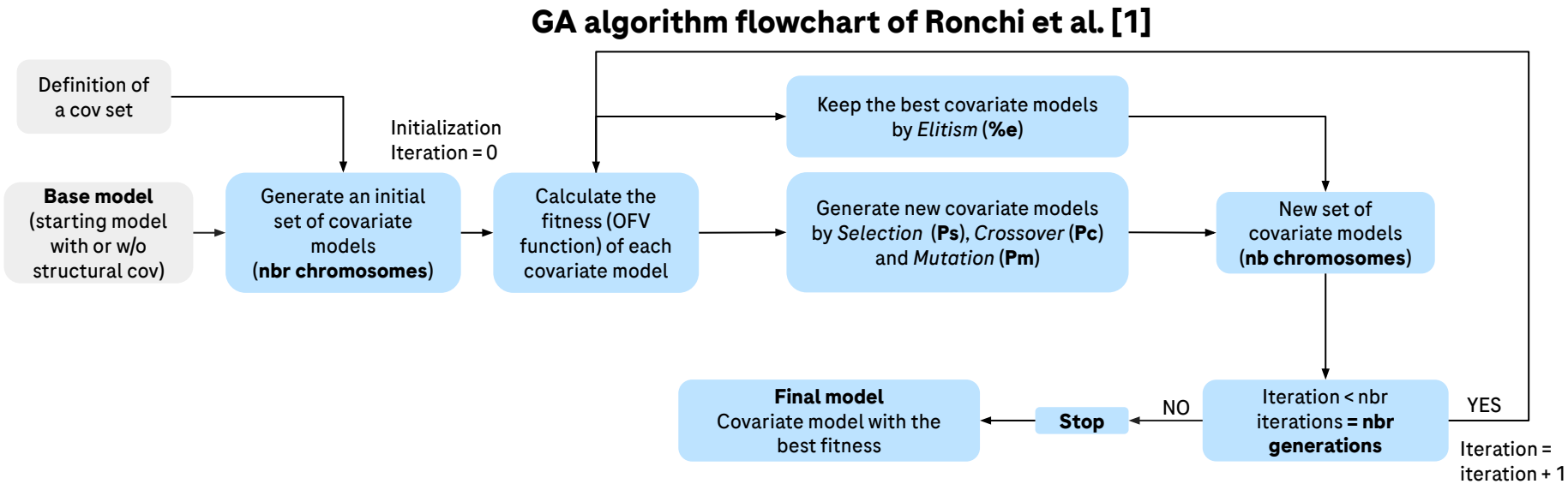

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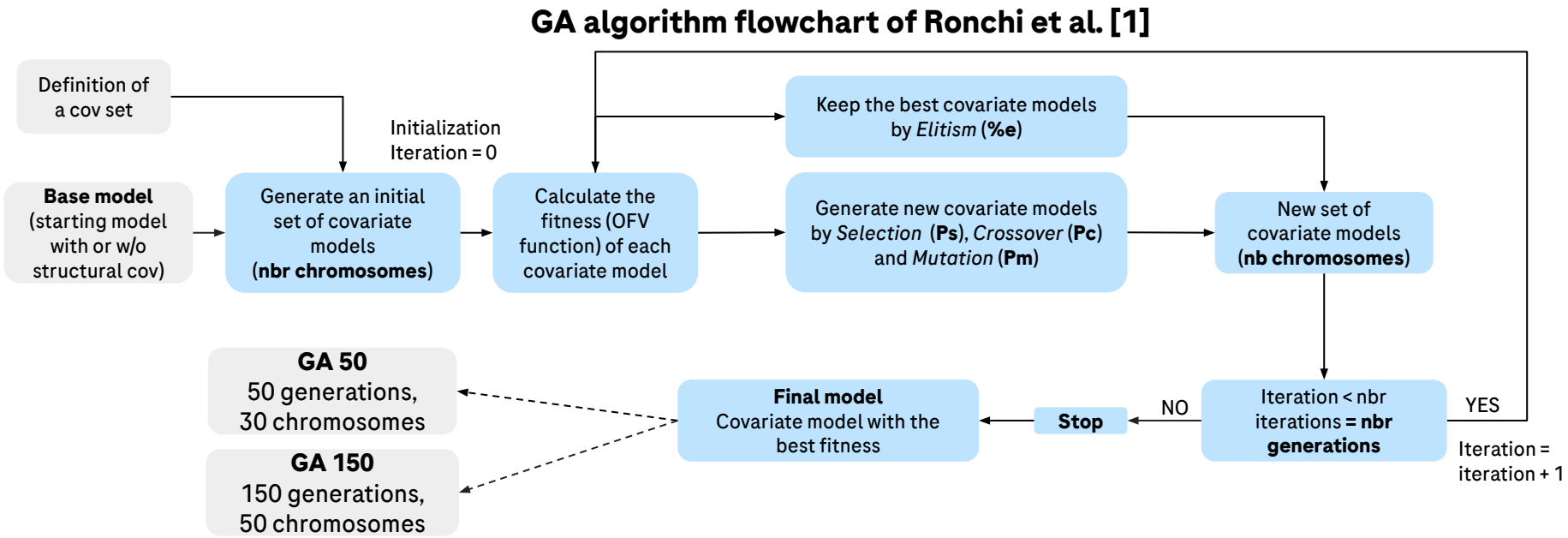

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Methods evaluation

- **OFV, BICc & runtime**
  - OFV = -2LL
  - BICc = $-2LL + P_R \times \ln(N) + P_F \times \ln(n_{tot})$

→ with LL the log likelihood, P_R the number of μ, $\beta_{par,cov}$ and $\dim(\Omega)$, P_F the number of error model parameters = 1, N the number of patients and n_{tot} the total number of observations

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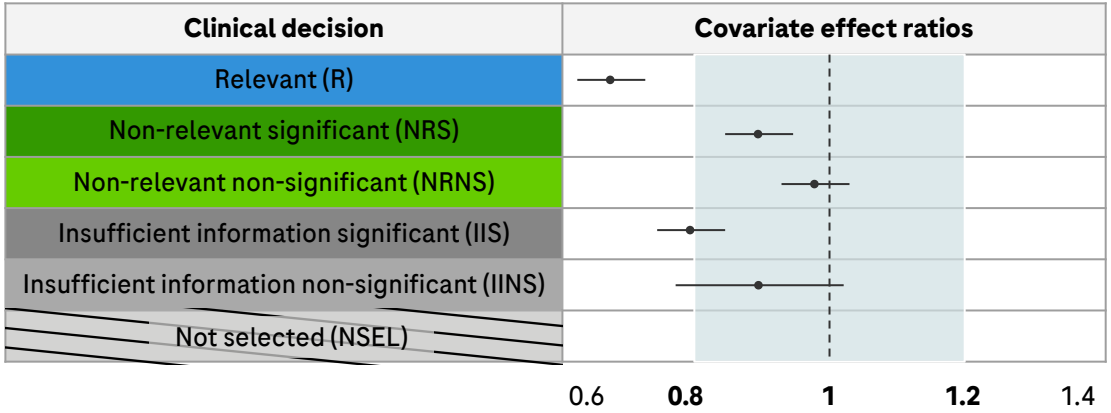
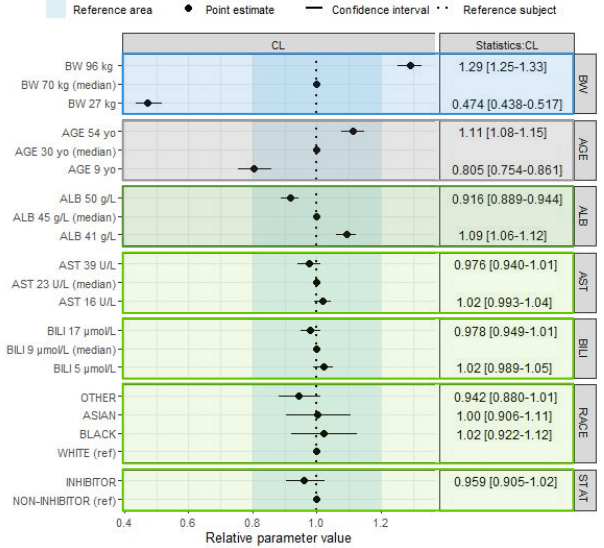
- **CCR assessment using forest plots**
  - Software: R 4.1.2, Package: PMXForest 1.2.6, PMXFrem 1.2.2
  - Number of samples: 1000



Example of one forest plot of FREM applied on the dataset simulated under the **Covariate model** with the **Saturated covariate set**



Reference subject: white individual of 70 kg, 30 years old, with an albumin level at 45 g/L, an aspartate aminotransferase level at 23 U/L, a bilirubin level at 9 µmol/L and without FVIII inhibitor

Results

OFV, BICc & runtime

	Simulation case: Base model						
	Ref model	**FM**	**FREM**	**SCM+**	**LASSO**	**GA 150**	**GA 50**
	Prespecified covariate set						
OFV	24 135	**24 110**	19 786*	24 126	24 121	24 126	24 126
P_R	8	24	90	9	16	9	11
BICc	24 191	24 261	20 330*	**24 188**	24 225	**24 188**	24 200
Runtime (h)	0.04	**0.44**	2.05	0.66	3.31	5.99	2.15

*FREM OFV & BICc are not comparable with other methods due to differences regarding the dataset (covariates treated as observations), the way of coding covariate effects (as random-effects) and the Ω matrix (omega block for FREM vs diagonal matrix for the other methods)

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	Prespecified covariate set													
OFV	24 135	**24 110**	19 786*	24 126	24 121	24 126	24 126	24 056	**24 038**	19 715*	24 056	24 039	24 044	24 050
P_R	8	24	90	9	16	9	11	14	24	90	14	21	16	19
BICc	24 191	24 261	20 330*	**24 188**	24 225	**24 188**	24 200	**24 148**	24 189	20 259*	**24 148**	24 172	**24 148**	24 172
Runtime (h)	0.04	**0.44**	2.05	0.66	3.31	5.99	2.15	0.04	**0.44**	2.18	0.81	5.38	9.89	2.32

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P_R	8	24	90	9	16	9	11	14	24	90	14	21	16	19
BICc	24 191	24 261	20 330*	**24 188**	24 225	**24 188**	24 200	**24 148**	24 189	20 259*	**24 148**	24 172	**24 148**	24 172
Runtime (h)	0.04	**0.44**	2.05	0.66	3.31	5.99	2.15	0.04	**0.44**	2.18	0.81	5.38	9.89	2.32
	Saturated covariate set													
OFV	24 135	**24 103**	19 786*	24 126	24 119	24 121	24 114	24 056	**24 032**	19 715*	24 048	24 046	24 044	24 042
P_R	8	33	90	9	17	11	15	14	33	90	15	20	16	22
BICc	24 191	24 308	20 330*	**24 188**	24 229	24 195	24 212	24 148	24 237	20 259*	**24 146**	24 173	24 148	24 181
Runtime (h)	0.04	**0.44**	2.05	1.55	4.51	5.99	2.09	0.04	**0.44**	2.18	2.09	6.33	10.73	3.71

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OFV, BICc & runtime

	Simulation case: Base model							Simulation case: Covariate model						
	Ref model	**FM**	**FREM**	**SCM+**	**LASSO**	**GA 150**	**GA 50**	**Ref model**	**FM**	**FREM**	**SCM+**	**LASSO**	**GA 150**	**GA 50**
	Prespecified covariate set													
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BICc	24 191	24 261	20 330*	**24 188**	24 225	**24 188**	24 200	**24 148**	24 189	20 259*	**24 148**	24 172	**24 148**	24 172
Runtime (h)	0.04	**0.44**	2.05	0.66	3.31	5.99	2.15	0.04	**0.44**	2.18	0.81	5.38	9.89	2.32
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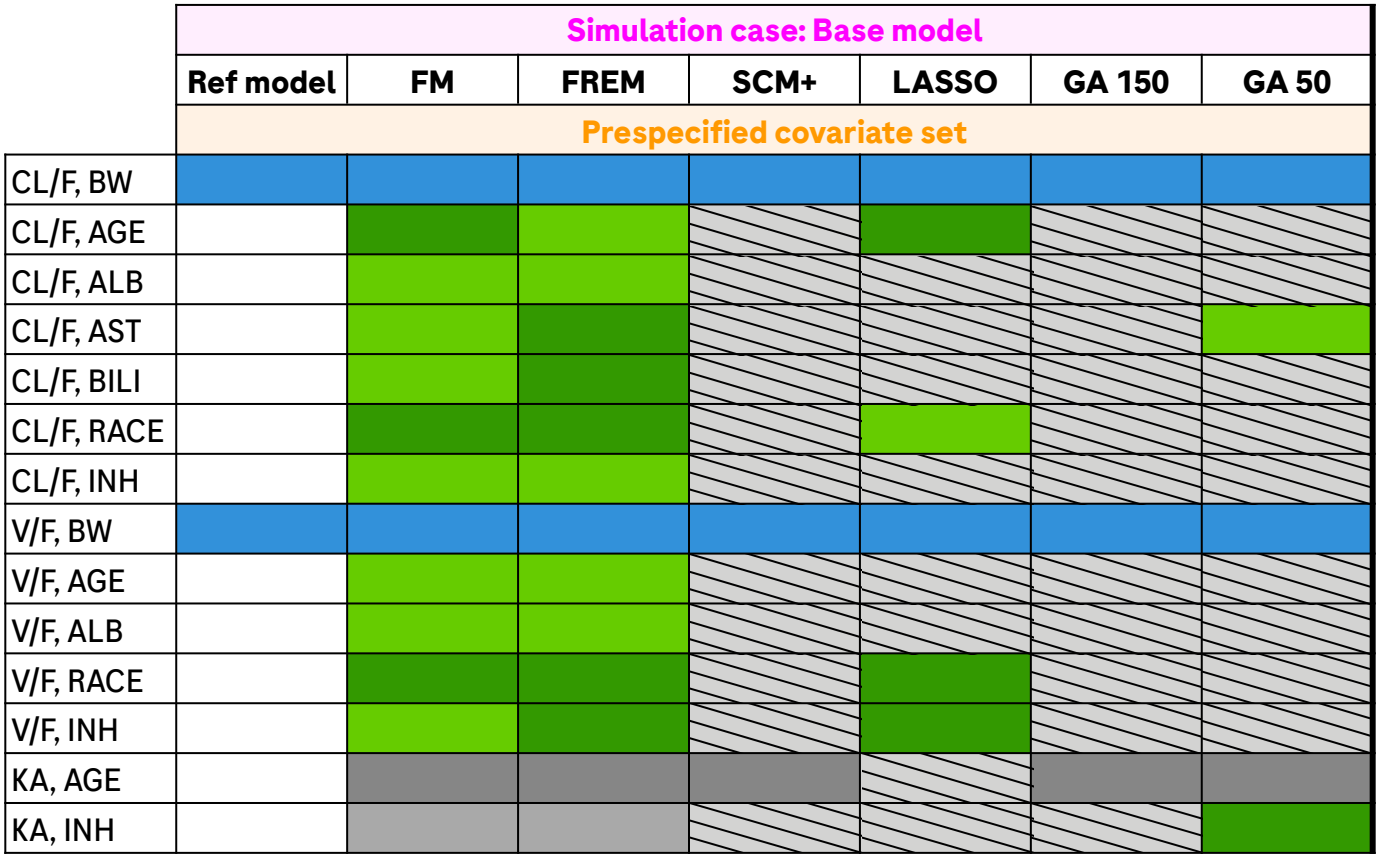
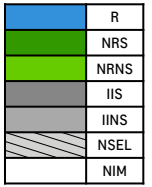
Key messages:

- FM outperformed SCM+, LASSO & GA in terms of OFV
- SCM+ & GA150 got the best BICc due to more parsimonious model
- TOP 3 of the fastest methods : FM, SCM+ & FREM

*FREM OFV & BICc are not comparable with other methods due to differences regarding the dataset (covariates treated as observations), the way of coding covariate effects (as random-effects) and the Ω matrix (omega block for FREM vs diagonal matrix for the other methods)

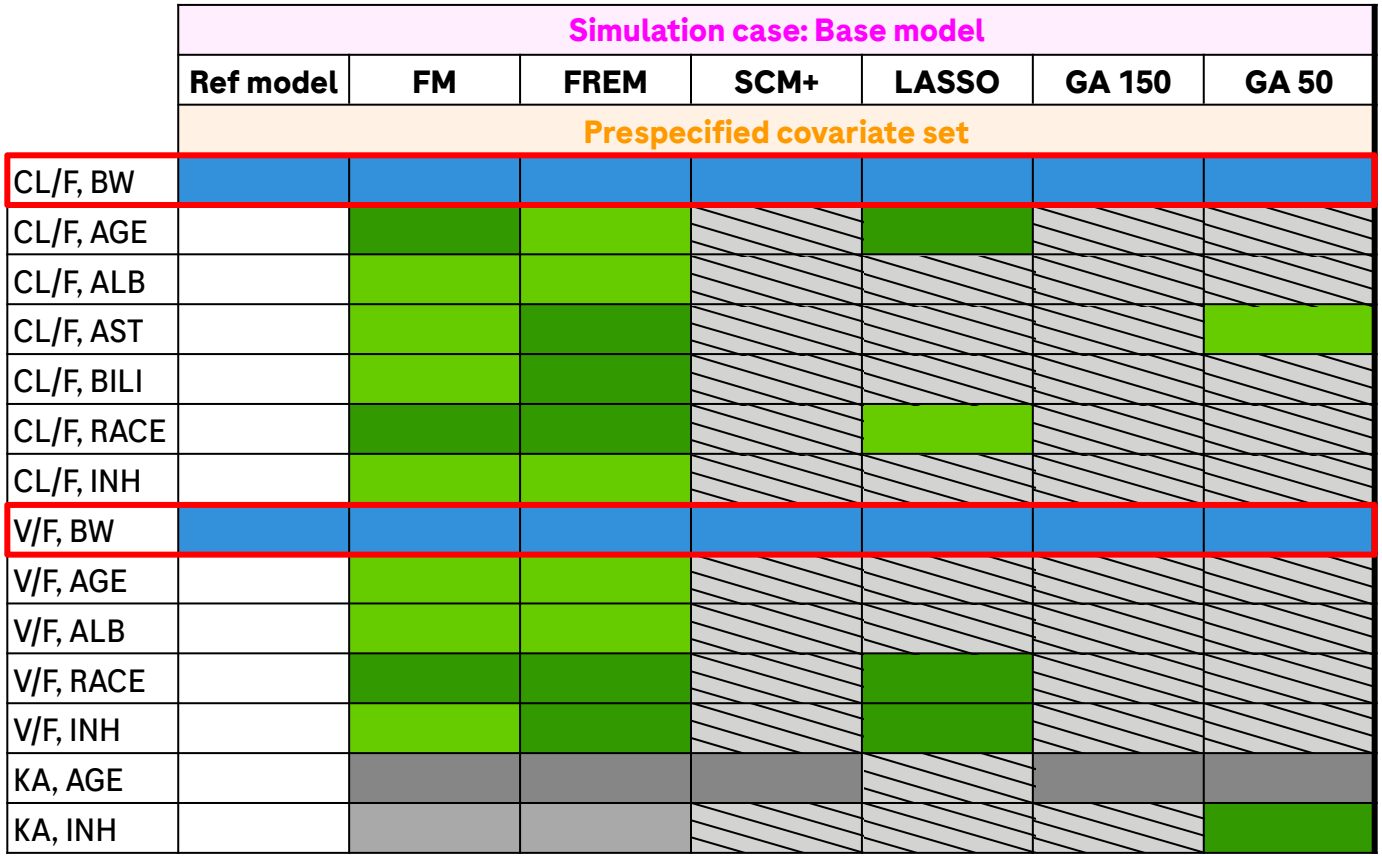
CCR assessment

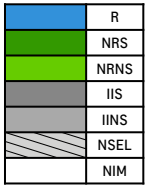




NSEL: not selected,
NIM: not in the model

CCR assessment





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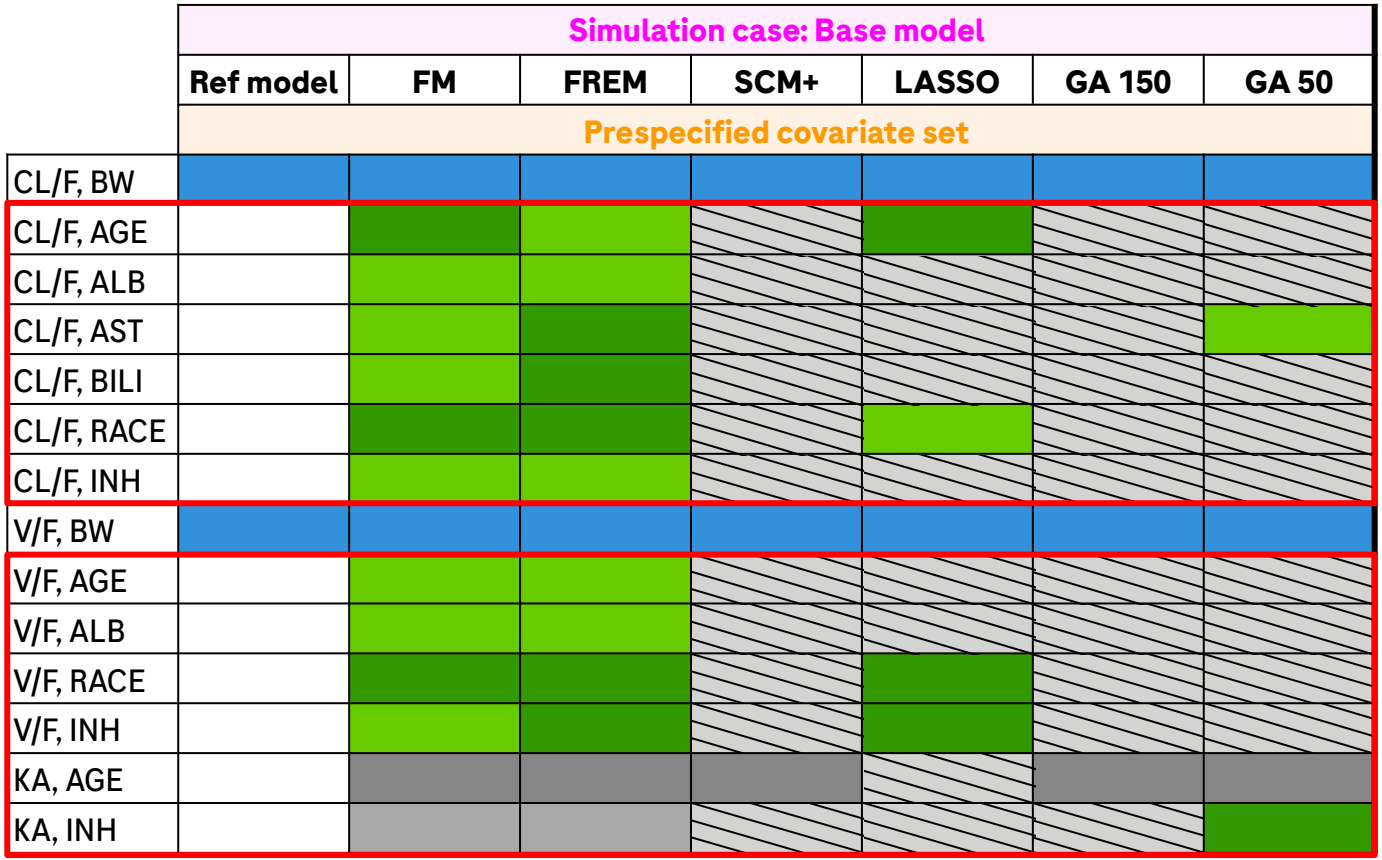

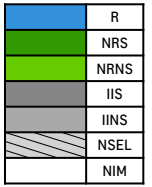

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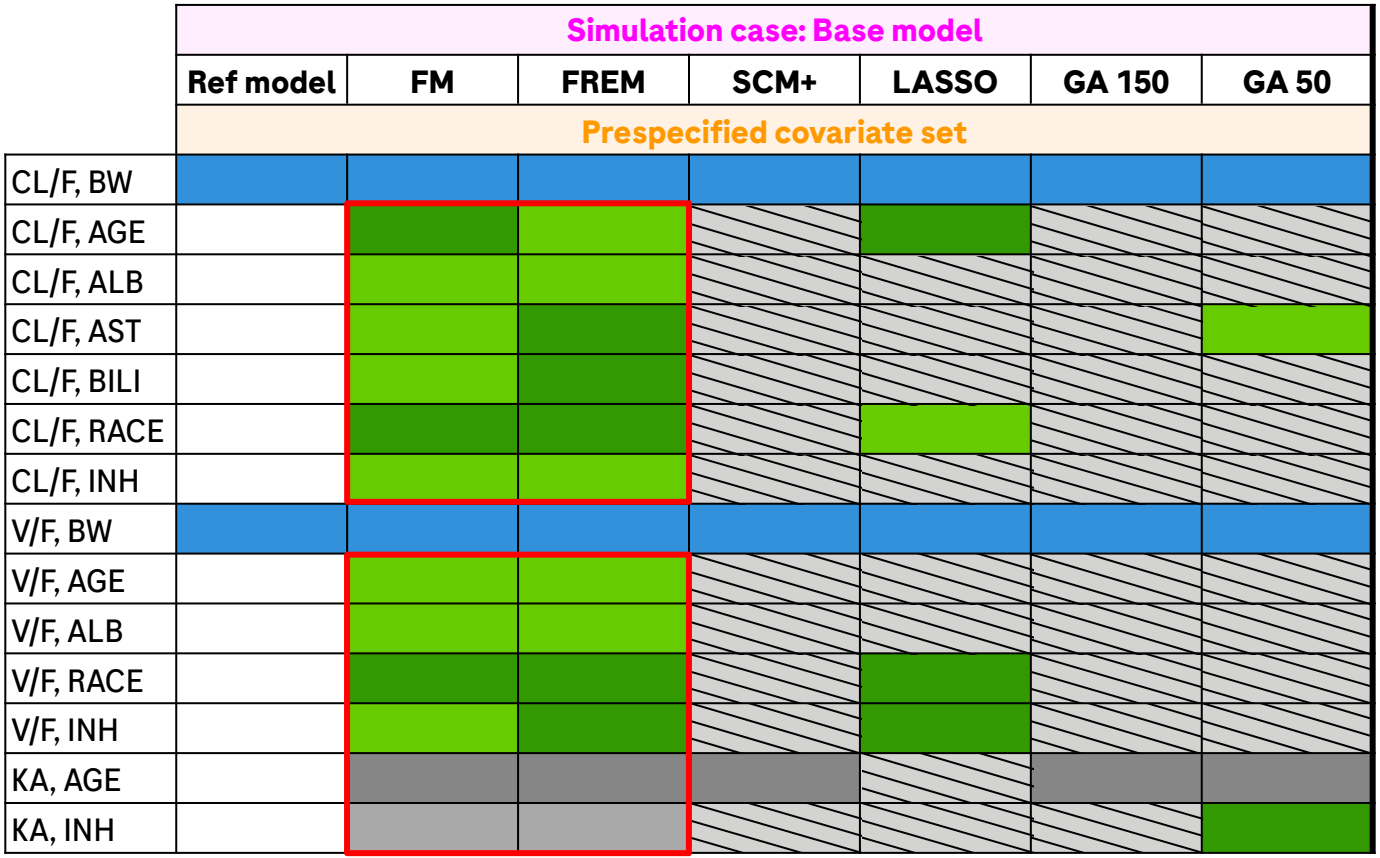

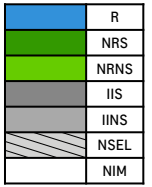

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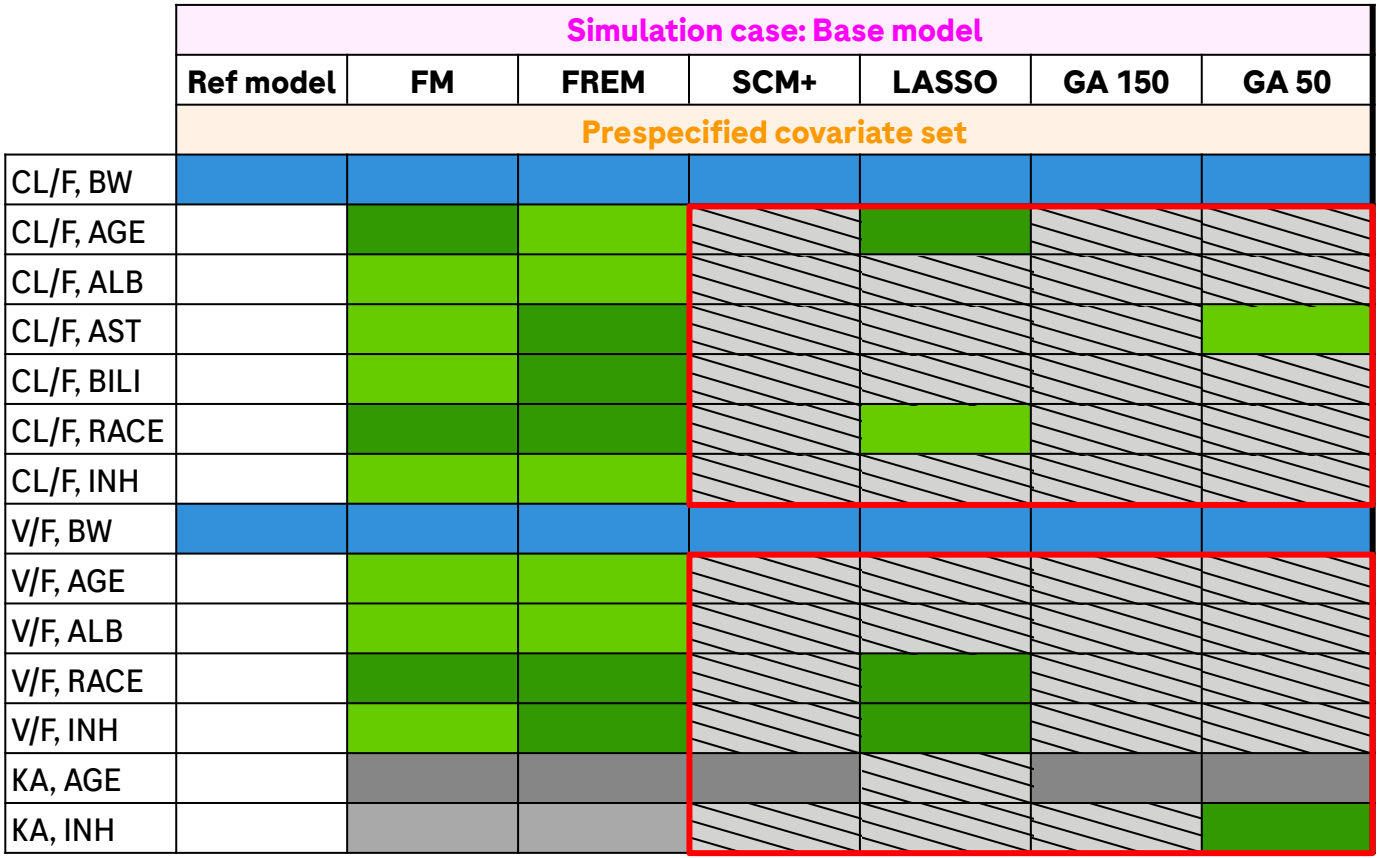
CCR assessment



R
NRS
NRNS
IIS
IINS
NSEL
NIM

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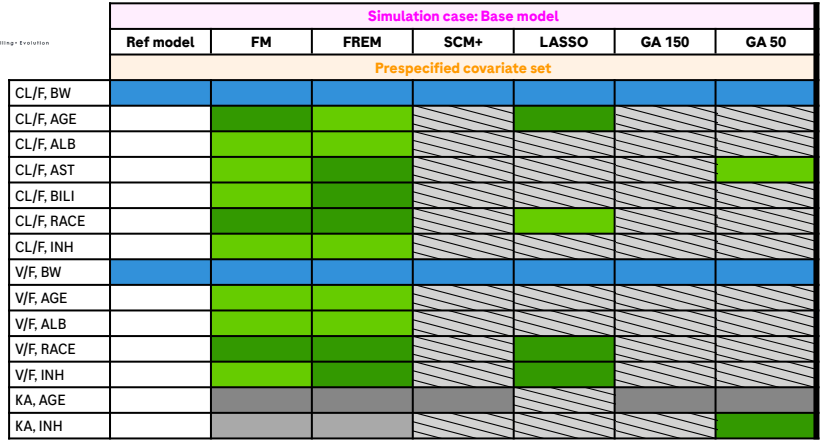

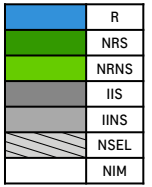

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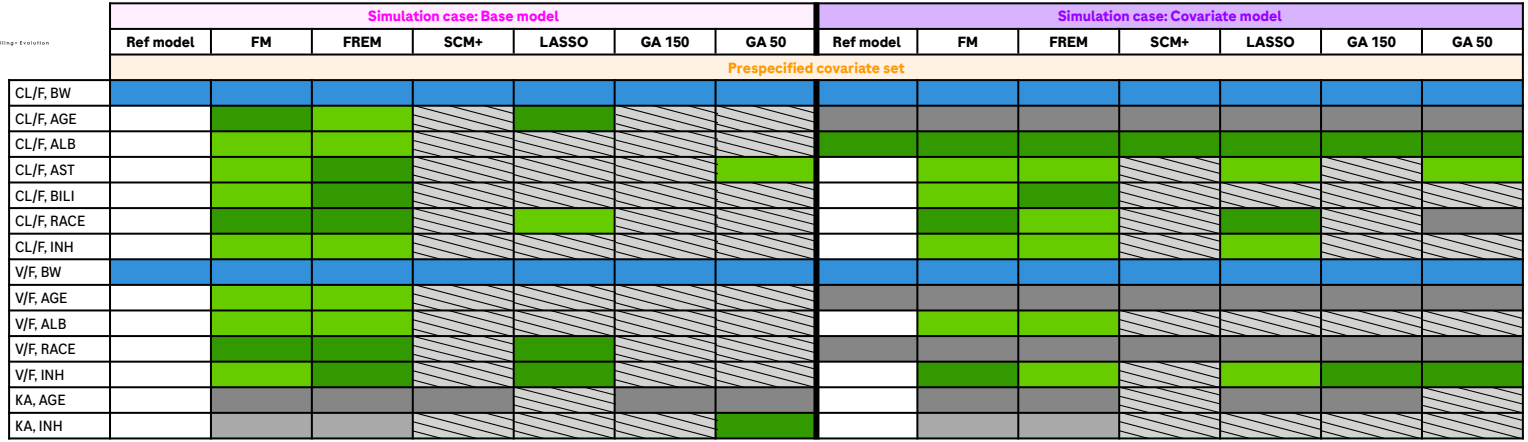

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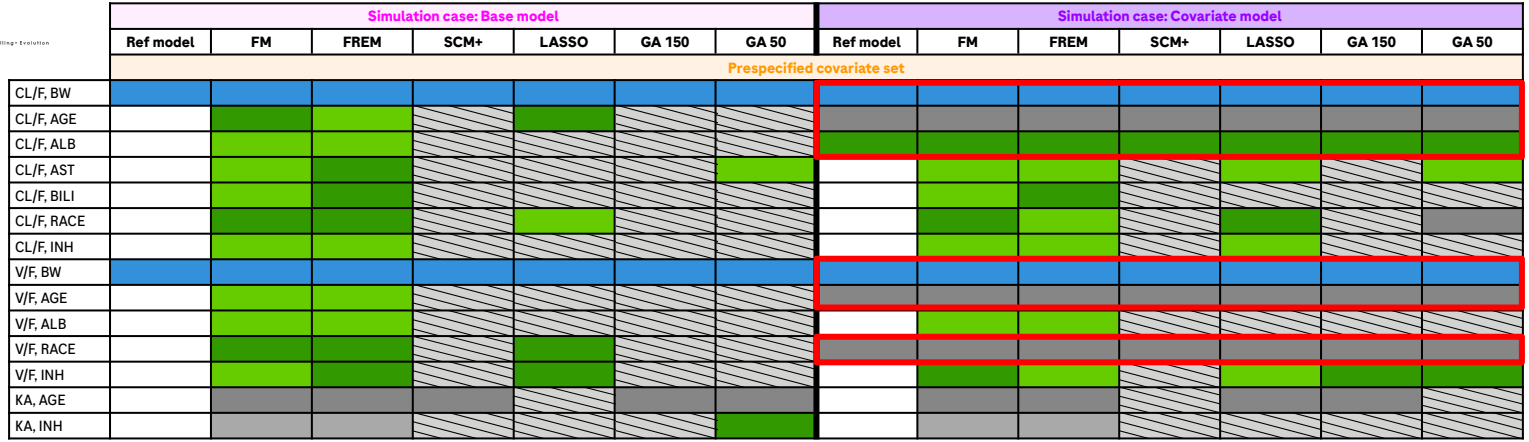

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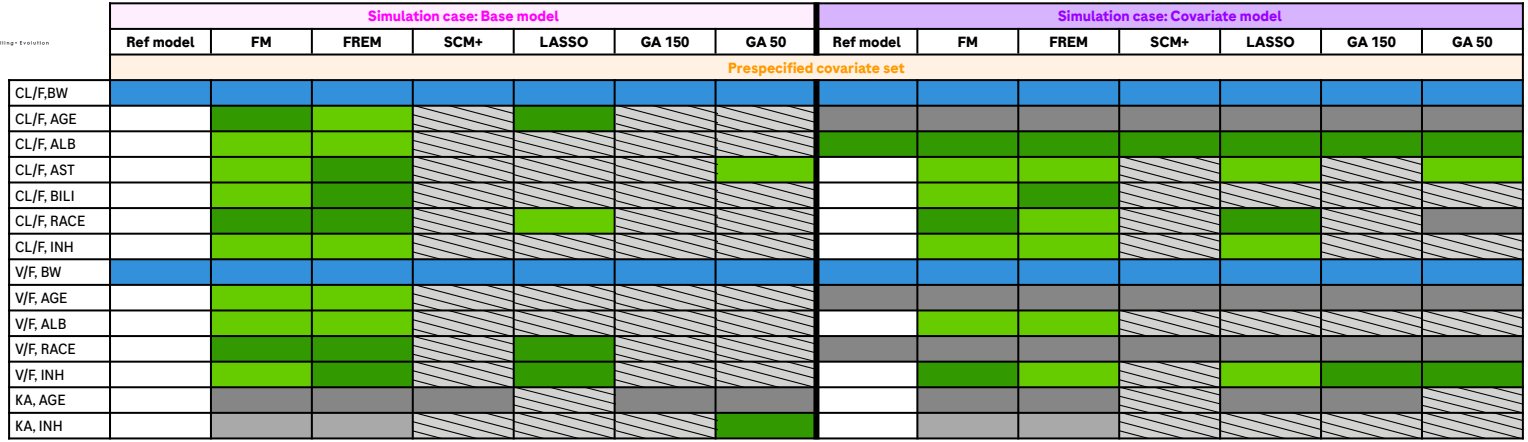

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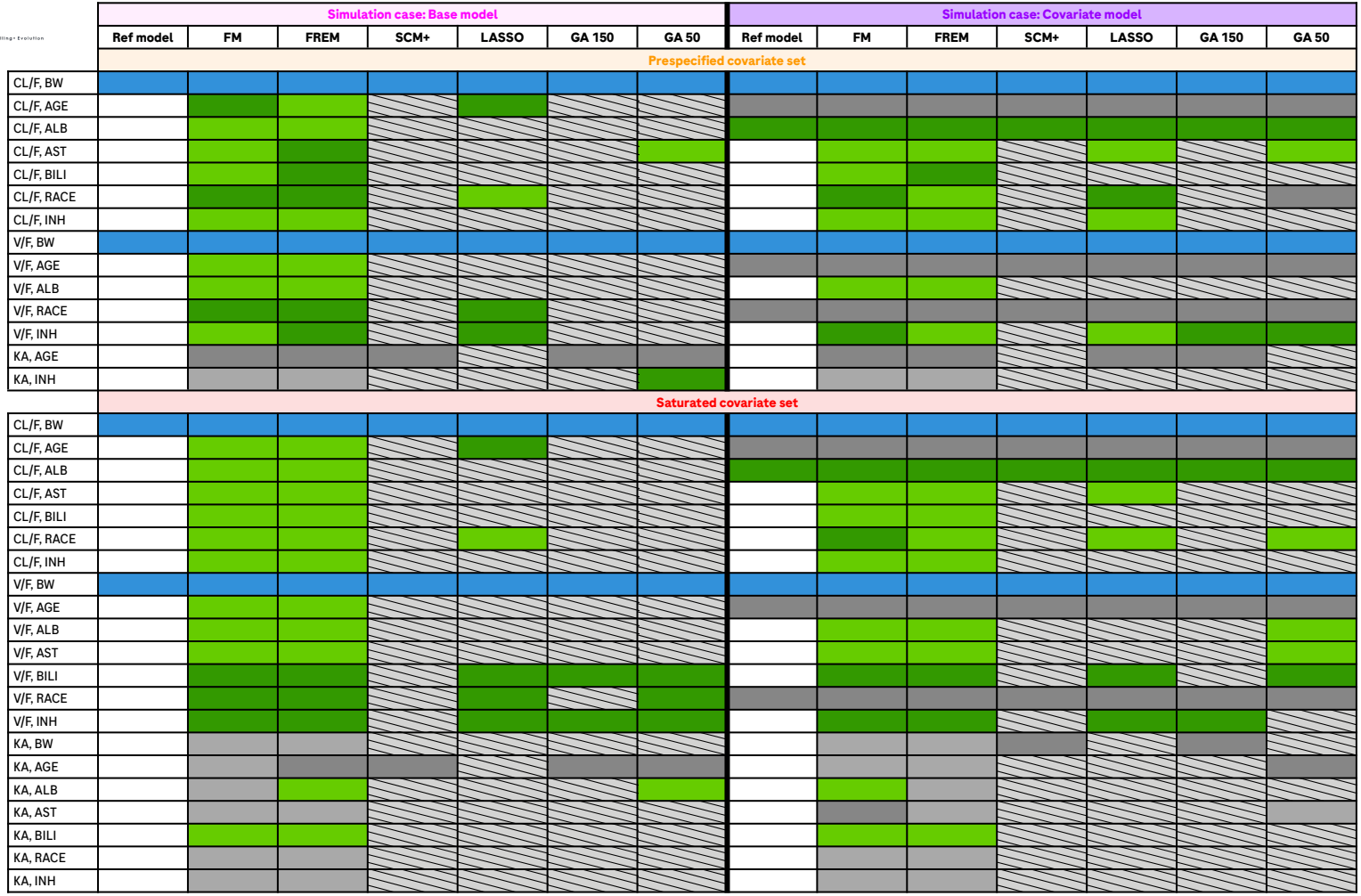

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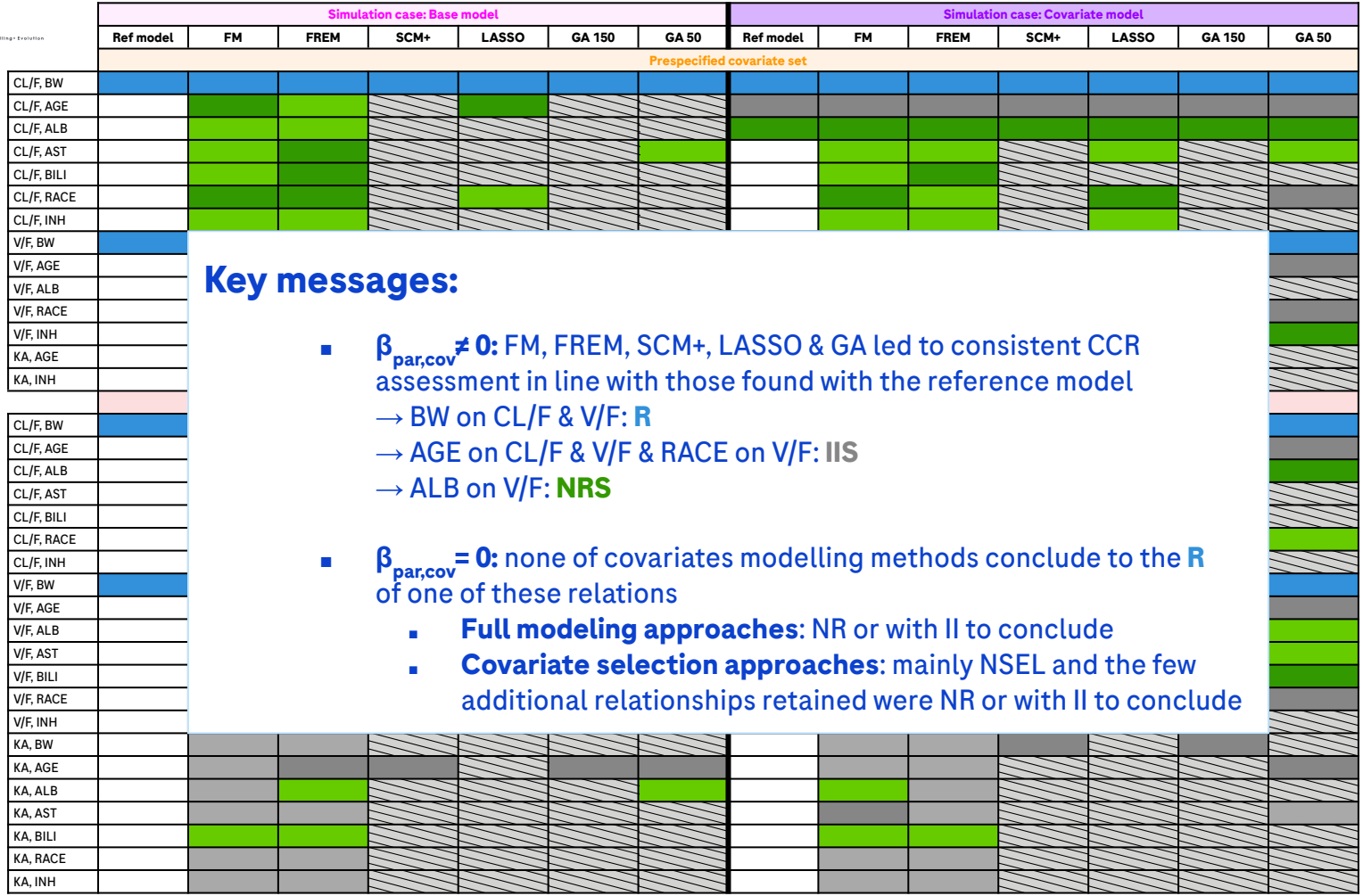

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Key messages:

- $\beta_{par,cov} \neq 0$: FM, FREM, SCM+, LASSO & GA led to consistent CCR assessment in line with those found with the reference model
  → BW on CL/F & V/F: **R**
  → AGE on CL/F & V/F & RACE on V/F: **IIS**
  → ALB on V/F: **NRS**

- $\beta_{par,cov} = 0$: none of covariates modelling methods conclude to the **R** of one of these relations
  - **Full modeling approaches**: NR or with II to conclude
  - **Covariate selection approaches**: mainly NSEL and the few additional relationships retained were NR or with II to conclude

Conclusion

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  - Highly comparable results making both methods very suitable for CCR assessment
  - Better runtime than GA & LASSO
- Covariate selection approaches (SCM+, LASSO, GA150 & GA50):
  - SCM+ & GA150 selected more parsimonious models than GA50 & LASSO → better BICc
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    - With the full modeling methods, we get the information whether if it is NR or II
- Further evaluations are necessary to enhance the robustness of those results by using simulation frameworks with increased complexity in model structures, expanded covariate sets, and a larger number of simulated datasets

BACKUP SLIDES

Covariate correlation matrix

Covariates distribution from the 389 patients included in the emicizumab population PK model development of Retout et al. (2020)

Continuous covariates	Median [min–max]
Age (years)	30.0 [1.22 - 77.00]
Body weight (kg)	69.1 [9.50–156]
Albumin (g/L)	45.0 [33.0–56.6]
Aspartate aminotransferase (U/L)	23.0 [11.0–91.0]
Bilirubin (µmol/L)	9.0 [0.33–46.0]

Categorical covariates	Categories	N [%]
Status	Non-inhibitor	195 [50%]
	FVIII inhibitor	194 [50%]
Race	White/Caucasian	244 [63%]
	Black	31 [8%]
	Asian, including Japanese	89 [23%]
	Other or unknown	25 [6%]

Emicizumab clinical trial information

	Phase III study HAVEN 1	Phase III study HAVEN 2	Phase III study HAVEN 3	Phase III study HAVEN 4	Phase I/II study
Number of patients	112	61	148	48	18
Number of PK samples per patient (median [min–max])	14 [4–17]	12 [7–17]	Arm A & D: 11 [6–14] Arm B & C: 11 [1–14]	Run-in part: 25 [25–26] Expansion part: 8 [7–9]	Cohort 1: 65 [64–71] Cohort 2: 58 [21–62] Cohort 3: 52 [30–61]
Subcutaneous dosing regimen	3 mg/kg QW for 4 weeks fb 1.5 mg/kg QW	3 mg/kg QW for 4 weeks fb 1.5 mg/kg QW	Arm A & D: 3 mg/kg QW for 4 weeks fb 1.5 mg/kg QW Arm B & C: 3 mg/kg QW for 4 weeks fb 3 mg/kg Q2W	Run-in part: 6 mg/kg Q4W Expansion part: 3 mg/kg QW for 4 weeks fb 6 mg/kg Q4W	Cohort 1: 1 mg/kg fb 0.3 mg/kg QW Cohort 2: 3 mg/k fb 1 mg/kg QW Cohort 3: 3 mg/kg QW

[1] Retout et al. Clin Pharmacokinet. 2020

Parameter estimates on real data

		Base model		Covariate model				Covariate model	
Parameters (units)		**value**	**RSE (%)**	**value**	**RSE (%)**	**Parameters (units)**		**value**	**RSE (%)**
Fixed effects	μ_{ka} (1/day)	0.538	6.4	0.543	6.6	Covariate effects	$\theta_{CL/F, AGE}$	0.127	30.4
	$\mu_{V/F}$ (L)	10.933	1.6	11.138	1.6		$\theta_{CL/F, ALB}$	-0.948	22.5
	$\mu_{Cl/F}$ (L/day)	0.288	1.8	0.289	1.7		$\theta_{V/F, BLK}$	-0.212	20.3
Covariate effects	$\theta_{V/F, BW}$	1.066	2.6	0.867	6.1		$\theta_{V/F, AGE}$	0.139	25.8
	$\theta_{Cl/F, BW}$	0.939	2.9	0.801	7.5				
Between subject variability	ω_{ka}	0.712	16.7*	0.709	15.9*				
	$\omega_{V/F}$	0.281	9.4*	0.265	8.5*				
	$\omega_{Cl/F}$	0.300	9.5*	0.285	8.3*				
Error model	a - fixed (µg/mL)	0.0250	/	0.0250	/				
	b	0.147	2.0	0.147	2.0				

* Relative SE (RSE) computed for the corresponding variance

CCR assessment with multiple ratios

→ Single decision when more than one ratio (i.e. continuous covariates with P10 and P90 ratios or categorical covariates with more than 2 categories)

Case	Decision
R & … & {R|NRS|NRNS|IIS|IINS} & …	R
NRS & … & {NRS|NRNS} & …	NRS
NRNS & … & NRNS & …	NRNS
IIS & … & {NRS|NRNS|IIS|IINS} & …	IIS
IINS & … & {NRS|NRNS|IINS} & …	IINS

NLMEM and parameter estimation

- Let be y_{ij}, the response of individual $i \in \{1, \dots, N\}$ at sampling time t_{ij} with $j \in \{1, \dots, n_i\}$:

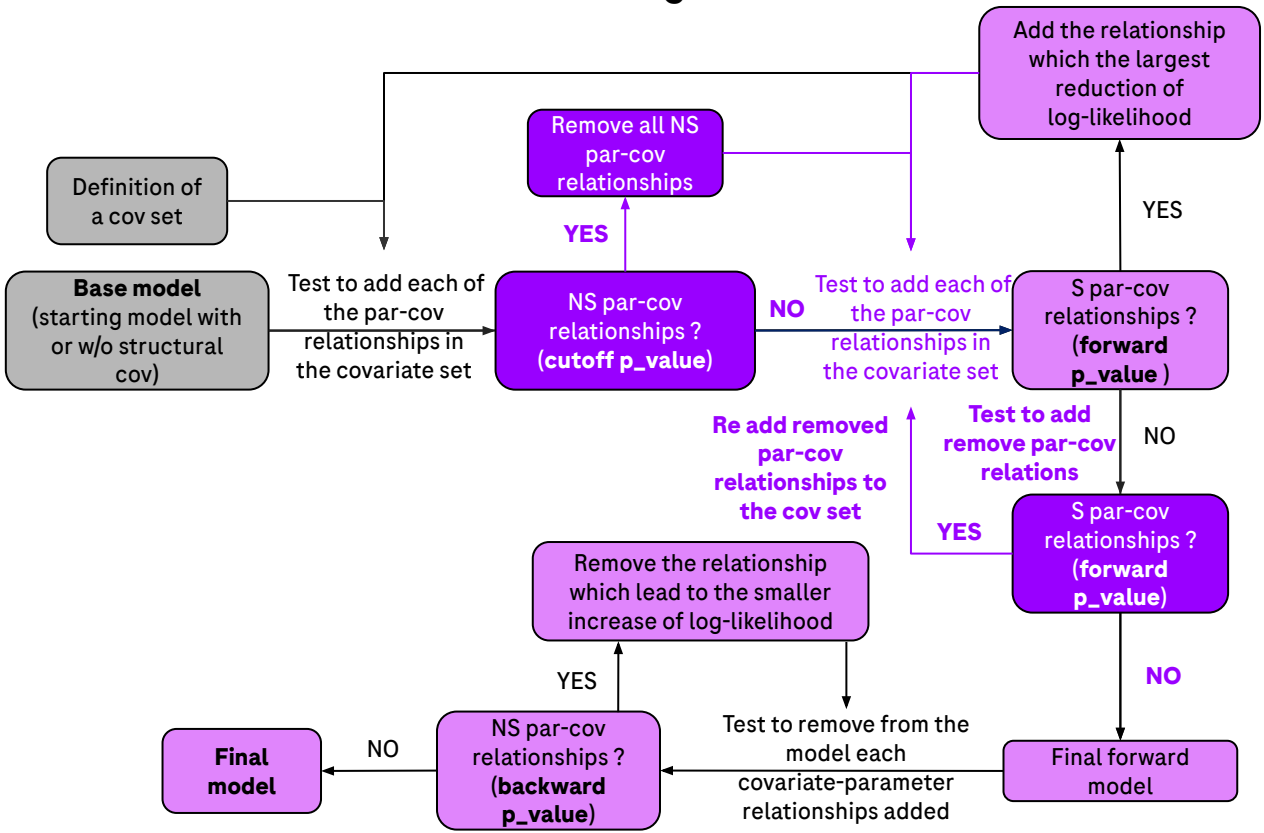
$$y_{ij} = f(t_{ij}, \phi_i) + (a + b \times f(t_{ij}, \phi_i)) \times \varepsilon_{ij}$$

  - $f(t_{ij}, \phi_i)$: nonlinear structural PK model
  - $\phi_i = h(\mu, \eta_i, \mathbf{C_i}, \beta)$: vector of individual PK parameters for subject i
    - μ: vector of fixed effects
    - $\eta_i \sim N(0, \Omega)$: vector of random-effects of individual i, with Ω the variance-covariance matrix
    - **C_i: vector of covariate values for the individual i**
    - **β: vector of covariate effects with $\beta_{par,cov}$ the effect of a covariate (cov) on a parameter (par)**
  - $\varepsilon_{ij} \sim N(0,1)$: measurement error for the individual i, at the time t_{ij}
  - a, b: additive, proportional term of the residual unexplained variability
- Log-normally distributed PK parameters to ensure positiveness
- Vector of parameters to estimate with their standard error (SE): $\theta = \{\mu, \beta, \Omega, a, b\}$
- First order conditional estimation with interaction (FOCEi) algorithm for parameters estimation
- SE derived from the covariance matrix computed as $R^{-1}SR^{-1}$, with R and S the Hessian and the Cross-Product Gradient matrix, respectively
- PK data analysis performed with NONMEM version 7.4

SCM [1,2] / SCM+ [3]

- Forward iterative loop (par-cov relationships tested to be added in an univariate manner) followed by a backward iterative loop (par-cov relationships tested to be removed in an univariate manner)
- Additional step for SCM+ compared to SCM → reduction of the covariate scope

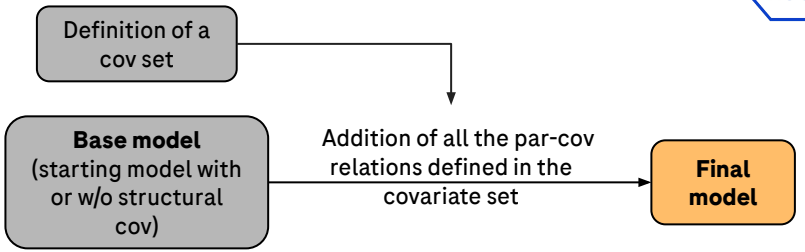
SCM and SCM+ PsN algorithm flowchart



[1] Jonsson et al. *Pharm Res*. 1998; [2] Lindbom et al. *Comput Methods Programs Biomed*. 2005; [3] Svensson et al. *CPT: Pharmacomet Syst Pharmacol*. 2022

Full model [1,2] & FREM [3]

- All the par-cov relationships of the covariate set are estimated simultaneously



FM

$$P_{1,i} = \mu_{P1} + \beta_{P1,C1}(C_{1,i} - \overline{C}_1) + \beta_{P1,C2}(C_{2,i} - \overline{C}_2) + \eta_{P1,i}$$
$$P_{2,i} = \mu_{P2} + \beta_{P2,C1}(C_{1,i} - \overline{C}_1) + \beta_{P2,C2}(C_{2,i} - \overline{C}_2) + \eta_{P2,i}$$

$$\begin{bmatrix}\eta_{P_{1,i}} \\ \eta_{P_{2,i}}\end{bmatrix} \sim N(\vec{0}, \Omega)$$

FREM

$$P_{1,i} = \mu_{P1} + \eta_{P1,i}$$
$$P_{2,i} = \mu_{P2} + \eta_{P2,}$$

$$C_{1,i} = \overline{C}_1 + \eta_{C1,i}$$
$$C_{2,i} = \overline{C}_2 + \eta_{C2,i}$$

$$\begin{bmatrix}\eta_{P_{1,i}} \\ \eta_{P_{2,i}} \\ \eta_{C_{1,i}} \\ \eta_{C_{2,i}}\end{bmatrix} \sim N(\vec{0}, \Omega_{FREM})$$

$$\Omega_{FREM} = \begin{pmatrix}\Omega_{par} & \Omega_{cov,par} \\ \Omega_{par,cov} & \Omega_{cov}\end{pmatrix} = \begin{pmatrix}\omega^2_{P_1} & \omega_{P_2P_1} & \omega_{C_1P_1} & \omega_{C_2P_1} \\ \omega_{P_1P_2} & \omega^2_{P_2} & \omega_{C_1P_2} & \omega_{C_2P_2} \\ \omega_{P_1C_1} & \omega_{P_2C_1} & \omega^2_{C_1} & \omega_{C_2C_1} \\ \omega_{P_1C_2} & \omega_{P_2C_2} & \omega_{C_1C_2} & \omega^2_{C_2}\end{pmatrix}$$

$$B = \begin{pmatrix}\beta_{C_1P_1} & \beta_{C_2P_1} \\ \beta_{C_1P_2} & \beta_{C_2P_2}\end{pmatrix} = \Omega_{cov,par}\Omega_{cov}^{-1}$$

[1] Gastonguay. 20th PAGE meeting. 2011; [2] Xu et al. Br J Clin Pharmacol. 2018; [3] Yngman et al. *CPT: Pharmacomet Syst Pharmacol.* 2022

Covariate modeling - 5 algorithm settings

- Covariate selection methods

SCM+
Software: PsN 5.3.2
P-cutoff = 0.05
P-forward = 0.05
P-backward = 0.01*

LASSO
Software: PsN 5.3.2
Start_t = 1
Step_t = 0.05
Stop_t = 10*
Cutoff = 0.05

→ fit the selected covariate model with the right relation shape

GA
Software: R 4.0.5 & Perl 5.30.2
Selection pressure = 0.75
Crossover probability = 0.7
Mutation probability = 0.025
Chromosomes preserved by elitism = 10%

GA 150
150 generations,
50 chromosomes

GA 50
50 generations,
30 chromosomes

- Full modeling methods

FM
Software: PsN 5.3.2
Retries = 5*

FREM
Software: PsN 5.3.2

*Not the PsN algorithm default value