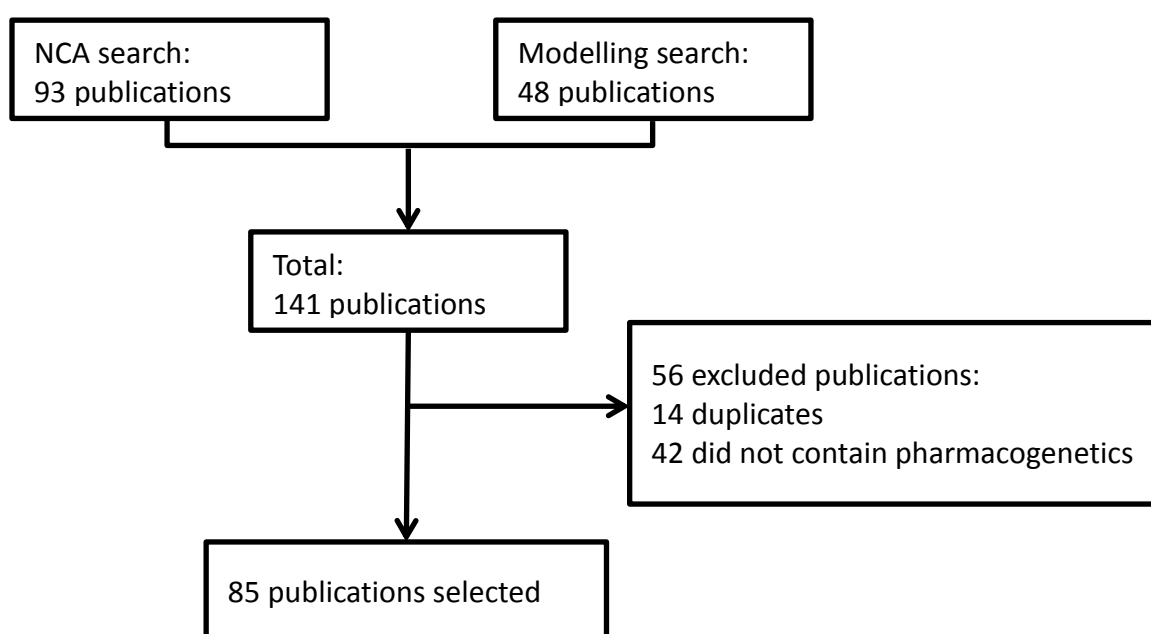


## Supplementary materials

### Methods for literature review

We performed a bibliographic survey of publications indexed in the Pubmed database to investigate differences in the methods used for pharmacogenetic studies. Selection was limited to publications on clinical trials written in English between January 1<sup>st</sup> 2010 and December 31<sup>th</sup> 2013 for which abstract was available. Two searches based on keywords have been used to retrieve publications dealing with NCA or modelling respectively.



**Fig.** Flow diagram of the literature review.

*NCA search: (((((polymorph\* OR genetic\* OR pharmacogenet\*[Title/Abstract])) AND (pharmacokinet\* AND concentration\*[Title/Abstract])) AND (non-compartment\* OR noncompartment\* OR NCA OR AUC\*[Title/Abstract])) AND Clinical Trial[ptyp] AND hasabstract[text] AND ( "2010/01/01"[PDat] : "2012/12/31"[PDat] ) AND Humans[Mesh] AND English[lang])*

*Modelling search: (((((polymorph\* OR genetic\* OR pharmacogenet\*[Title/Abstract])) AND (pharmacokinet\* AND concentration\*[Title/Abstract])) AND ("population PK" OR "population pharmacokinetic" OR model\* OR nonlinear OR non-linear OR mixed effect\* OR Nonmem OR Monolix[Title/Abstract])) AND Clinical Trial[ptyp] AND hasabstract[text] AND ( "2010/01/01"[PDat] : "2012/12/31"[PDat] ) AND Humans[Mesh] AND English[lang])*

## Softwares

The C++ software Hapgen version 2.1.2 (1) was used to simulate SNPs from reference haplotype panels provided by the Hapmap Project. Among the 176 SNPs present on the DNA microarray, 55 were also present in the Hapmap reference panel. For the others, we chose the closest variant in the Hapmap database. The SNPs selected from the Hapmap database to target the SNPs from the IRIS DNA microarray were very close with a median of 1730 bases pair departure.

The software Monolix version 4.2.2 (2) is a software using the SAEM algorithm for parameters estimation in nonlinear mixed effects models, which was used to derive the EBE using the PK model and the simulated PK profiles.

The C++ software PLINK version 1.07 (3), is a free and open-source whole genome association analysis toolset, which was used to performed the stepwise procedure.

The statistical software R version 2.15.2 (4) was used to simulate the PK profiles. Some R packages were also used such as “ridge” (5), a package for ridge regression with automatic selection of the regularization parameter.

HyperLasso (6) is a C++ program and was used for Lasso and HyperLasso regression methods. Of note, the phenotype is standardized within this program so  $\sigma$  is equal to 1 in the formula to set  $\gamma$ .

## Results for $S_{\text{large}}$ scenario

**Table.** Empirical estimates of Family-Wise Error Rate under  $H_0$  for  $S_{\text{large}}$  scenario

		FWER			
Method		C24h	C192h	AUC	CL
Ridge regression	without correction <sup>a</sup>	13.5	26	19	19
Lasso	without correction <sup>a</sup>	14.5	22	15	16.5
HyperLasso	without correction <sup>a</sup>	14.5	23	16	17.5
Stepwise procedure	without correction <sup>a</sup>	14.5	23	16	17
Ridge regression	after empirical correction <sup>b</sup>	18	18.5	19	19
Lasso	after empirical correction <sup>b</sup>	17.5	22	20	21
HyperLasso	after empirical correction <sup>b</sup>	18	23	20	21
Stepwise procedure	after empirical correction <sup>b</sup>	20.5	23	22.5	21.5

a. Set of empirical family wise error rates (FWER) obtain without correction.

b. Set of empirical FWER obtain after correction of thresholds or penalisation parameters.

The 95% prediction interval around 20 for 200 simulated data sets is [14.5-25.5].

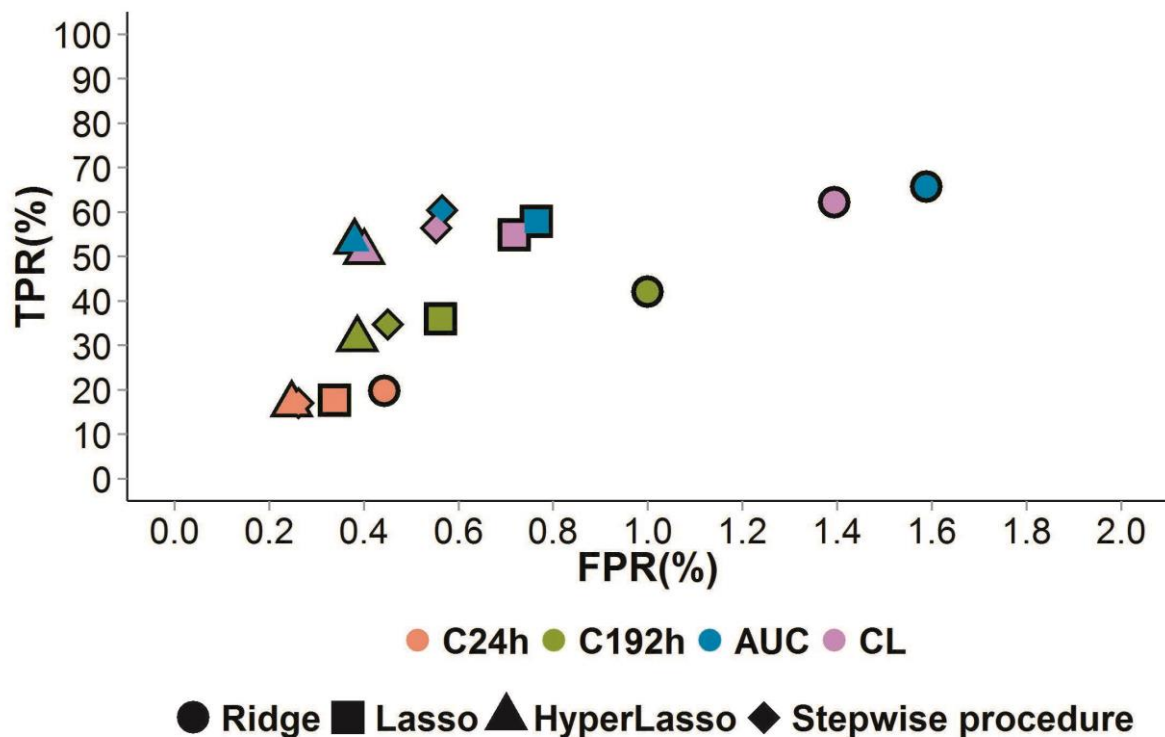
## Results for $S_{\text{independent}}$ scenario

**Table.** Empirical estimates of Family-Wise Error Rate under  $H_0$  for  $S_{\text{independent}}$  scenario

		FWER			
Method		C24h	C192h	AUC	CL
Ridge regression		20.5	19.5	16.5	22
Lasso		16.5	17.5	14.5	20
HyperLasso		16.5	17.5	14.5	20
Stepwise procedure		19.5	20	19	21.5

The 95% prediction interval around 20 for 200 simulated data sets is [14.5-25.5].

## Results for $S_{\text{linearPK, noIIV}_F}$ scenario



**Fig.** Percentage of True Positive Rate (TPR) versus False Positive Rate (FPR) (dots) for scenario  $S_{\text{linearPK}}$  without variability on F. Each PK phenotype is represented by one color and each association method by one symbol.

The remaining difference between TPR for CL and AUC is due to the correction applied on the association methods. The correction depends on the number of tested parameters: one for NCA approach (AUC) and three for model-based approach (CL, Q and  $V_2$ ).

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5. Cule E, De Iorio M. Ridge regression in prediction problems: automatic choice of the ridge parameter. *Genet Epidemiol*. 2013;37(7):704-714.
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