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Perl speaks NONMEM (PsN) and Xpose

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<https://uupharmacometrics.github.io/PsN>

<http://xpose.sf.net>



What is PsN?

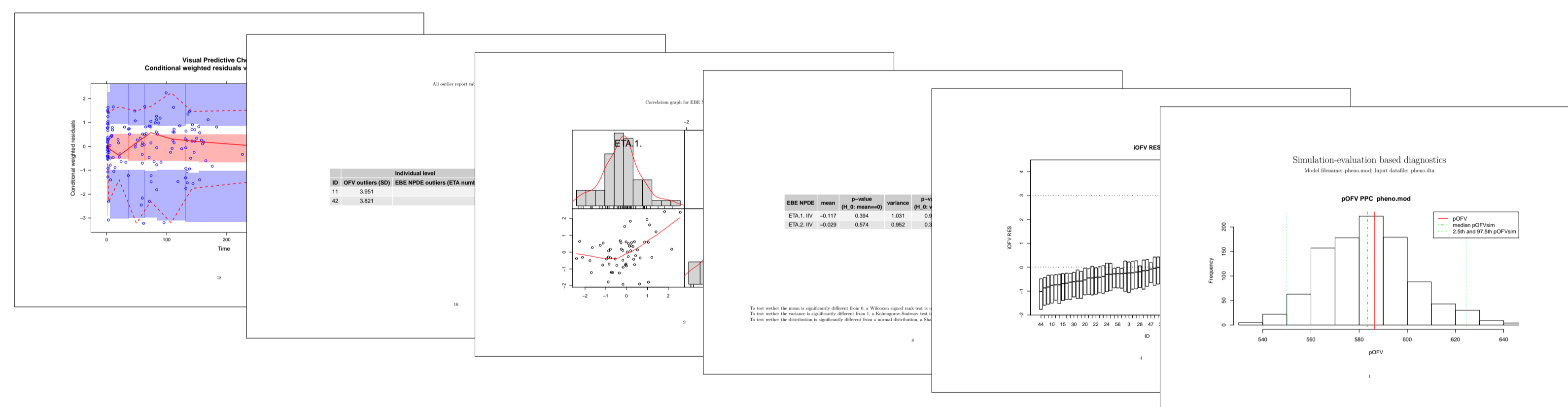
PsN is a toolbox for population PK/PD model building using NONMEM. It has a broad functionality ranging from simple wrapping of nmfe runs and parameter estimate extraction to advanced computer-intensive statistical methods and NONMEM job handling in large distributed computing systems. PsN4 supports all NONMEM versions from 6.1 through 7.4

New in PsN 4.7.0

- Major extensions to the **simeval** tool for simulation-evaluation diagnostics for **identification of outliers** [1]
- Updates to **frem**, a tool for **full random effects modelling** for covariate building [2]
- A new tool, **resmod**, to evaluate different residual models [3]
- The addition of support for rmarkdown when using rplots facilitating the automatic creation of reports.
- Support for NONMEM 7.4
- The migration of the development and public webpages to github for simplified interaction with the community.

Automatic diagnostic plots

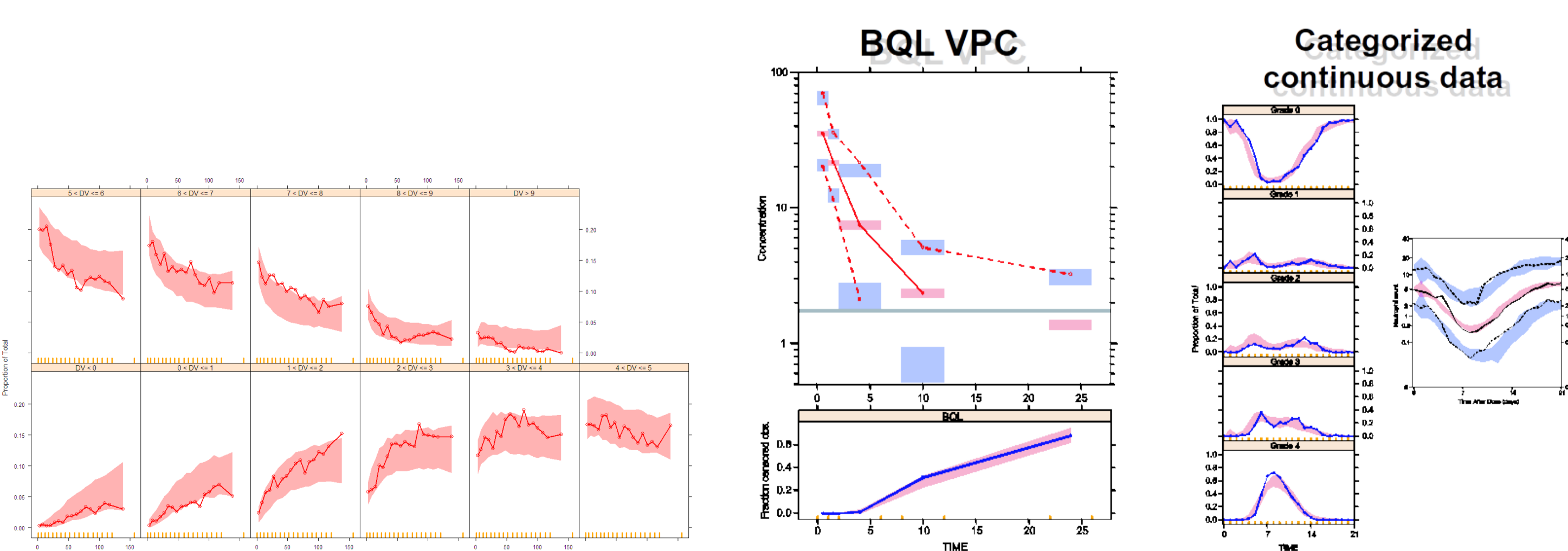
PsN can create and run an R script based on a template. PsN comes with a set of default templates, e.g. for simeval, but the user can easily modify these templates or create new ones for specific projects. For example, `simeval pheno.mod -samples=1000 -rplots=2` will in the run directory by default create the file `PsN.simeval.plots.pdf` containing the following plots (and more):



Model diagnostics using PsN and Xpose

VPC/NPC

- PsN controls the simulation of new datasets and does the computation needed for the VPC or NPC. Xpose is invoked via the `-rplots` option.
`vpc run22.mod -samples=1000 -rplots=1`
- Options to handle odd-type data e.g.:
 - Categorical data
 - Censored continuous (e.g. BLQ) data
 - Categorized continuous data
 - Survival data
- Options to perform prediction corrected VPC and prediction + variability corrected VPC
`vpc run22.mod -samples=1000 -predcorr -rplots=1`
- Wide range of customizable binning and stratification settings
`vpc run22.mod -samples=1000 -stratify_on=DOSE -rplots=1`
- Automatic handling of log transformed data

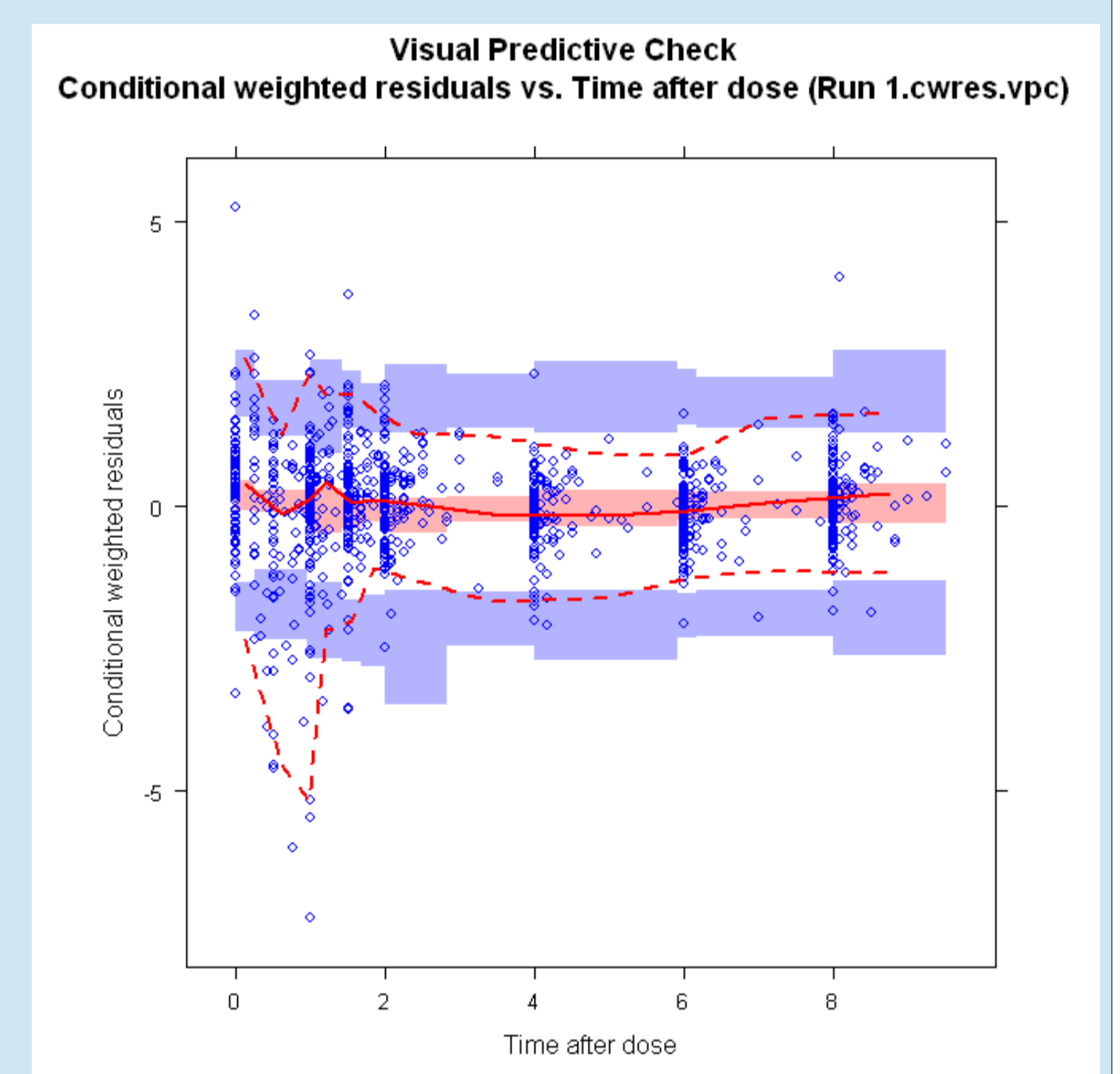


What is Xpose?

Xpose is an open-source R package for post-processing of NONMEM (and PsN) output. It takes one or more standard NONMEM table files (or PsN result files) as input and generates graphs or other analyses. Xpose tries to make it easier for a modeler to use diagnostics in an intelligent manner.

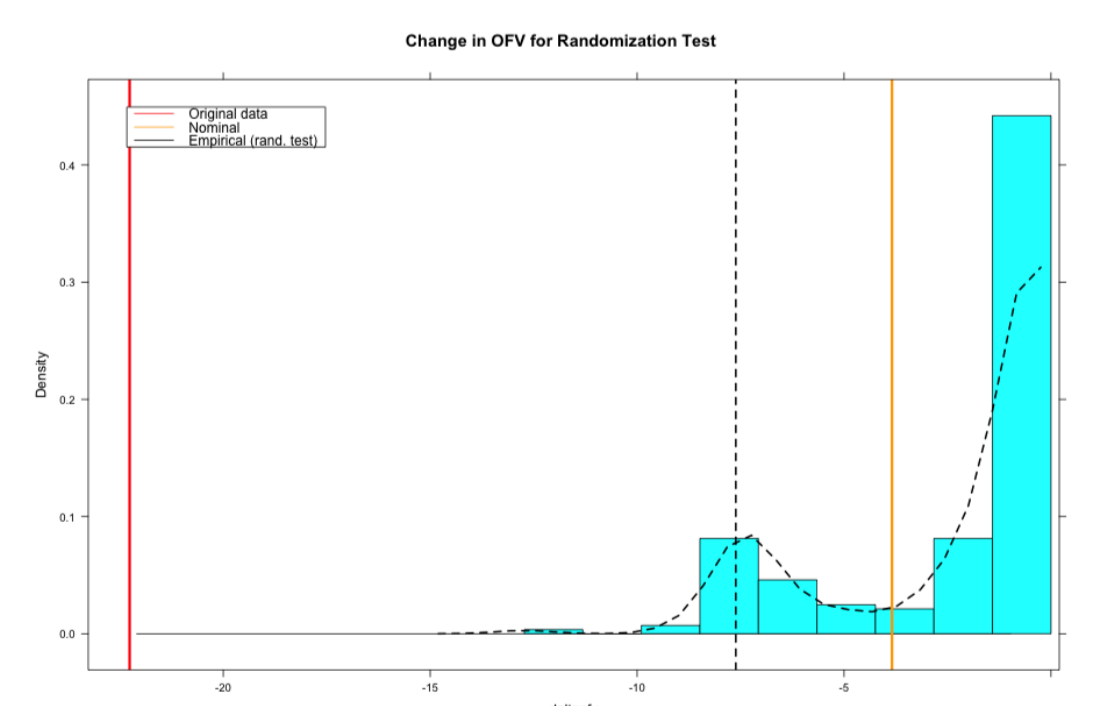
Features of Xpose

- **Tools for data visualization and data checkout:** Graphs and tables intended to summarize raw data, for example concentrations versus time or histograms of the covariates.
- **Model evaluation tools:** Plots and tables created to evaluate all aspects of a pharmacometric model. Including:
 - **Overall goodness of fit assessment:** Xpose has a number of composite displays (multiple graphs and tables of different kinds on the same page) that provide diagnostics for multiple aspects of the fit and summarize a NONMEM run.
 - **Numerical evaluations:** summaries of and tools to create numerical diagnostics.
 - **Population and individual prediction based diagnostics:** plots that use PRED and IPRED to diagnose the appropriateness of the model.
 - **Residual based diagnostics:** Plots that use residuals to diagnose the appropriateness of the model.
 - **Parameter distribution diagnostics:** Plots of parameter distributions.
 - **Simulation based diagnostics:** Mirror plots, visual predictive checks (VPC), numerical predictive checks (NPC).
- **Model comparison tools:** Graphs for comparing various aspects of two models fit to the same data.
- **Model development tools:** Used to help the modeler decide what to do next with the model. Most of these functions focus on aspects of covariate inclusion.



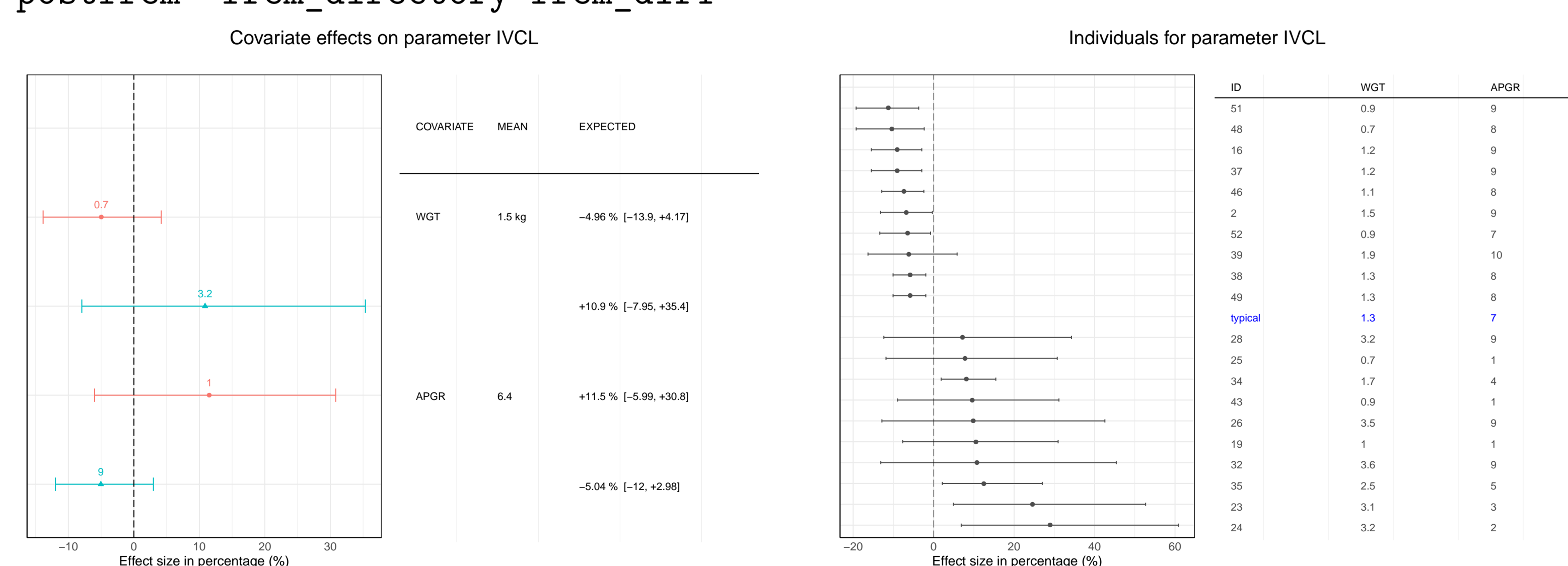
Randomization test

- PsN randomizes the dataset (e.g. based on treatment group) and controls the estimation from both the base model and the full model. The `-rplots` option makes PsN call Xpose to create the plot.
`randtest -samples=1000 -randomization_column=DOSE run89.mod -base_model=run0.mod -rplots=1`



Full random effects modelling (FREM)

- The PsN FREM tool will estimate all parameter-covariate relationships simultaneously
`frem pheno.mod -covariates=WGT,APGR postfrem -frem_directory=frem_dir1`



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[1] Anna Largajolli, Siv Jönsson, and Mats O. Karlsson. The OFVPPC: A simulation objective function based diagnostic. *PAGE 23 (2014) Abstr 3208*, 2014.

[2] Gunnar Yngman, Joakim Nyberg, E. Niclas Jonsson, and Mats O. Karlsson. Practical considerations for using the full random effects modeling (frem) approach to covariate modeling. *PAGE 26 (2017) Abstr 7365*, 2017.

[3] Moustafa M.A. Ibrahim, Rikard Nordgren, Maria C. Kjellsson, and Mats O. Karlsson. Moustafa ibrahim model-based diagnostics post-processing for fast automated model building; show-cased with residual error models and cwres. *PAGE 26 (2017) Abstr 7276*, 2017.