Supplemental Material

Population pharmacokinetic method to predict within-subject variability using single-period clinical data

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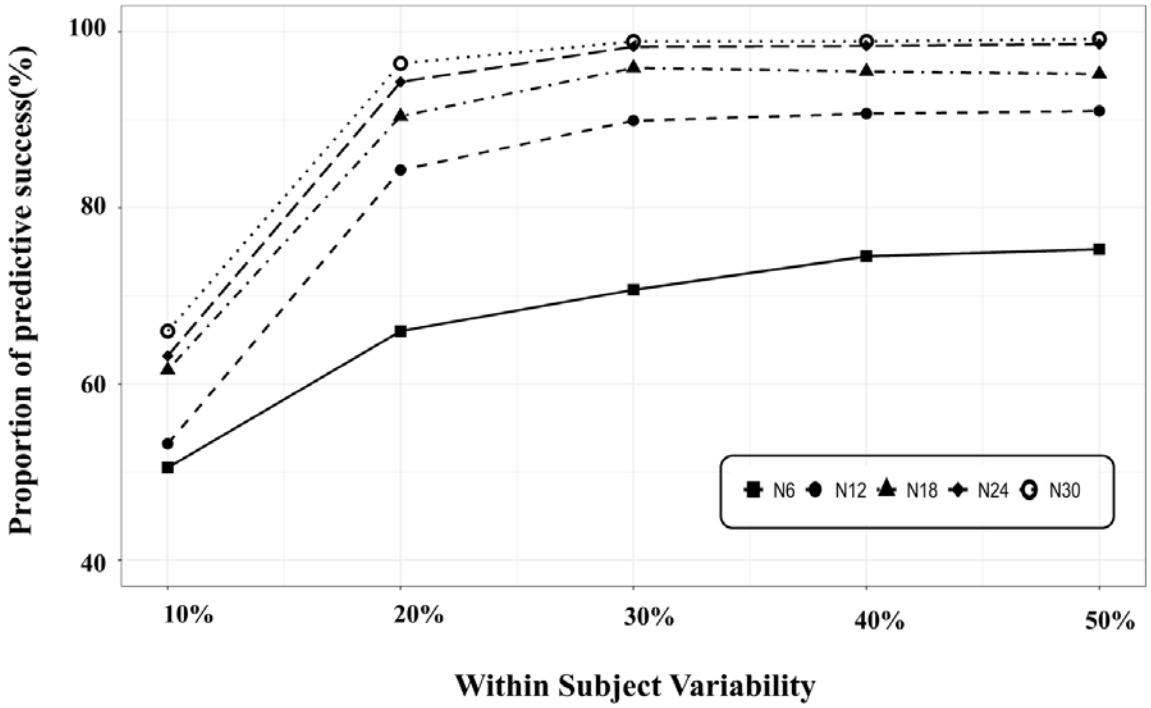

Figure S1. The proportion of predictive success for the first experiment.

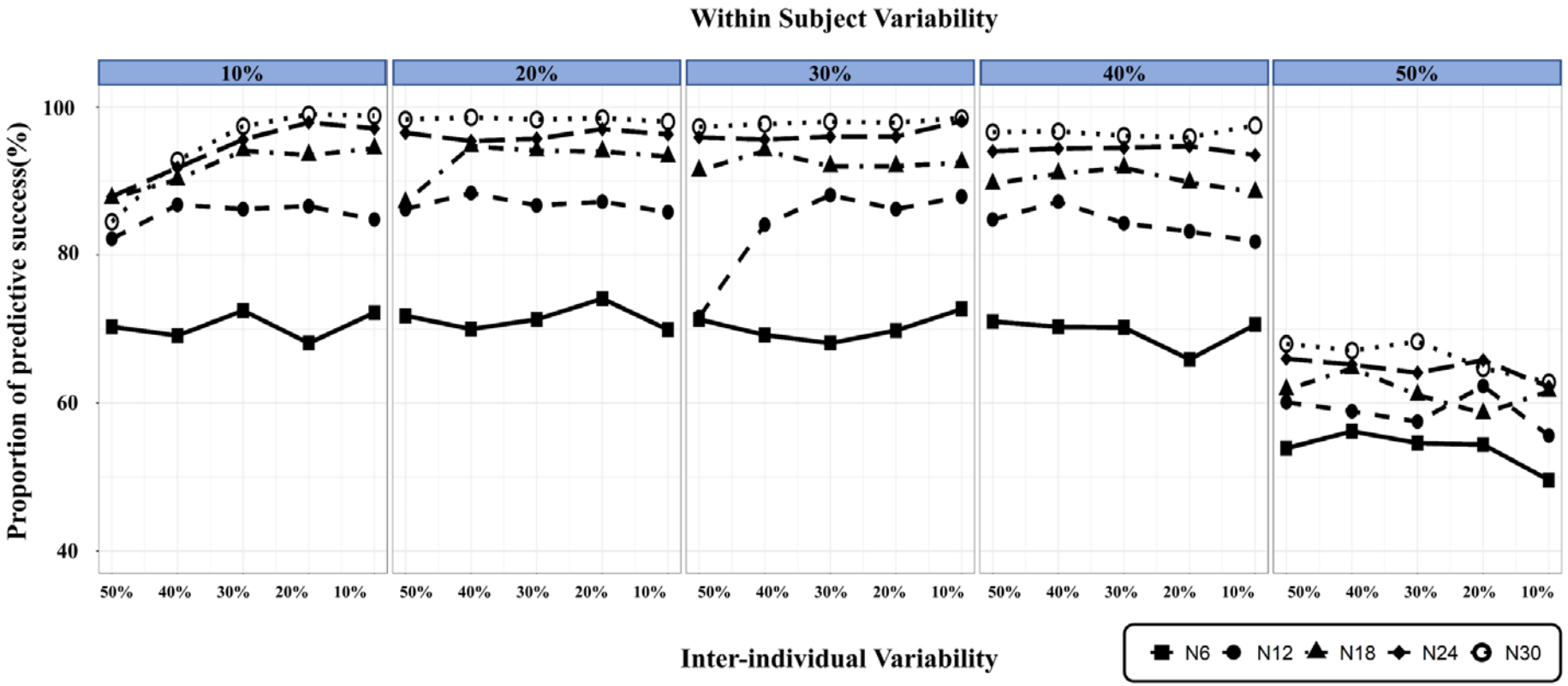

Figure S2. The proportion of predictive success for the second experiment.

Table S1. Tabulated summary for results of comparison with and without covariance between omegas

Evaluation scenario			Proportion of predictive success for RV(%)	
WV(%)	**IIV(%)**	**No. of subject**	**With Covariance between ω1 and ω2***	**Without Covariance between ω1 and ω2****
50	10	18	52	62
50	50	18	50	62
10	50	18	89	88

* Preform of NONMEM PK model for 100 simulation dataset generated by mrgsolve R package,
**Perform of NONMEM PK model for 1000 simulation dataset generated by basic R code. The ω1 and ω2 meant IIV on CL and Vd, respectively.

Text S1. Example as a R code for generating simulation dataset

```
## Individual PK parameters(IIV 10%)
data.sample <- 1:1000
start.number <- min(data.sample)
i <- start.number
  for (i in data.sample) {
     set.seed(seed[i])
     x <- rlnorm(100000, meanlog = 10, sdlog = 1)
     y <- rlnorm(100000, meanlog = 50, sdlog = 5)
     CL <- sample(log(x)[log(x)>0],12)      # Preventing for generating negative number at CL
     Vd <- sample(log(y)[log(y)>0],12)      # Preventing for generating negative number at Vd
     id <-seq(1:12)
     data <- data.frame(id,CL,Vd)
     write.table(data,paste("data",i,".csv",sep=""),sep=",",row.names = F)
}
## Calulation the concentration using parameters(CL, Vd)
total <- 1:1000
min.total <- min(total)
k <- min.total
for(k in total){
   one <- read.table(paste("data",k,".csv",sep=""),sep = ",",header=TRUE)
   kel <- one$CL/one$Vd
   one <- cbind(one,kel)
   number <- 1:12
   begin <- min(number)
   i <- begin
   for(i in number){
      special.ID <-DO[DO$ID==i,]
      timenumber <- 1:12
      time.start <- min(timenumber)
      j <- time.start
      for(j in timenumber){
         #iv PK equation(WV = 0.3)
         conco <- (100*exp(-one$kel[i]*special.ID$TIME[j])/(one$Vd[i]))
         eps <- rnorm(12, mean = 0, sd = 0.3)
         eps.sample <- sample(eps,1)
    conco2 <- conco*(1+eps.sample)      ##Proportional model
# Preventing for generating negative number at plasma concentration
         while(conco2<0){
            eps <- rnorm(12, mean = 0, sd = 0.3)
            eps.sample <- sample(eps,1)
            conco2 <- conco*(1+eps.sample)      ##Proportional model
         }
         if(j==time.start)
            DV <- conco2
         else DV <-rbind(DV,conco2)
      }
      real <- cbind(special.ID, DV)
      if(i==begin)
         set <- real
```

```
      else set <-rbind(set, real)
   }
write.table(set, paste("CONC",k,".csv",sep = ""),sep = ",", row.names = FALSE)}
```

Text S2. C++ and R script code when used mrgsolve R package

```
## Example of CPP file
$PROB
- 1 COMP iv PK model
- Random effect : yes
$PARAM
TVCL = 10
TVV = 50
$CMT
CENT
$MAIN
double CL=TVCL*exp(ETA(1));
double V=TVV*exp(ETA(2));
$ODE
dxdt_CENT = -(CL/V)*CENT;
$OMEGA >> annotated=TRUE, block = TRUE
   ECL: ETA on Clearance
   EV: ETA on Volume
0.25
0.0625 0.25
$SIGMA
0.25
$TABLE
double IPRED = CENT/V;
double DV = IPRED*(1+EPS(1));
$CAPTURE
DV IPRED

## Example of R script file
# problem : WV0.5_IIV0.5_omegacovariance0.5
# subject NO. = 18
# load packages
library(mrgsolve)
library(tidyverse)
library(dplyr)
# giving seed number
set.seed(20191203)
# loading cpp file
mod<-mread("WV0.5_IIV0.5_COV0.5","C:/Users/Wonho
Kang/Desktop/TEST_OMBLOCK/WV0.5_IIV0.5_COV0.5/N18")
total <- 1:100
min.total <- min(total)
i <- min.total
for(i in total){
   nn=18
   idata<-tibble(ID=seq(nn))
   tmptolerance = -1
   tmpcount = 0
   while (tmptolerance < 0){
   tmpcount = tmpcount +1
```

```
    df<-mod %>%
    ev(amt=100) %>%
    idata_set(idata) %>%
    mrgsim(end=24, delta=0.1) %>%
filter(time==0|time==0.083|time==0.167|time==0.333|time==0.5|time==1|time==2|time==4|time==6|ti
me==8|time==12|time==24 )
    tmptolerance = min(df$DV)
    print(tmpcount)
    }
    #add MDV
    df<-df %>% mutate(MDV=0)
    df$MDV[which(df$DV==0)]<-1
    #add AMT
    df<-df %>% mutate(AMT=0)
    df$AMT[which(df$MDV==1)]<-100
    #rename TIME
    df<-df %>% rename(TIME=time)
    df<-df %>% arrange(ID,TIME)
    df<-df[c("ID","TIME","DV","MDV","AMT")]
    names(df) <- c("#ID","TIME","DV","MDV","AMT")
    write.table(df,paste("datafile",i,".csv",sep = ""),sep = ",",quote=FALSE,row.names=FALSE)
  }
```

Text S3. NONMEM PK Model code

```
$PROBLEM Simulation dataset2_IIV50%_WV30%_N18
$INPUT ID TIME DV MDV AMT
$DATA datafile1.csv IGNORE=@
$SUBROUTINES ADVAN6 TOL=8
$MODEL
  COMP (CENT, DEFDOSE, DEFOBS)
$PK
    CL =    THETA(1) * EXP(ETA(1))
    V    =    THETA(2) * EXP(ETA(2))
    KEL = CL/V
    S1=V
$DES
    DADT(1) = -KEL*A(1)
$ERROR
    IPRED = F
    DEL=0
    IF(IPRED.EQ.0) DEL=1
    W=IPRED+DEL
    IRES = DV-IPRED
    IWRES = IRES/W
    Y = F+W*EPS(1)
$THETA
(0, 10) ; CL
(0, 50) ; V
$OMEGA
  0.25
  0.25
$SIGMA
  0.09
$EST METHOD=1 MAXEVAL=9999 NOABORT INTER PRINT=5 NSIG=2 SIGL=8
$TABLE ID TIME DV MDV AMT IPRED IWRES CWRES ONEHEADER NOPRINT FILE = sdtab1
$TABLE ID ETA1 ETA2 ONEHEADER NOPRINT FILE = patab1
```