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ABBREVIATION AND DEFINITION OF TERMS

Notation	Description
λ	Drug-resistance rate constant.
BICR	Blinded independent central review.
BID	Twice daily.
CI	Confidence interval.
CV	Coefficient of variation.
CWRES	Conditional weighted residuals.
DRF	Data request form.
DV	Dependent variable.
E-R	Exposure-response.
ECOG	Eastern Cooperative Oncology Group.
FDA	Food and Drug Administration.
GBDM	Global Biometrics and Data Management.
IIV	Inter-individual variance.
IMP	Monte Carlo importance sampling.
IPRED	Individual predictions.
IRC	Independent review committee.
IV	Intravenous.
IWRES	Individual weighted residuals.
K_D	Cell-kill rate constant.
K_L	Tumor growth rate constant.
MTD	Maximum tolerated dose.
OFV	Objective function value.
ORR	Objective response rate.
OS	Overall survival.
PD-1	Programmed Death-1.
PD-L1	Programmed Death Ligand-1.
PFS	Progression-free survival.
PK	Pharmacokinetic.
PKPD	Pharmacokinetic-pharmacodynamic.
PMAP	Population modeling analysis plan.
PO	Oral.
PRED	Population predictions.
PS	Performance status.
Q2W	Every 2 weeks.
QD	Once daily.

Notation	Description
RCC	Renal cell carcinoma.
RECIST	Response Evaluation Criteria in Solid Tumors.
RP2D	Recommended Phase 2 dose.
RSE	Relative standard error.
SAEM	Stochastic approximation expectation–maximization.
SCM	Stepwise covariate model building procedure.
SLD	Sum of the longest tumor diameters.
TGI	Tumor growth inhibition.
TKI	Tyrosine kinase inhibitor.
TS _{ratio}	Tumor size ratio.
TTG	Time to tumor growth.
TTP	Time to progression.
TTR	Time to response.
VEGFR	Vascular endothelial growth factor receptor.
VPC	Visual predictive check.

1. INTRODUCTION

Renal cell carcinoma (RCC) is the most common kidney cancer and constitutes about 3% of all malignant tumors in adults [1]. Renal cell carcinoma (RCC) is often first detected at an advanced stage, with 25-30% of patients with metastatic disease at diagnosis.

There has been significant progress in the treatment of patients with advanced RCC with the use of targeted oral therapies and immunotherapies [2]. Prior to the introduction of targeted therapies, cytokines, including high-dose interleukin 2 and interferon- α were the standard of care for advanced RCC [3]. With the introduction of tyrosine kinase inhibitors (TKIs), the use of cytokines have been largely diminished. For many years, the TKIs sunitinib and pazopanib were considered the preferred first line treatments based on improvements in progression-free survival (PFS) in their pivotal studies [3].

Monoclonal antibodies that block the Programmed Death-1 (PD-1)/Programmed Death Ligand-1 (PD-L1) interaction are novel immunotherapeutic approaches for advanced RCC, which have shown single-agent efficacy in patients whose disease has progressed following vascular endothelial growth factor receptor (VEGFR) pathway inhibitor therapy. Avelumab is a human immunoglobulin G1 monoclonal antibody directed against PD-L1. Axitinib is a TKI targeted against VEGFR and is approved as monotherapy treatment of second line RCC. Recently, the Food and Drug Administration (FDA) approved the use of avelumab in combination with axitinib for the treatment of first-line advanced RCC. The efficacy and safety of avelumab in combination with axitinib was demonstrated in the JAVELIN Renal 101 trial (Study B9991003). In this study, the median PFS for this combination was 13.8 months compared to 8.4 months with sunitinib monotherapy.

Early tumor shrinkage, as well as other TGI metrics, have been shown to be good predictors of the probability of survival in cancer patients [4, 5, 6]. The use of these metrics to predict clinical outcomes has the potential to support early decision making in phase 1b/2 studies [7]. Several longitudinal TGI models have been described in patients with first and second line RCC who were treated with traditional cytokine therapy or TKIs [8, 9]. Currently, the time course of tumor size has not been characterized in patients receiving immunotherapy or combination therapies.

2. OBJECTIVE(S)

- Develop a longitudinal model for the time course of tumor size in first line RCC patients.
- Evaluate treatment effect on the time course of tumor size with interferon- α , sunitinib, sorafenib, axitinib, or combination therapy with avelumab + axitinib.
- Summarize tumor growth inhibition metrics that could be subsequently tested in future analyses to predict clinical outcomes.

3. STUDY OVERVIEW

A total of 4 studies were included: A6181034, A4061051, B9991002, and B9991003. In these studies, there were 5 different treatments: interferon- α , sunitinib, axitinib, sorafenib, and avelumab + axitinib. For the analysis, only patients with RCC in the first-line setting were evaluated.

3.1. Study Design

3.1.1. Study A6181034

Study A6181034 (N=750) was a randomized, multi-center, international, Phase 3 study of sunitinib (Arm A) vs interferon- α (Arm B) as first-line therapy in subjects with metastatic RCC. The primary objective of the study was to compare PFS in sunitinib treated arm versus the interferon- α arm.

Patients received treatment with either sunitinib in repeated 6 week cycles, consisting of 4 weeks of 50 mg daily administration followed by 2 weeks off treatment (Schedule 4/2), or interferon- α , 9 million units, administered as a subcutaneous injection on 3 non-consecutive days each week.

3.1.2. Study A4061051

Study A4061051 (N=288) was a Phase 3, 2-arm, randomized, open-label, multicenter study to evaluate the efficacy and safety of axitinib versus sorafenib in treatment-naïve patients (first line) with metastatic RCC. The primary objective of this first line portion of the study was to compare the PFS between the two treatments. A total of approximately 247 treatment-naïve patients were randomized in a 2:1 ratio between axitinib vs sorafenib, and stratified by Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 vs 1.

Patients received axitinib at the starting dose of 5 mg twice daily (BID) with continuous dosing. Dose adjustments, including axitinib dose increase or dose reduction, were to be based on tolerability in the individual patient to levels of 2, 3, 5, 7, or 10 mg BID. The active comparator was sorafenib, dosed at 400 mg BID continuously. Dose adjustments of sorafenib was allowed to 400 mg once daily (QD) or 400 mg every other day.

3.1.3. Study B9991002

Study B9991002 (N=55) was a Phase 1b, open label, multi-center, multiple dose, safety, pharmacokinetic (PK), and pharmacodynamic study of avelumab in combination with axitinib in adult treatment-naïve patients with advanced RCC. The primary objective of this study was to assess the safety and tolerability of avelumab in combination with axitinib to estimate the maximum tolerated dose (MTD) and select the recommended Phase 2 dose (RP2D). Evaluating antitumor activity and survival were secondary endpoints. This clinical study was composed of two phases. The dose finding phase was in patients with RCC with clear cell histology who did not receive prior systemic therapy for advanced disease. From this phase, the MTD and RP2D of avelumab was determined to be 10 mg/kg every 2 weeks (Q2W) and the dose for axitinib was determined to be 5 mg BID. The dose expansion phase

evaluated this combination dosing regimen in a cohort of treatment-naïve patients.

Axitinib was given orally 5 mg BID, with or without food, on a continuous dosing schedule, as according to the approved prescribing information. Avelumab was given as a 1-hour intravenous (IV) infusion Q2W. All patients were to be continued on treatment with study drugs until confirmed disease progression, patient refusal, patient lost to follow up, unacceptable toxicity, or the study was terminated by the Sponsor, whichever occurred first.

3.1.4. Study B9991003

Study B9991003 (N=886) is an ongoing Phase 3, multinational, multicenter, randomized, open-label, parallel 2-arm study in which 442 patients have been randomized to the avelumab in combination with axitinib arm (Arm A) and 444 patients have been randomized to the sunitinib arm (Arm B).

- Arm A: avelumab 10 mg/kg IV Q2W in a 6-week cycle + axitinib 5 mg oral (PO) BID
- Arm B: sunitinib 50 mg PO QD on Schedule 4/2 (4 weeks on treatment followed by 2 weeks off treatment)

The primary objective of this study is to demonstrate that avelumab in combination with axitinib is superior to sunitinib monotherapy in prolonging PFS or overall survival (OS) in treatment-naïve patients with advanced RCC with PD-L1-positive tumors. Additional objectives include assessment of safety and PK and evaluation of efficacy in first-line treatment irrespective of PD-L1 expression. The data included in this analysis report are from an interim analysis of this ongoing study where one of the primary endpoints of PFS was met but the study is ongoing for OS.

Patients were stratified according to ECOG PS (0 versus 1) and region (United States versus Canada/Western Europe versus the rest of the world). Treatment with study drugs continues until confirmed disease progression assessed by blinded independent central review (BICR) as per the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1, patient refusal, patient lost to follow up, unacceptable toxicity, or if the study is terminated by the Sponsor, whichever comes first. Crossover between treatment arms was not permitted.

3.2. Study Assessments

3.2.1. Study A6181034

The primary efficacy endpoint was PFS. Tumor assessments were performed both by the local study site and by a blinded, third-party, core imaging laboratory. The primary analysis of efficacy endpoints was based on the central radiology assessment. Tumor assessments were made by using RECIST at baseline, Day 28 of cycles 1-4, and Day 28 every 2 cycles thereafter.

3.2.2. Study A4061051

The primary endpoint was PFS by independent review committee (IRC). Tumor assessments were made by using RECIST at baseline, Weeks 6 and 12, and every 8 weeks thereafter.

3.2.3. Study B9991002

Efficacy endpoints for this study were secondary endpoints (eg., objective response rate (ORR), PFS, and OS). Anti-tumor activity was assessed by radiological tumor assessments and was based on RECIST. Tumor assessments included all known or suspected disease sites. Tumor assessments were made at baseline, every 6 weeks up to 12 months, and every 12 weeks thereafter.

3.2.4. Study B9991003

The primary endpoints for this study are PFS and OS. Anti-tumor activity was assessed through radiological tumor assessments conducted at screening, at 6 weeks from randomization, then every 6 weeks up to 18 months after randomization and every 12 weeks thereafter until documented confirmed disease progression by BICR assessment regardless of initiation of subsequent anti-cancer therapy. In addition, radiological tumor assessments were conducted whenever disease progression was suspected (e.g., symptomatic deterioration).

4. DATA FOR ANALYSIS

4.1. Analysis Data Files

The pharmacokinetic-pharmacodynamic (PKPD) Programming group within Global Biometrics and Data Management (GBDM) was responsible for generating the analysis data file using a validated process. Global processes and procedures were followed. Programming plans, data request forms (DRFs), and quality control documentations can be found in each respective study folders in improve (Pfizer's internal population PK repository; source data are referenced in this report by a unique numeric locator).

4.2. Data Exclusions

Patients who did not have dosing records (eg., in other words, never received treatment) or patients who do not have tumor assessments for determination of SLD were excluded in the analysis.

4.3. Missing Data and Imputations

No imputations were made for missing dosing or SLD data.

5. METHODS

5.1. Prior Knowledge/Modeling Experience

Anti-tumor activity is commonly evaluated in early development studies using ORR, where achievement of a predefined ORR is often the main decision criteria to inform about drug efficacy. The relative change in tumor size was recorded according to RECIST as the SLDs across specific targeted lesions. Using SLD-time data, TGI models could be used to

characterize the tumor dynamics, which includes several processes occurring simultaneously; tumor growth kinetics, treatment-related shrinkage as well as potential tumor resistant development.

Longitudinal exposure-response (E-R) TGI models have been used to evaluate the anti-tumor effect of a drug based on continuous tumor size measurements and key parameters derived from these TGI have been successfully used to predict survival outcomes and evaluate the influence of drug exposure in key efficacy endpoints. A thorough review of tumor models that have been developed since 2008 is provided in Ribba et al. [10].

A nonlinear TGI model was previously developed by Claret et al. in first line RCC patients using Studies A6181034 and A4061051 [9]. In the Claret model, it was found that there was a linkage between early tumor shrinkage (at week 8) to PFS. Using an external validation dataset, this model was qualified in predicting risk of PFS in the first line RCC.

5.2. Modeling: Software and Strategy

In this analysis, NONMEM version 7.4.3, PsN version 4.8.0, and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) were used during the modeling. NONMEM was used for the nonlinear mixed effects modeling of the tumor size over time. PsN was used for stepwise covariate model building procedure (SCM). R was used for all data manipulation, graphics, and table creation.

5.3. Base Model Description

The primary tumor dynamic model presented in this report took the general form described by Claret et al [9]. This model utilized longitudinal tumor size data to estimate drug-specific (cell-kill rate constant (K_D) and drug-resistance rate constant (λ)) and disease-specific parameters such as baseline tumor size (y_0) and tumor growth rate constant (K_L). The equation is provided below:

$$y(t) = y_0 \cdot e^{[K_L \cdot t - \frac{K_D}{\lambda} \cdot (1 - e^{-\lambda \cdot t})]} \quad (1)$$

In this model, the tumor growth rate constant (K_L) is proportional to the size of the tumor at time t . It also includes a cell-kill rate constant (K_D) that is proportional to the size of the tumor at time t . The growth rate is assumed to be linear and the drug effect is the result of the cell kill and tumor resistance to treatment. The cell kill follows an exponential decrease over time driven by the parameter λ . The rate of decay characterizes the tumor resistance over time to cell-killing.

Using this model, the time to tumor growth (TTG) was obtained using the derivative of the differential equation as follows:

$$TTG = \frac{\ln(K_D \cdot \lambda) - \ln(K_L)}{\lambda} \quad (2)$$

where K_L , K_D , and λ are defined as before. For computation in NONMEM of the time units, rates were scaled to year⁻¹ for the typical values and the individual post hoc rates were

converted back to the week⁻¹ unit.

Another informative metric often used as early predictor of efficacy outcomes is the tumor size ratio (TS_{ratio}) for a pre-defined period of time, this ratio is calculated as the tumor size at a given time over the tumor size at baseline:

$$TS_{ratio} = \frac{TS_t}{TS_{t=0}}. \quad (3)$$

5.4. Random Effects Model Development

Random effects were added to the parameters to account for inter-individual differences in the rate of the tumor growth (K_L), rate of the cell-kill decay (K_D), and the drug-resistance parameter (λ). The specific parameterization of these random effects were as follows:

$$\begin{aligned} K_{D,TV} &= \theta_1 \\ K_{L,TV} &= \theta_2 \\ \lambda_{TV} &= \theta_3 \end{aligned}$$

where $K_{D,TV}$, $K_{L,TV}$, and λ_{TV} are the typical values for the population, and the individual post hoc estimates for subjects $i = 1, \dots, N$ are:

$$\begin{aligned} K_{Di} &= K_{D,TV} + \eta_{1i} \\ K_{Li} &= K_{L,TV} + \eta_{2i} \\ \lambda_i &= \lambda_{TV} + \eta_{3i} \end{aligned}$$

where η_1 , η_2 , and η_3 are assumed to follow a multivariate normal distribution with mean 0 and a diagonal variance-covariance matrix Ω . To evaluate if the random effects were accounting for variation across individuals, the shrinkage and η significance (p-values) were evaluated. The p-values were evaluated to see if the η mean is significantly different than 0 and the shrinkage was evaluated using a maximum acceptable value of 20% to determine if individual parameter estimates are appropriate.

5.5. Inclusion of Covariates

Selected covariates were tested for significance using SCM application in PsN with statistical criteria of $\alpha=0.05$ for forward inclusion, which corresponds to an objective function value (OFV) change of 3.84 based on a Chi-square distribution with df=1. The effect of treatment was modeled by adding a parameter linearly as $1 + \theta \cdot (\text{Treatment})$. For example, to evaluate the potential effect of different treatments on cell killing (eg. K_D), the differential equation was described as:

$$K_{D,TV} = \theta_1 \cdot (1 + \theta \cdot \text{Treatment}) \quad (4)$$

where θ is an estimated parameter to characterize the effect of treatment on the cell death.

The effect of treatment was also tested on K_L and λ parameters.

Baseline SLD (in raw scale and natural logarithm scale) was also assessed on model parameters as a linear, exponential or power function. No other covariates were evaluated in this model.

5.6. Final Model Development

The final model development started with a full model containing the parameters from the base model along with the covariates that were included from SCM through forward inclusion. This full model was then be subjected to stepwise backward elimination. The significance threshold for retaining covariates in the final model was determined using the likelihood ratio test to assess the significance of a covariate in the model when eliminated from the full model. The test for elimination of an individual covariate parameter, given the others were kept in the model, was performed at a pre-specified significance level of $\alpha=0.001$, which corresponds to an OFV change of 10.84 based on a Chi-square distribution with $df=1$.

A covariate was removed from the full model in a stepwise fashion, and the change in OFV was calculated. If removal of any covariate resulted in a statistically significant increase (worsening) in OFV with $p<0.001$, the covariate giving the smallest insignificant increase was removed from the full model, and a next round of elimination of a covariate was performed. This process was repeated until all remaining covariates were determined to be statistically significant. The final model was obtained from the last stage of the elimination algorithm, in which all of the remaining covariate parameters, when tested 1 at a time, resulted in statistically significant likelihood ratio tests (ie, $p<0.001$).

In order to obtain the most parsimonious and stable final model, the candidate covariate model resulting from the backward elimination step in SCM was subjected to a separate NONMEM run with \$COV step executed to examine any sign of model over parameterization and poorly estimated parameters.

TGI metrics were defined from the output of the final model in the subsequent linkage to survival modeling, which are described separately.

6. RESULTS

6.1. Analysis Data

Analysis datasets were individually prepared for each of the 4 studies by the GBDM programming group. The datasets included patient identification, study and treatment information, time of efficacy assessments (in weeks), efficacy assessments for SLD, PFS and OS, and other demographic, safety laboratory, and disease data. The source datasets were described in their respective data file specification documents in [Appendix 2](#). Prior to TGI modeling, a merged dataset was created and only included tumor assessments for SLD by subsetting the flag for efficacy column (FLAGE = 3). Model code for pre-processing of data and data exclusions are presented in [Appendix 3](#).

6.2. Observed Data

A total of 1839 patients with baseline SLD measurements were included in the analysis. A summary of the baseline SLD by protocol and by study treatment is presented in [Table 1](#). The median (range) baseline SLD in the analysis dataset was 91 (10-707.5) mm, with a lower median value observed in Study B9991002 (55.2 mm) and in B9991003 (65.5-69.8 mm).

Table 1. Summary of Baseline SLD by Study Protocol and Treatment

Protocol	Treatment	n	Mean (Stdev)	Median (Min-Max)
A4061051	Sorafenib	83	145.7 (100.4)	124.7 (16.8-466.7)
A4061051	Axitinib	175	142.2 (107.2)	119.0 (15.4-707.5)
A6181034	IFN α	328	137.6 (102.4)	108.0 (12.0-503.0)
A6181034	Sunitinib	352	150.1 (108.6)	121.0 (10.0-622.0)
B9991002	Avelumab+Axitinib	54	61.7 (34.3)	55.2 (10.1-173.0)
B9991003	Sunitinib	424	91.0 (66.4)	69.8 (10.1-368.2)
B9991003	Avelumab+Axitinib	423	87.0 (65.8)	65.5 (10.0-318.0)
Overall	Overall	1839	116.2 (92.4)	91.0 (10.0-707.5)

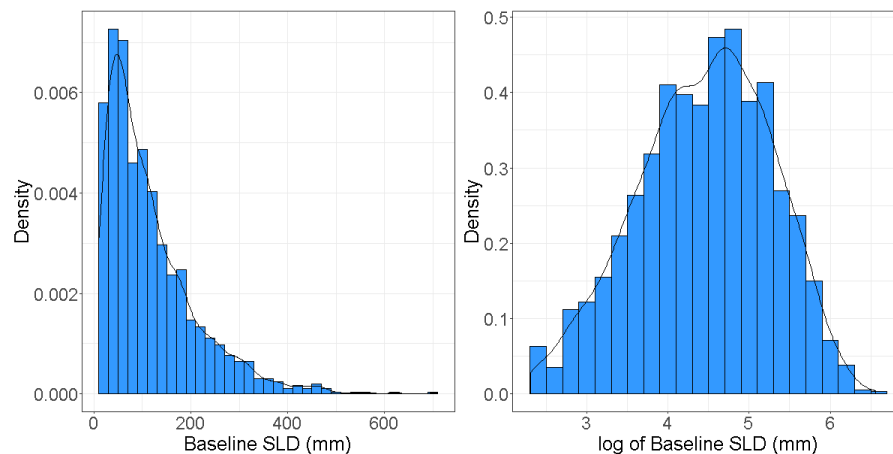
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Baseline SLD measurements are in mm.

Table abbreviations: SLD = sum of the longest tumor diameters, Stdev = standard deviation

Figure 1 presents the histogram density of baseline SLD in raw and natural log transformed scales. Natural log transformed baseline SLD appears to be more normally distributed than the raw scale. The median baseline SLD values for B9991002 and B9991003 studies were lower than the other two studies.

Figure 1. Histogram of Baseline SLD

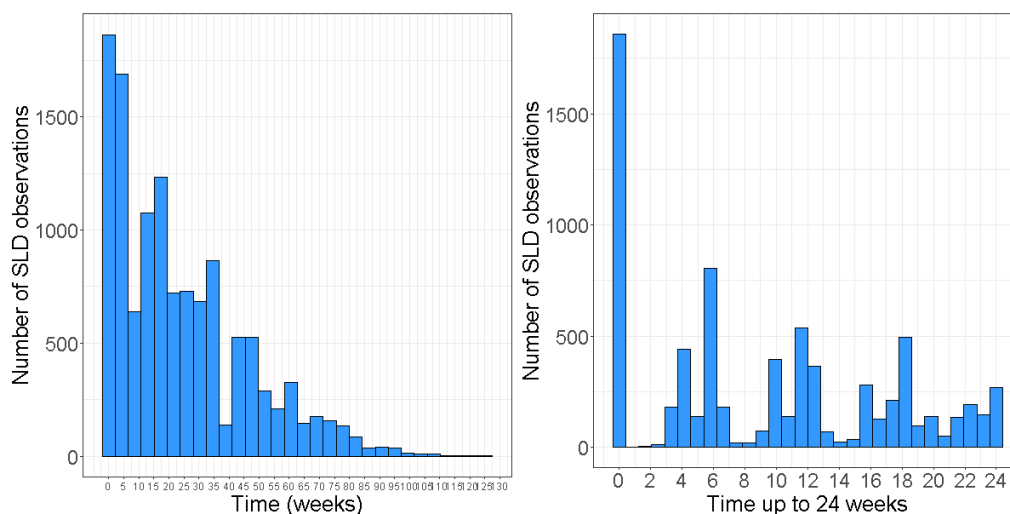


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Figure abbreviations: SLD = sum of the longest tumor diameters

The number of SLD observations by time are presented in [Figure 2](#) and [Table 2](#). The pattern in number of observations over time was consistent with the planned study visits (generally every 6 weeks). A majority of the observed SLD occurred by 24 weeks.

Figure 2. Number of SLD Observations by Time



Repository artifact ID FI-2009670.

Figure abbreviations: SLD = sum of the longest tumor diameters

Table 2. Summary of SLD Observations over Time

TIMEBLOCK	N	n SLD Observations
Baseline	1839	1858
0 - 6 weeks	1338	1347
6 - 12 weeks	1478	1598
12 - 18 weeks	1237	1331
18 - 24 weeks	1233	1301
24 - 36 weeks	1170	1854
36 - 52 weeks	847	1517
> 52 weeks	551	1550
Total	1839	12356

Repository artifact ID FI-2097928.

SLD measurements are in mm.

Table abbreviations: N = number of patients with observations, n = number of SLD observations, SLD = sum of the longest tumor diameters

Table 3 presents the percent change from baseline of SLD by protocol and study treatment. The INF- α treatment resulted in the lowest median percent decrease from baseline at -0.6%, while the avelumab+axitinib treatment had the highest median percent decrease from baseline at -37% to -48%.

Table 3. Summary of Percent Change in SLD by Study Protocol and Treatment

Protocol	Treatment	N	n	Mean (Stdev)	Median (Min-Max)
A4061051	Axitinib	168	1130	-25.8 (26.4)	-26.5 (-100.0-129.5)
A4061051	Sorafenib	78	462	-12.0 (27.3)	-14.2 (-73.3-136.4)
A6181034	INF α	325	1155	-5.0 (24.3)	-0.6 (-87.5-108.9)

Table 3. Summary of Percent Change in SLD by Study Protocol and Treatment

Protocol	Treatment	N	n	Mean (Stdev)	Median (Min-Max)
A6181034	Sunitinib	348	2001	-25.8 (23.5)	-24.4 (-100.0-94.4)
B9991002	Avelumab+Axitinib	54	448	-42.3 (34.5)	-47.7 (-100.0-121.6)
B9991003	Avelumab+Axitinib	412	2934	-36.8 (28.6)	-37.4 (-100.0-156.0)
B9991003	Sunitinib	415	2368	-20.6 (27.9)	-17.4 (-100.0-80.2)

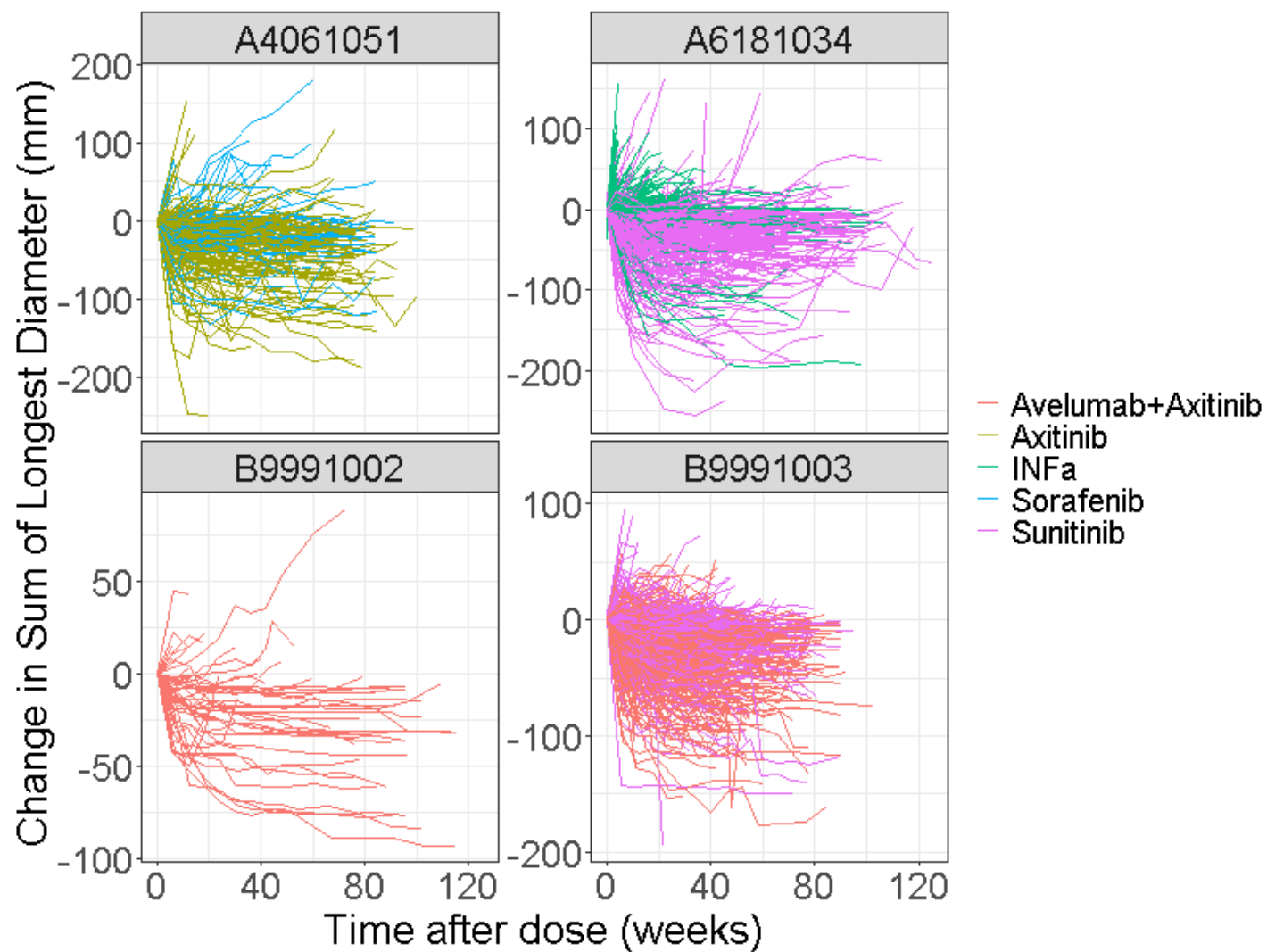
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Data are SLD - baseline SLD divided by baseline SLD, as a percentage.

Table abbreviations: N=number of patients with post baseline SLD; n=number of post baseline SLD observations; SLD = sum of the longest tumor diameters, Stdev = standard deviation

The change in SLD over time for each patient by study and treatment is presented in [Figure 3](#).

Figure 3. Change in SLD over time by Study



Repository artifact ID FI-640386.

Figure abbreviations: SLD = sum of the longest tumor diameters

6.3. Deviations from the Population Modeling Analysis Plan (PMAP)

The equation for TTG is defined in [Section 5.3](#). The population modeling analysis plan (PMAP) incorrectly described an equation for time to maximum tumor shrinkage rather than TTG.

6.4. Base Model Results

The final base model followed the Claret approach and included K_L , K_D , and λ parameters. The estimation method used was by Stochastic approximation expectation–maximization (SAEM)/Monte Carlo importance sampling (IMP) with the OFV reported from the IMP step. The residual error was thetarized and included both a proportional and additive term. The results (eg. parameter estimates, relative standard error (RSE), and shrinkage) from the modeling of the change in tumor size over time following the Claret approach is presented in Table 4.

Table 4. Base Model Parameter Estimates

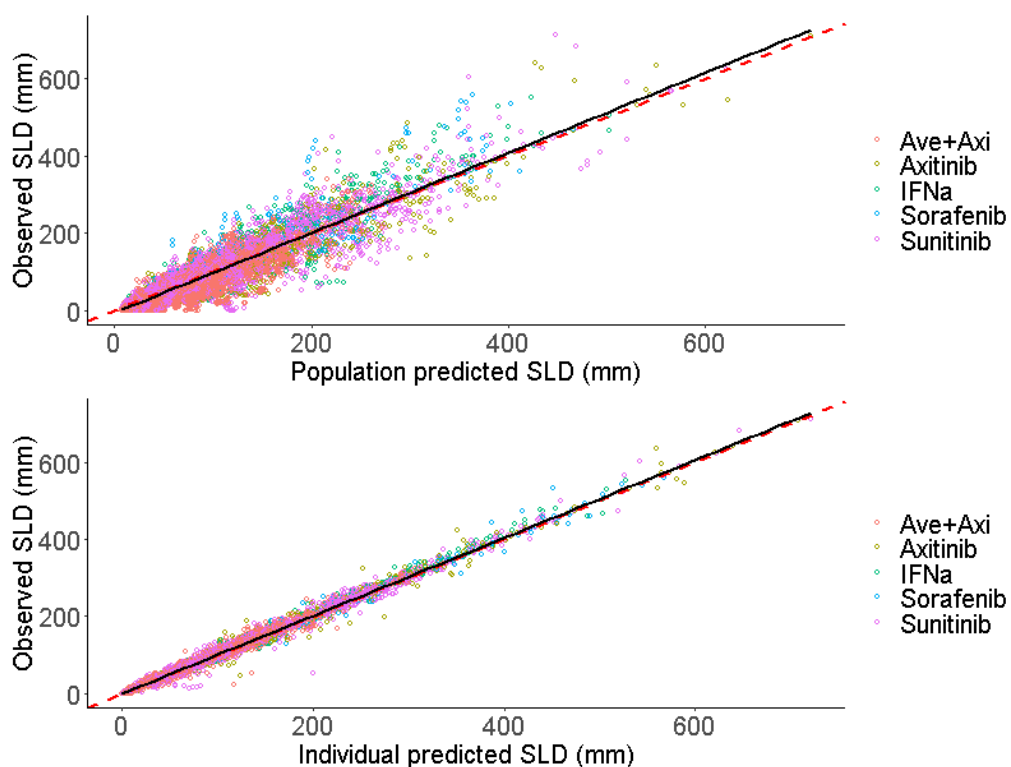
Parameter	Estimate	RSE (%)	Shrinkage (%)
$\theta_{K_L}(\text{years}^{-1})$	0.138	10.0	-
$\theta_{K_D}(\text{years}^{-1})$	1.519	4.5	-
$\theta_{\lambda}(\text{years}^{-1})$	3.874	7.2	-
$\theta_{\sigma;prop}$	0.081	6.6	-
$\theta_{\sigma;add}$	2.266	8.7	-
ω_{K_L}	2.450	7.9	34.9
ω_{K_D}	0.947	7.1	20.4
ω_{λ}	1.879	15.5	36.2
OFV	66317.840	-	-

Repository artifact ID FI-651640.

Table abbreviations: add = additive error, K_D = cell-kill rate constant, K_L = tumor growth rate constant, λ = drug-resistance rate constant, OFV = objective function value, prop = proportional error, RSE = relative standard error, SLD = sum of the longest tumor diameters

Prediction-based diagnostic plots of the dependent variable (DV), which was SLD, versus PRED and IPRED are presented in [Figure 4](#) and color coded by treatment.

Figure 4. Observed SLD versus PRED and IPRED

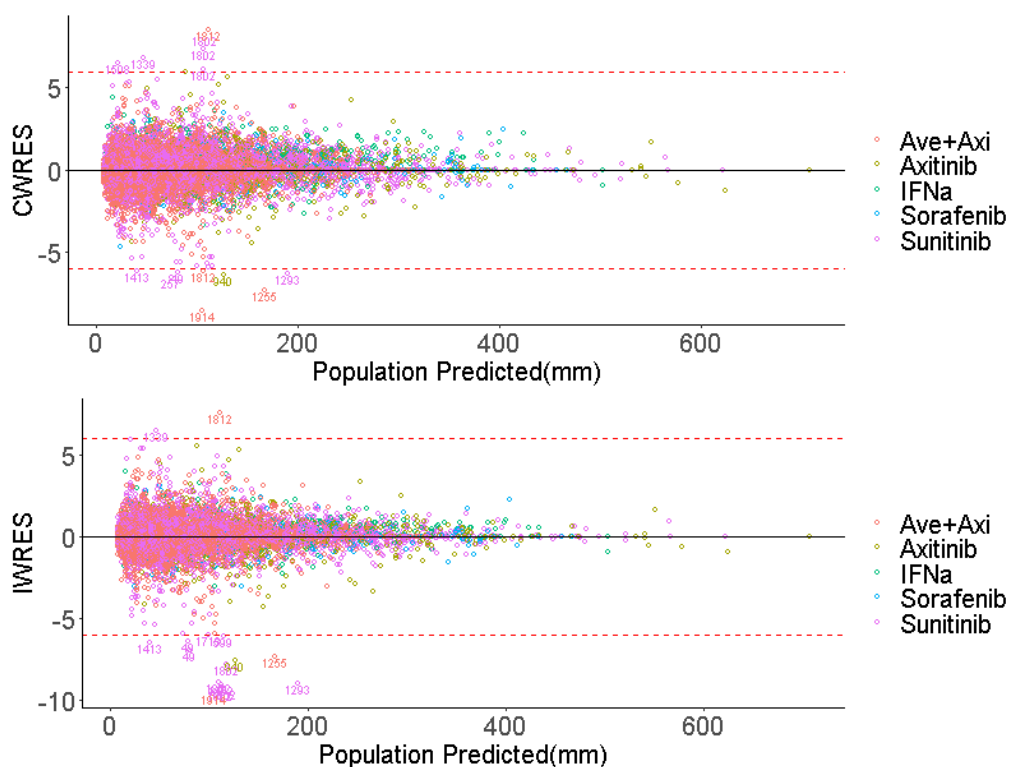


Repository artifact ID FI-766604.

Figure abbreviations: axi = axitinib, ave = avelumab, IFNa = interferon- α , SLD = sum of the longest tumor diameters

Residual-based diagnostic plots of conditional weighted residuals (CWRES) and individual weighted residuals (IWRES) versus PRED and time are presented in [Figure 5](#) and [Figure 6](#), respectively. Both CWRES and IWRES versus PRED and time were evenly distributed above and below the line of unity at 0.

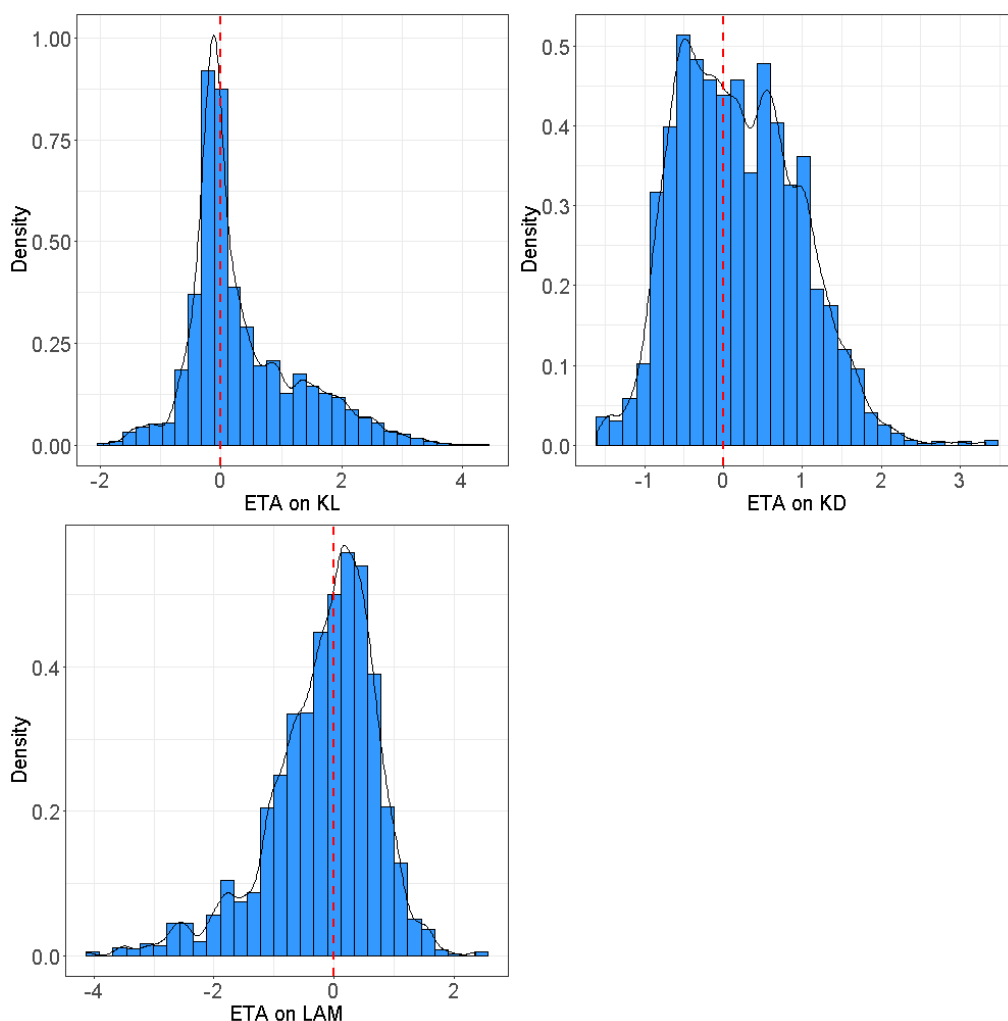
Figure 5. Residuals versus Population Predictions



Repository artifact ID FI-766610.

Figure abbreviations: axi = axitinib, ave = avelumab, CWRES = conditional weighted residuals, IFNa = interferon- α , IWRES = individual weighted residuals

Figure 7. Histograms of η on TGI Parameters



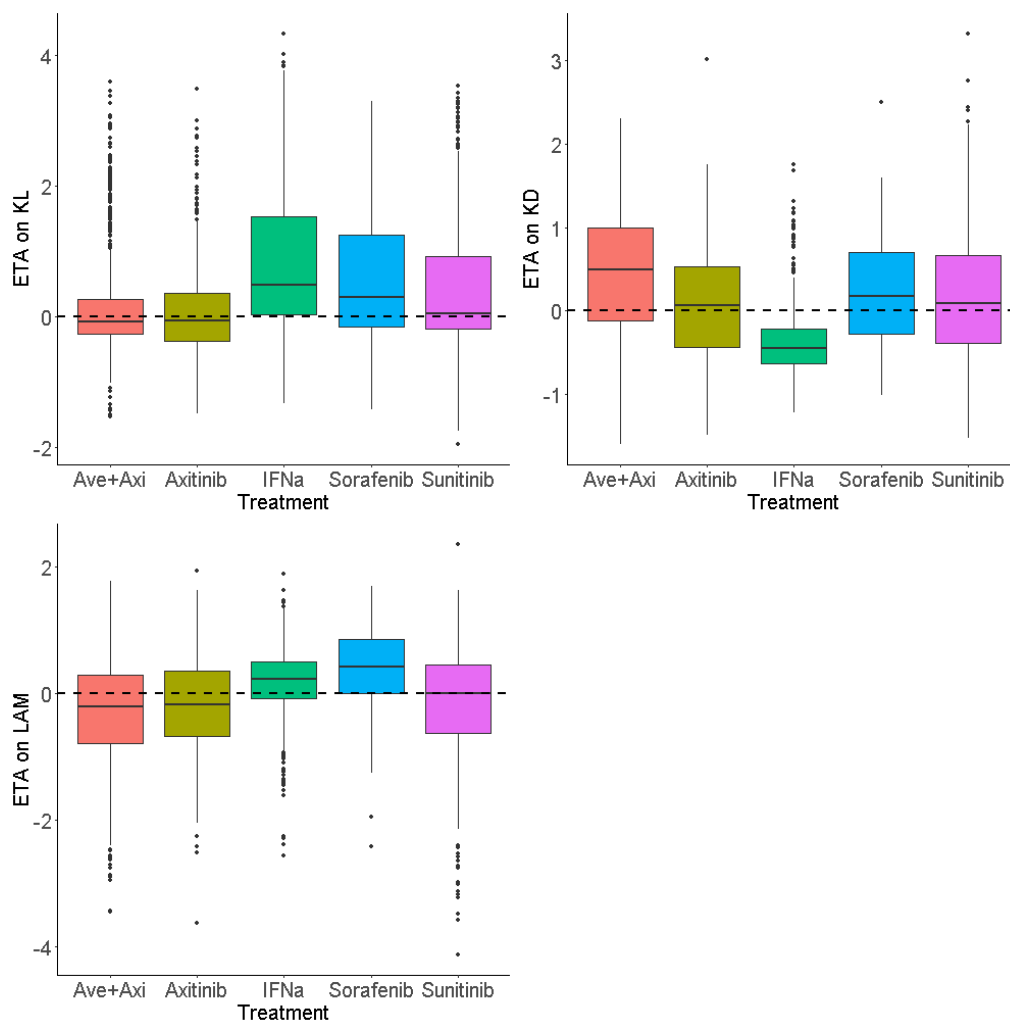
Repository artifact ID FI-766606.

Figure abbreviations: ETA = empirical Bayes estimate for inter-individual variability, K_D = cell-kill rate constant, K_L = tumor growth rate constant, λ = drug-resistance rate constant, TGI = tumor growth inhibition

As one of the analysis objects is to evaluate the treatment effect on TGI parameters, [Figure 8](#) presents η versus treatment boxplots. It appears that treatment may help to explain the inter-individual variance (IIV) for all 3 TGI parameters. For instance, interferon- α treatment appears to have higher K_L and λ , and lower K_D compared to the dotted line at 0, consistent with more rapid tumor size increase. Additionally, η versus protocol is presented in [Figure 9](#). η boxplots appeared well balanced by study, except B9991002 for η on K_D , but this study also had the fewest number of patients.

η versus baseline SLD scatterplots are presented in [Figure 10](#). Since the shrinkage on 2 of the parameters (K_L and λ) were $> 30\%$, the η plots should be interpreted with caution.

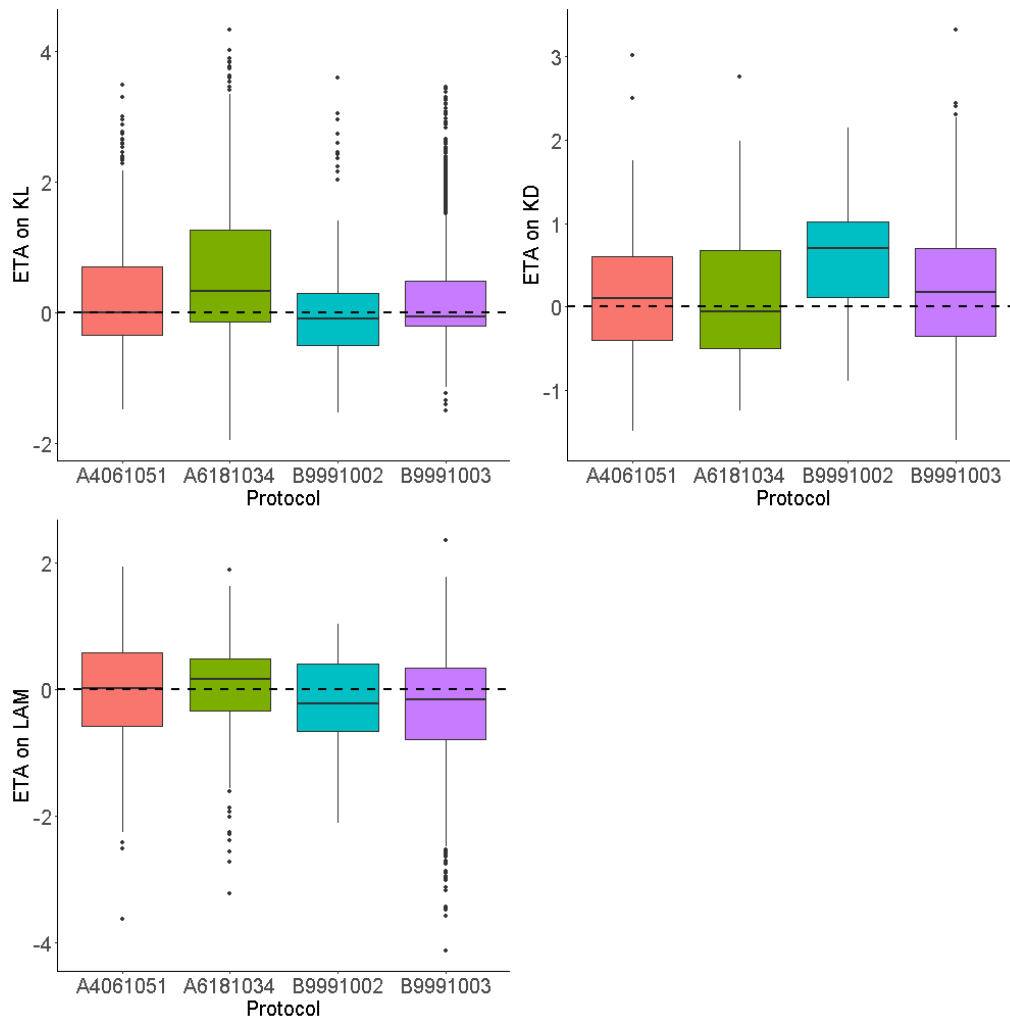
Figure 8. Boxplots of Inter-Individual Variability of Parameter Estimates versus Treatment



Repository artifact ID FI-766612.

Figure abbreviations: axi = axitinib, ave = avelumab, ETA = empirical Bayes estimate for inter-individual variability, IFNa = interferon- α , K_D = cell-kill rate constant, K_L = tumor growth rate constant, λ = drug-resistance rate constant

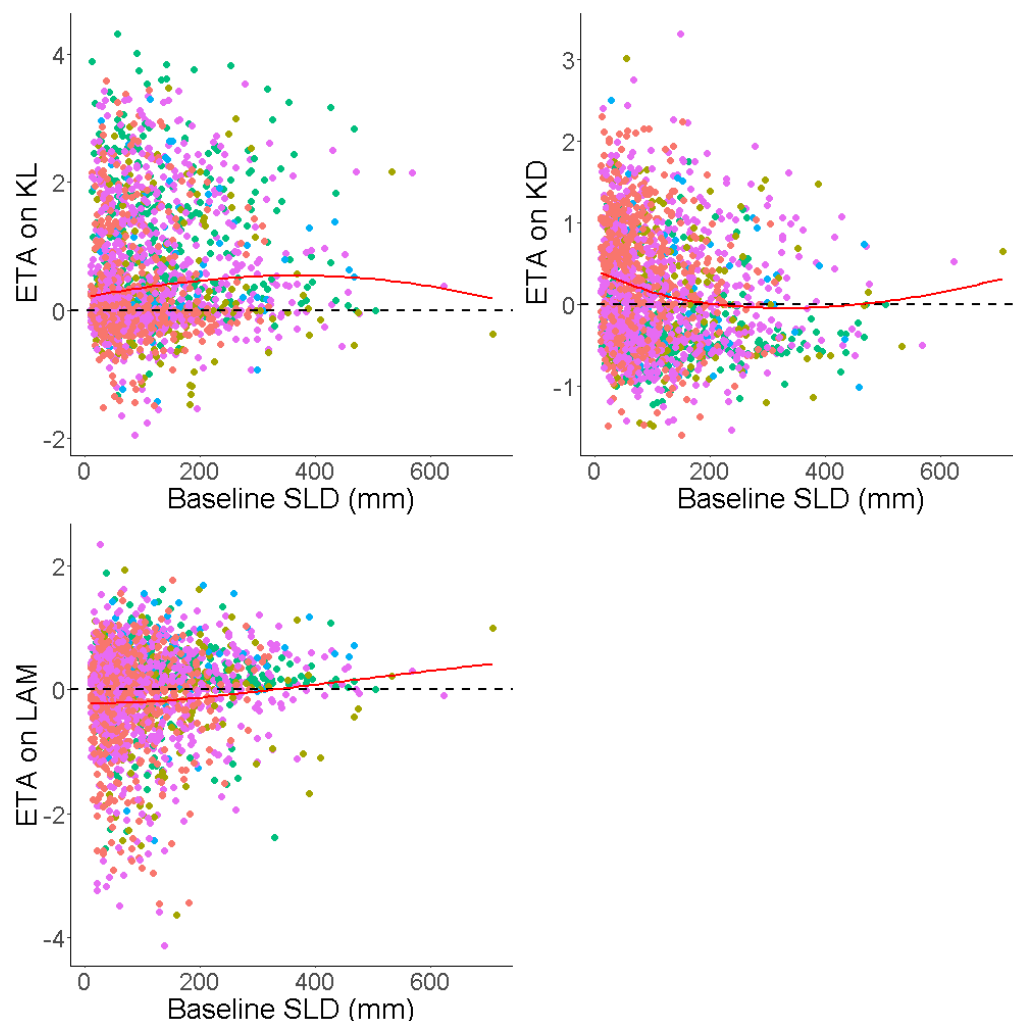
Figure 9. Boxplots of Inter-Individual Variability of Parameter Estimates versus Protocol



Repository artifact ID FI-9451084.

Figure abbreviations: ETA = empirical Bayes estimate for inter-individual variability, K_D = cell-kill rate constant, K_L = tumor growth rate constant, λ = drug-resistance rate constant

Figure 10. Scatterplots of Inter-Individual Variability of Parameter Estimates versus Baseline SLD



Repository artifact ID FI-766603.

Figure abbreviations: ETA = empirical Bayes estimate for inter-individual variability, K_D = cell-kill rate constant, K_L = tumor growth rate constant, λ = drug-resistance rate constant, SLD = sum of the longest tumor diameters, TGI = tumor growth inhibition

6.5. Full Model Results

Based on the graphical examination of the η s versus covariate plots and potential for treatment and baseline SLD to influence the TGI parameters, SCM was then employed to investigate whether these covariates were significant. Treatment was tested as a categorical covariate linearly with sunitinib as the reference treatment. Baseline SLD was tested as a continuous covariate using both the raw scale and natural logarithmic transformation.

Covariate selection was evaluated at a significance level of $\alpha = 0.05$ for forward inclusion, and at $\alpha = 0.001$ for backward elimination.

After forward inclusion, treatment was included on all parameters and baseline SLD was

included on K_D in the full model. Details of the SCM results are presented in [Appendix 6](#).

6.6. Final Model Results

The SCM process included a backward elimination step from the full model (at $\alpha = 0.001$) to produce the final model. After backwards elimination step, the final model included the effect of treatment on all 3 parameters and baseline SLD (in the raw scale as power function) on K_D .

The equations for each of the TGI parameters are listed below, using sunitinib as the reference treatment:

$$K_L = 0.14 \cdot (1 + \theta_{Treatment}) \quad (5)$$

$$K_D = 1.61 \cdot (1 + \theta_{Treatment}) \cdot \left(\frac{BSLD}{91}\right)^{0.051} \quad (6)$$

$$\lambda = 3.98 \cdot (1 + \theta_{Treatment}) \quad (7)$$

Bootstrap of the final model was conducted in PsN based on 1000 resampled datasets, stratified by treatment. The bootstrap median and 95% confidence interval (CI) values were compared to the final model estimates. Table 5 presents the final model and bootstrap parameter estimates. Overall, the final model estimates were similar to the bootstrap median values and all of the final model estimates were within the 95% CI of the bootstrap values.

Relative to sunitinib, INF- α exhibited 35.5% higher K_D , 9% lower K_L and 18% higher λ , consistent with the fast decrease in tumor size observed but lack of durability of response. The other TKI agents relative to sunitinib generally exhibited similar K_D , K_L , and λ where the bootstrap 95% CI for the estimates encompassed 0. For avelumab + axitinib treatment, K_D was 7.7% lower and K_L 9.2% higher, as compared to sunitinib, consistent with gradual decrease in observed tumor size over time.

Table 5. Final Model Parameter Estimates

Parameter	Estimate	RSE (%)	Shrinkage (%)	Bootstrap Median	Bootstrap 95% CI
$\theta_{K_L}(\text{years}^{-1})$	0.140	11.7	-	0.143	(0.1125; 0.1840)
$\theta_{K_D}(\text{years}^{-1})$	1.606	5.3	-	1.616	(1.4683; 1.7891)
$\theta_{\lambda}(\text{years}^{-1})$	3.976	9.2	-	3.958	(3.3120; 4.7091)
$\theta_{\sigma;prop}$	0.081	6.6	-	0.081	(0.0710; 0.0929)
$\theta_{\sigma;add}$	2.262	8.7	-	2.279	(1.8936; 2.6659)
BSLD on θ_{K_D}	0.051	20.8	-	0.050	(0.0293; 0.0723)
IFN α on θ_{K_D}	0.355	11.9	-	0.350	(0.2620; 0.4402)
Sorafenib on θ_{K_D}	-0.077	-76.6	-	-0.075	(-0.2003; 0.0450)

Table 5. Final Model Parameter Estimates

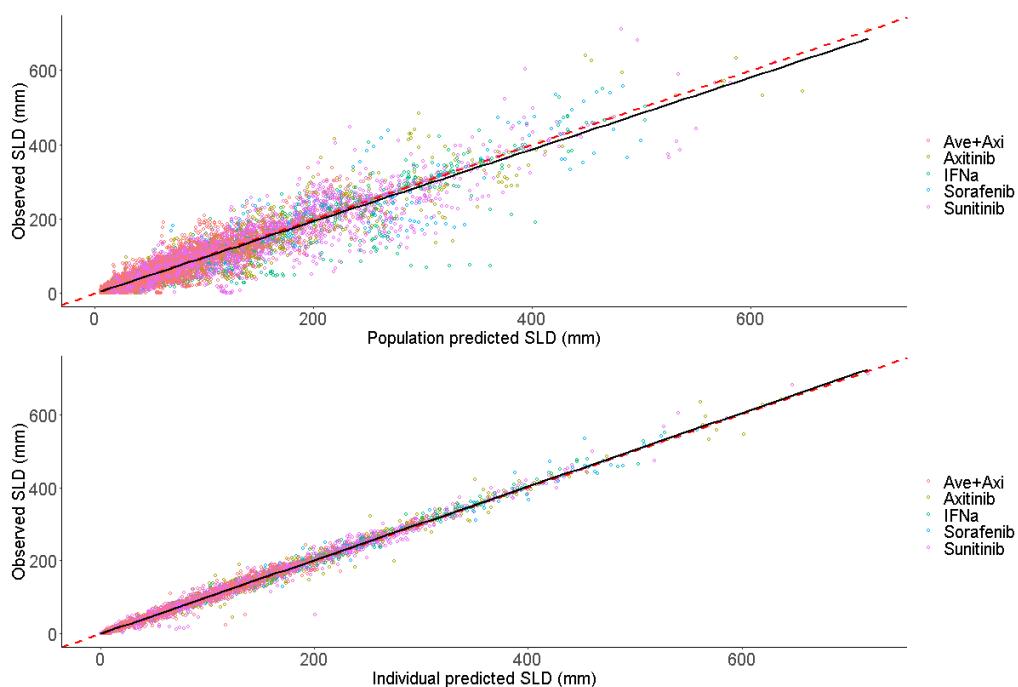
Parameter	Estimate	RSE (%)	Shrinkage (%)	Bootstrap Median	Bootstrap 95% CI
Axitinib on θ_{K_D}	0.010	324.3	-	0.006	(-0.0527; 0.0719)
Ave+axi on θ_{K_D}	-0.077	-26.1	-	-0.078	(-0.1180; -0.0337)
IFN α on θ_{K_L}	-0.090	-26.9	-	-0.094	(-0.1407; -0.0452)
Sorafenib on θ_{K_L}	-0.031	-112.3	-	-0.031	(-0.0953; 0.0435)
Axitinib on θ_{K_L}	0.064	57.9	-	0.071	(0.0011; 0.1532)
Ave+axi on θ_{K_L}	0.092	31.9	-	0.094	(0.0379; 0.1619)
IFN α on λ	0.183	79.4	-	0.210	(-0.0944; 0.5261)
Sorafenib on λ	-0.413	-28.7	-	-0.400	(-0.6222; -0.1702)
Axitinib on λ	0.053	137.4	-	0.041	(-0.0958; 0.2059)
Ave+axi on λ	0.062	83.7	-	0.058	(-0.0438; 0.1720)
ω_{K_L}	2.348	7.5	35.4	2.297	(1.9457; 2.6947)
ω_{K_D}	0.842	7.4	22.2	0.818	(0.7178; 0.9337)
ω_{λ}	1.681	15.2	36.4	1.659	(1.3342; 2.0491)
OFV	65923.894	-	-	65847.680	(63711.3600; 68021.9000)

Repository artifact ID FI-2009063.

Table abbreviations: add = additive error, Ave+axi = avelumab plus axitinib combination treatment, BSLD = baseline sum of longest tumor diameters, CI = confidence interval, K_D = cell-kill rate constant, K_L = tumor growth rate constant, λ = drug-resistance rate constant, OFV = objective function value, prop = proportional error, RSE = relative standard error, SLD = sum of the longest tumor diameters

Final model prediction-based diagnostic plots of the DV, which was SLD, versus PRED and IPRED are presented in [Figure 11](#) and color coded by treatment.

Figure 11. Observed SLD versus PRED and IPRED

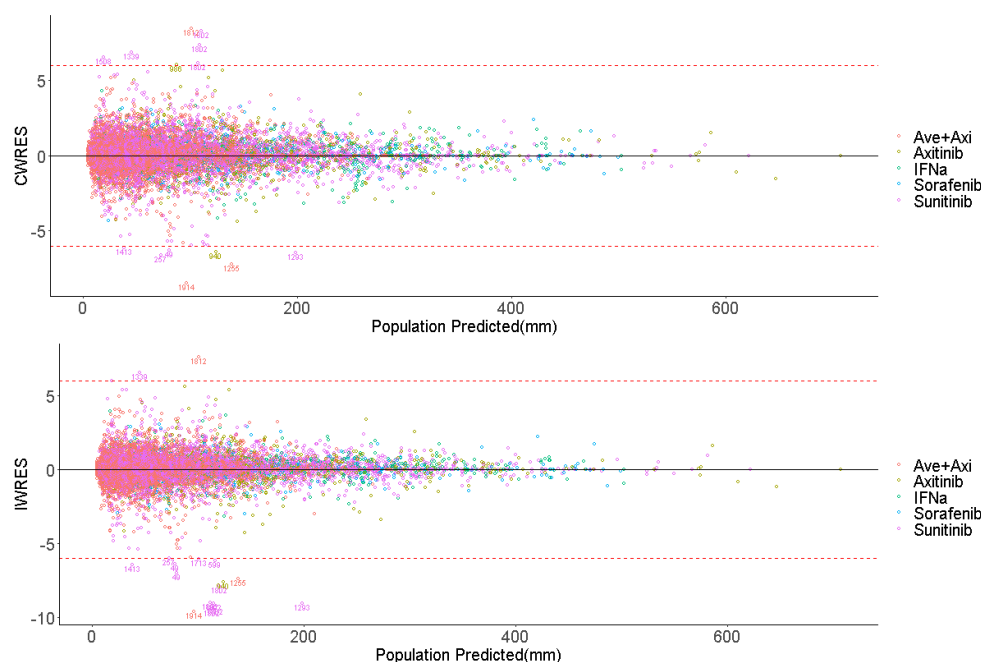


Repository artifact ID FI-482734.

Figure abbreviations: axi = axitinib, ave = avelumab, IFNa = interferon- α , SLD = sum of the longest tumor diameters

Final model residual-based diagnostic plots of CWRES and IWRES versus PRED and time are presented in [Figure 12](#) and [Figure 13](#), respectively. Both CWRES and IWRES versus PRED and time were evenly distributed above and below the line of unity at 0.

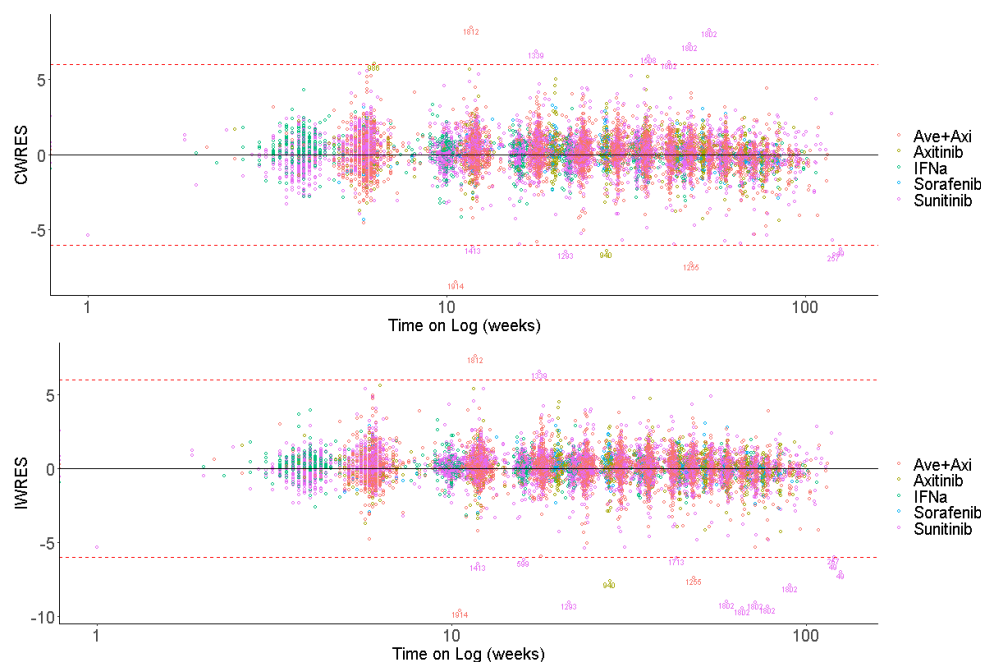
Figure 12. Residuals versus Population Predictions



Repository artifact ID FI-482743.

Figure abbreviations: axi = axitinib, ave = avelumab, CWRES = conditional weighted residuals, IFNa = interferon- α , IWRES = individual weighted residuals

Figure 13. Residuals versus Time



Repository artifact ID FI-482742.

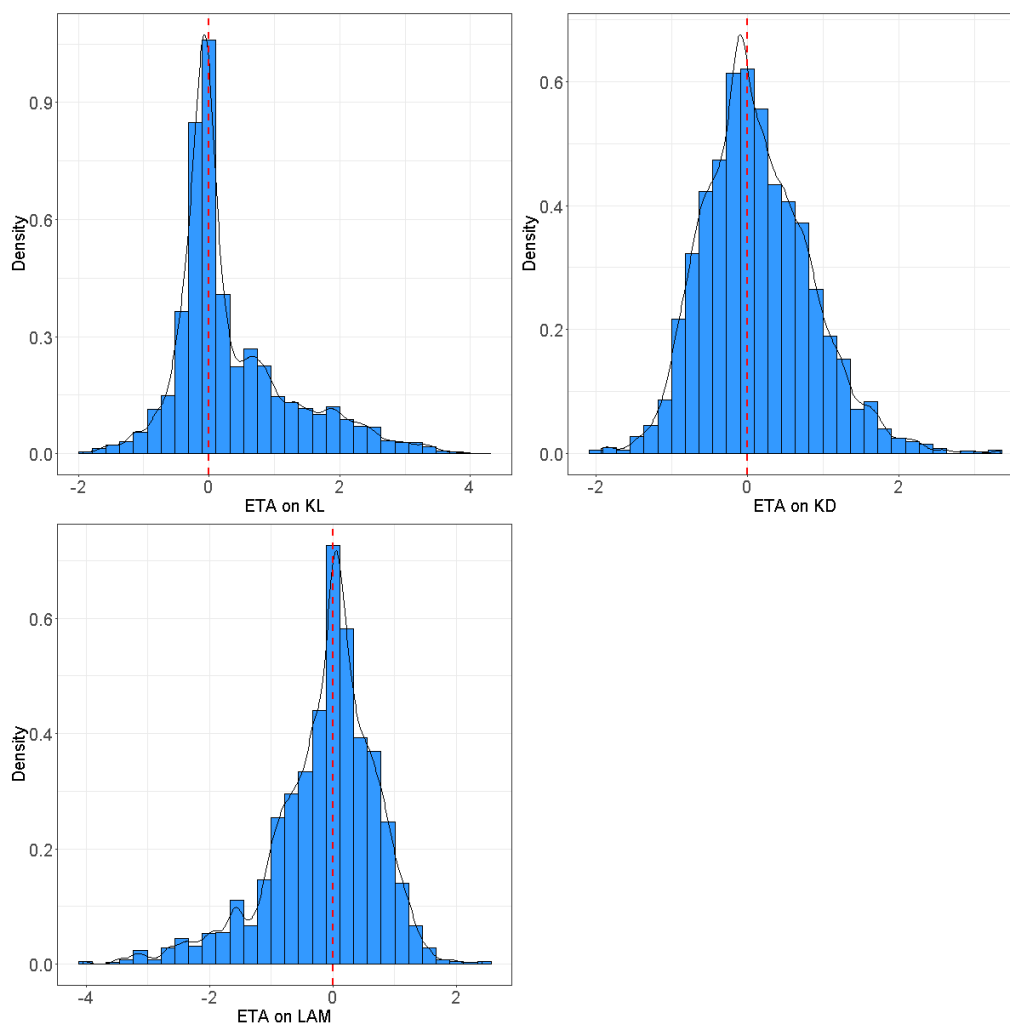
Time is on logarithmic scale.

Figure abbreviations: axi = axitinib, ave = avelumab, CWRES = conditional weighted residuals, IFNa = interferon- α , IWRES = individual weighted residuals

6.7. Graphical Summaries of Covariate Effects

Figure 14 presents the distribution of the η s for each parameter. Shrinkage was above 30% for K_L and λ parameters, indicating regression towards the mean. Therefore, visual interpretation of η plot diagnostics must be evaluated with caution. The histogram for K_D was more normally distributed around 0 in the final model as compared to the base model after inclusion of covariate effects of treatment and baseline SLD.

Figure 14. Histograms of η on TGI Parameters

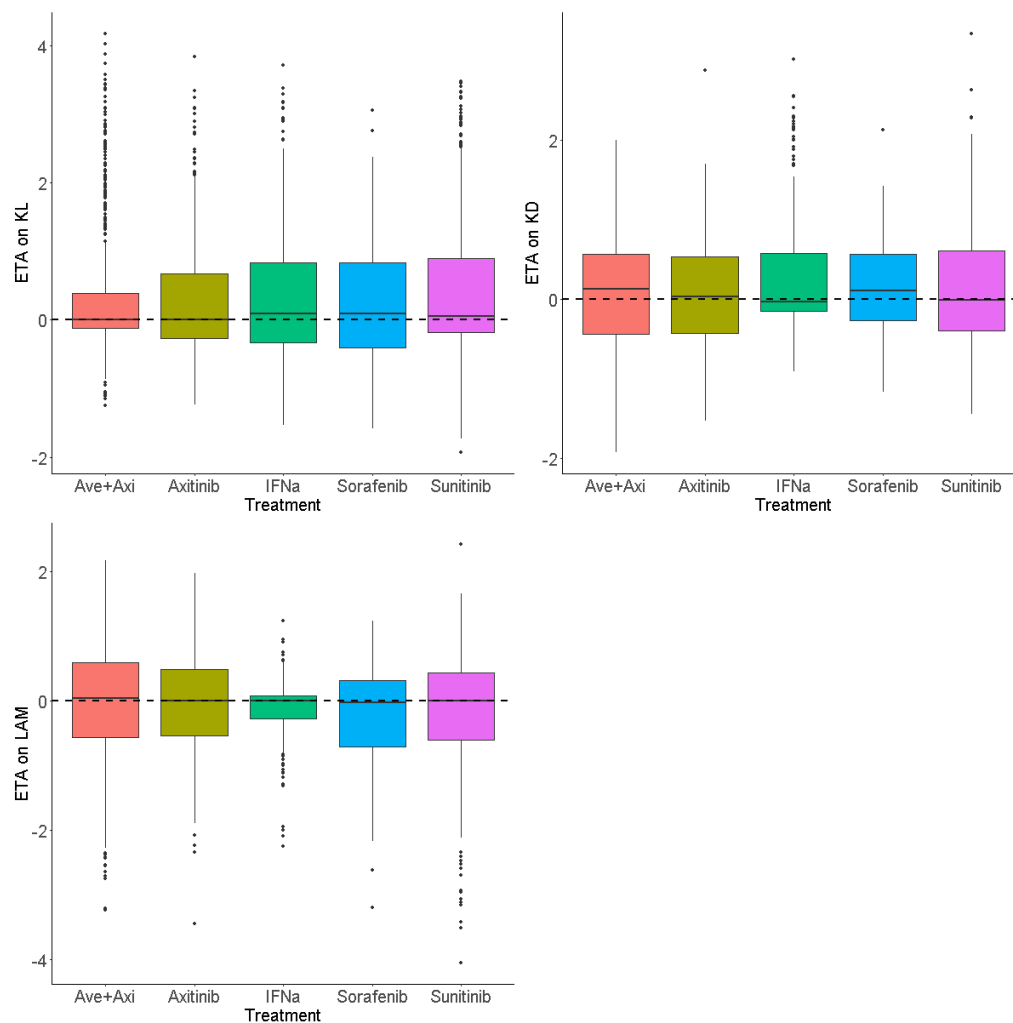


Repository artifact ID FI-482736.

Figure abbreviations: ETA = empirical Bayes estimate for inter-individual variability, K_D = cell-kill rate constant, K_L = tumor growth rate constant, λ = drug-resistance rate constant, TGI = tumor growth inhibition

Figure 15 presents η versus treatment boxplots. η versus baseline SLD scatterplots are presented in Figure 16. After inclusion of the effect of treatment on all model parameters in the final model, the boxplots appear more centered to the dotted line at 0. For baseline SLD, the scatterplot trends are generally flat, but there could be some bias not accounted for in K_L . However, baseline SLD on K_L was not significant from SCM covariate analysis.

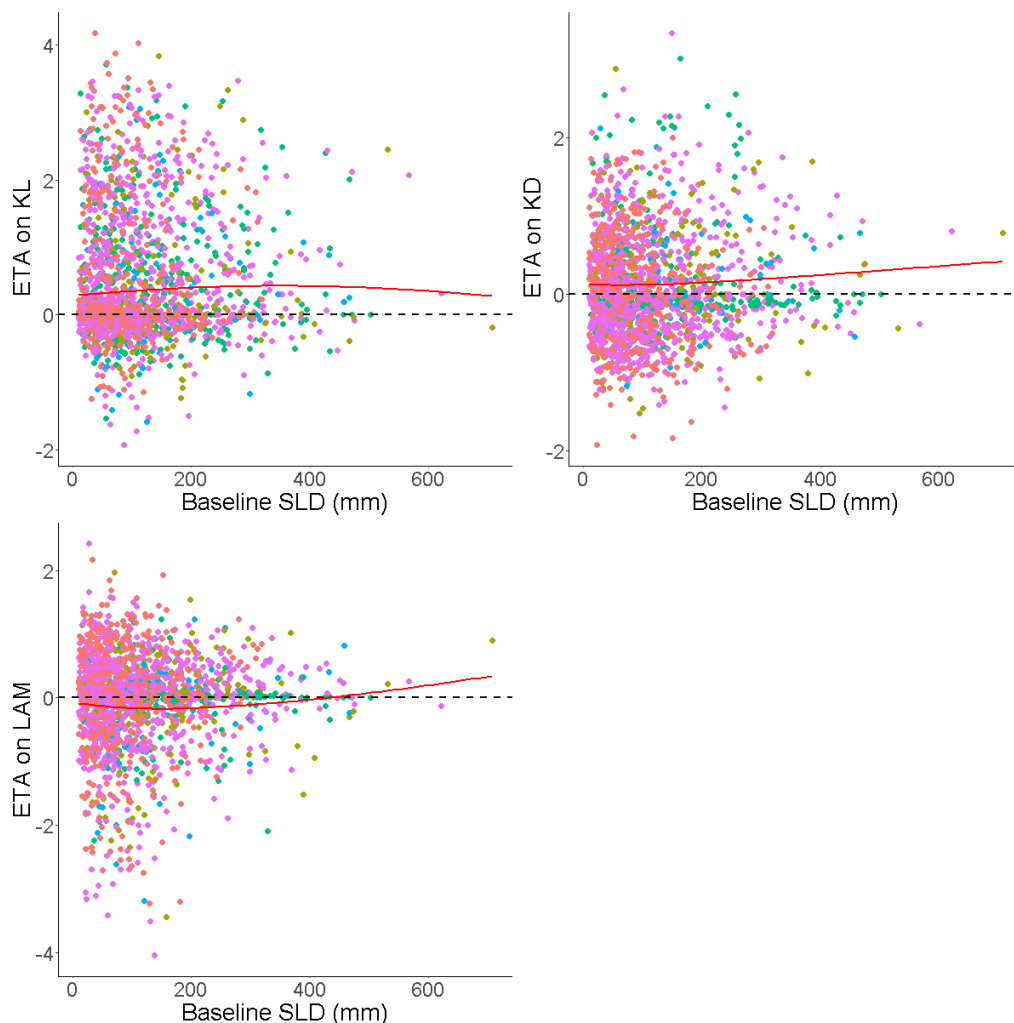
Figure 15. Boxplots of Inter-Individual Variability of Parameter Estimates versus Treatment



Repository artifact ID FI-482745.

Figure abbreviations: axi = axitinib, ave = avelumab, ETA = empirical Bayes estimate for inter-individual variability, IFNa = interferon- α , K_D = cell-kill rate constant, K_L = tumor growth rate constant, λ = drug-resistance rate constant

Figure 16. Scatterplots of Inter-Individual Variability of Parameter Estimates versus Baseline SLD



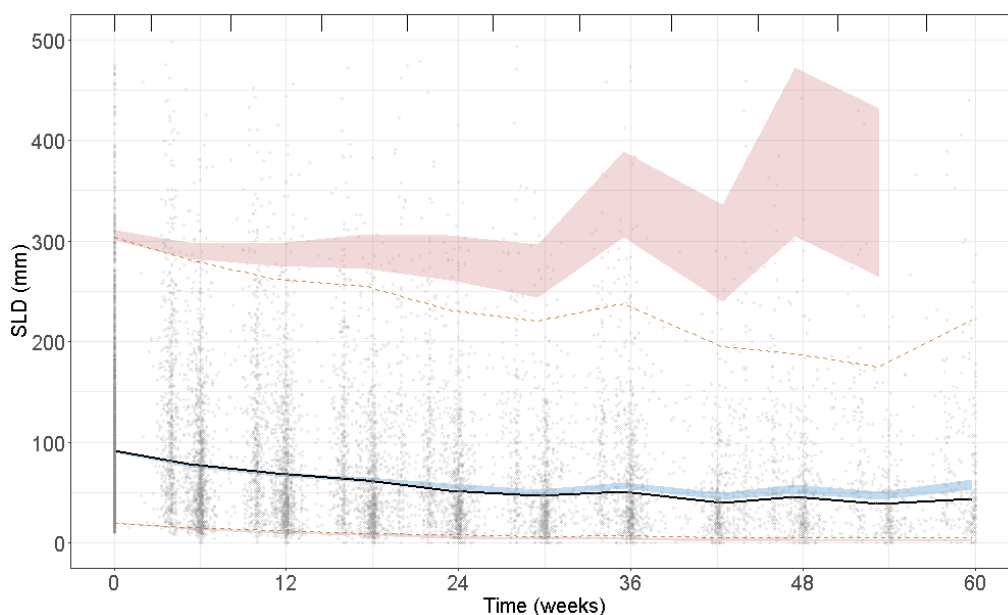
Repository artifact ID FI-482733.

Figure abbreviations: ETA = empirical Bayes estimate for inter-individual variability, K_D = cell-kill rate constant, K_L = tumor growth rate constant, λ = drug-resistance rate constant, SLD = sum of the longest tumor diameters, TGI = tumor growth inhibition

6.8. Final Model Predictive Performance

A visual predictive check (VPC) based on 500 simulations was performed using PsN with the final model. The final model performed well in predicting the observed data for early data up to around 12 weeks (Figure 17); with the 5th, 50th, and 95th percentiles of the observed data mostly lying within the 90% prediction intervals of the 5th, 50th, and 95th percentiles or the simulated data.

Figure 17. Final Model Visual Predictive Check

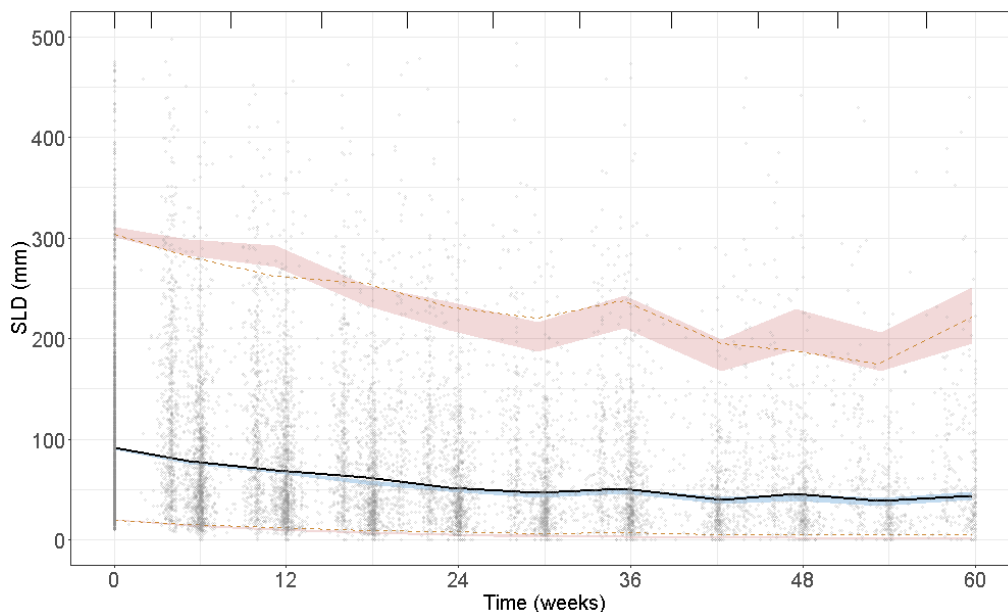


Repository artifact ID FI-1137284.

Figure abbreviations: SLD = sum of the longest tumor diameters

At later time points (approximately beyond week 12), the simulated data appear to be overpredicting the observed data. The observed data at later time points included patients remaining in the clinical trials who have not yet progressed. Based on the study design, patients who progressed, defined generally with an increase in tumor size (approximately 20%), will drop out of the clinical studies. Therefore, a VPC which assumes patients who have progressed (20% increase in tumor size) per RECIST 1.1 criteria ([12]) after week 12 have dropped out of the study was plotted (Figure 18 and Figure 19). In other words, all simulated data from baseline to week 12 were included and the tumor data after week 12 that indicated progression were removed from the VPC. After accounting for dropout of data from patients who progressed, the VPC demonstrates that the final model performed well in predicting data from clinical trial patients who remain on study.

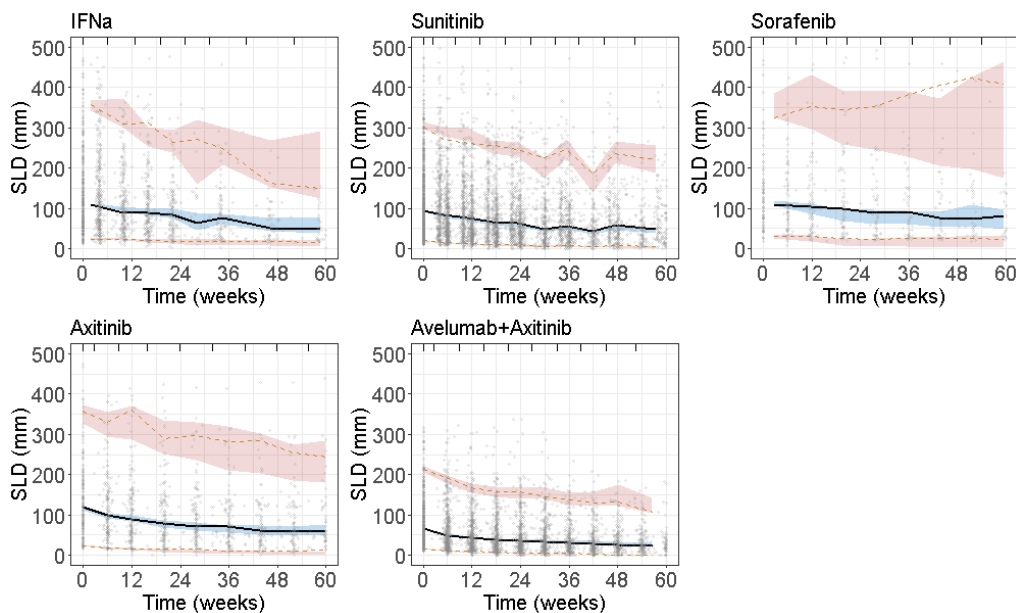
Figure 18. Final Model Visual Predictive Check Removing Progressive Disease - Pooled



Repository artifact ID FI-1137287.

Figure abbreviations: SLD = sum of the longest tumor diameters

Figure 19. Final Model Visual Predictive Check Removing Progressive Disease - by Treatment



Repository artifact ID FI-1137288.

Figure abbreviations: SLD = sum of the longest tumor diameters

6.9. Summary of Predicted TGI Metrics and Clinical Endpoints

As previously defined in [Section 5.3](#), metrics such as TS_{ratio} and TTG can be derived based on individual post hoc estimates of the TGI parameters (summarized in Table 6). TS_{ratio} at week 6 and week 8 were derived from the final model and presented by treatment (Figure 20). At both weeks 6 and 8, interferon- α treatment appeared to have higher tumor ratio, geometric mean of 1.0, compared to the other treatments. For the TKIs, the geometric mean week 6 and week 8 TS_{ratio} were around 0.9 and 0.8. The combination treatment of avelumab plus axitinib had lowest TS_{ratio} at 0.8 and 0.7 for weeks 6 and 8.

Table 6. Summary of TGI Parameters

Treatment	N	Tumor Ratio Week 6	Tumor Ratio Week 8	Time to tumor growth
Ave+Axi	477	0.8 (21.78%)	0.7 (27.59%)	9.0 (124.28%)
Axitinib	175	0.9 (27.24%)	0.8 (35.22%)	5.1 (248.69%)
IFNa	328	1.0 (17.17%)	1.0 (22.62%)	4.4 (233.62%)
Sorafenib	83	0.9 (13.35%)	0.9 (15.77%)	3.7 (108.50%)
Sunitinib	776	0.9 (21.24%)	0.8 (26.22%)	5.0 (156.69%)

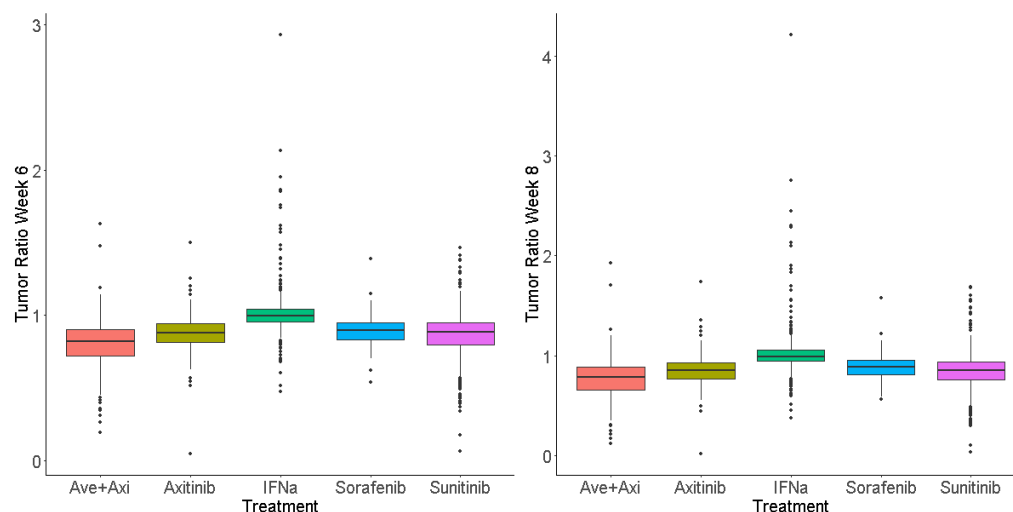
Repository artifact ID FI-10120735.

Data are geometric mean (geometric CV%).

Time to tumor growth units are in weeks.

Table abbreviations: CV=coefficient of variation, TGI=tumor growth inhibition

Figure 20. Boxplots of Tumor Ratio by Treatment

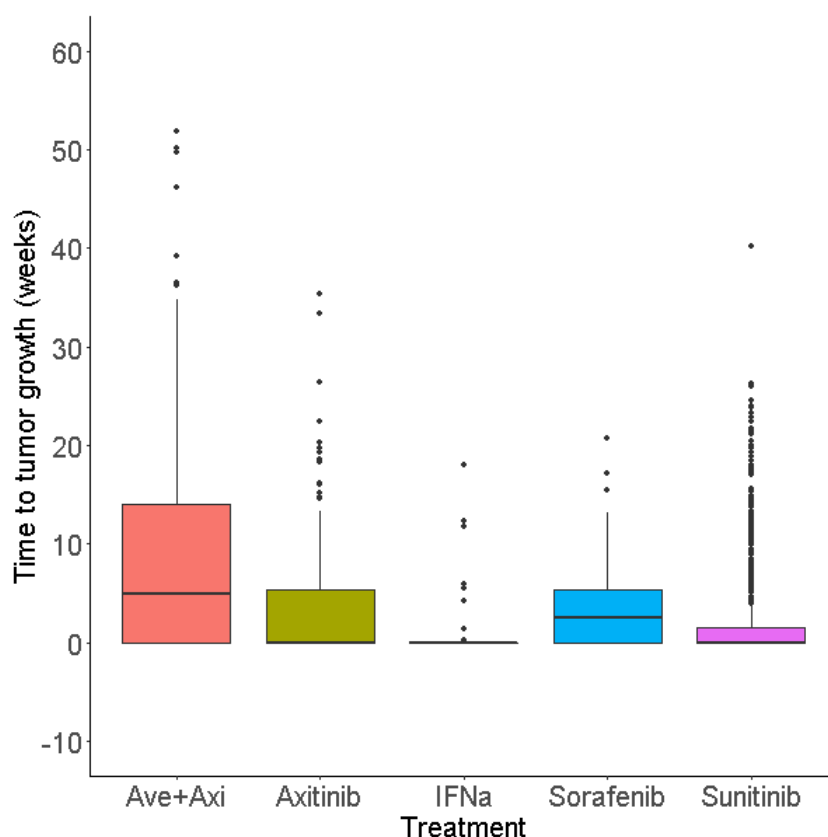


Repository artifact ID FI-482747.

Figure abbreviations: axi = axitinib, ave = avelumab, IFNa = interferon- α

TTG by treatment is presented in [Figure 21](#). TTG was the shortest for interferon- α treatment at 4.4 weeks and longest for combination treatment of avelumab plus axitinib at 9.0 weeks. The TKIs had predicted TTG values from 3.7 to 5.1 weeks.

Figure 21. Boxplots of Time to Tumor Growth by Treatment



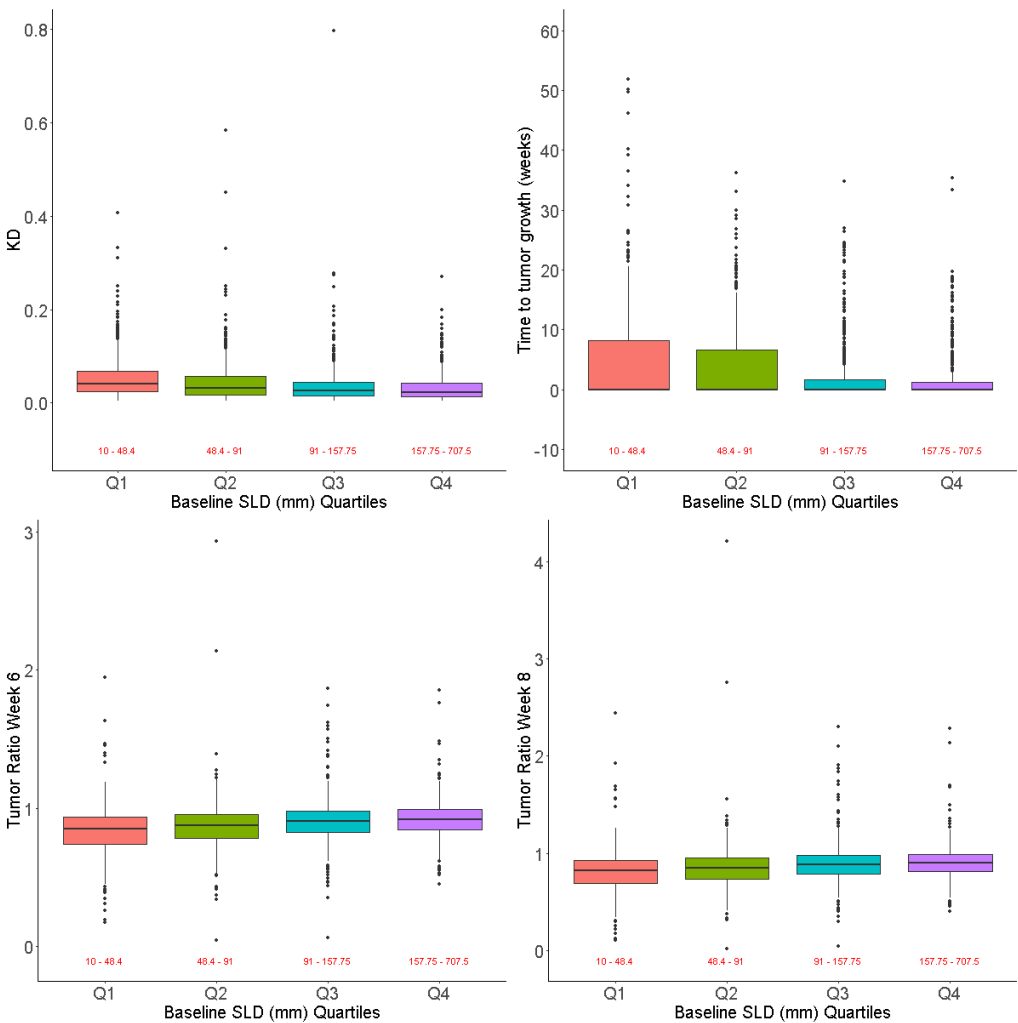
Repository artifact ID FI-482746.

Time to tumor growth is presented up to 300 weeks.

Figure abbreviations: axi = axitinib, ave = avelumab, IFNa = interferon- α

Baseline SLD was a significant covariate on K_D . [Figure 22](#) presents the post hoc results for K_D , TTG, TS_{ratio} at weeks 6 and 8 by baseline SLD quartiles. In terms of K_D , patients in lower quartile of baseline SLD trended to have higher K_D values than those in higher quartiles; however, there was significant overlap in the boxplot. Patients in lower quartile baseline SLD also trended to have longer TTG versus those of higher quartiles. In terms of TS_{ratio} at weeks 6 and 8, lower quartile baseline SLD patients generally had ratios below 1, whereas higher quartiles trended with higher TS_{ratio} . For all metrics, there was overlap in the boxplots between the lowest and highest quartile of baseline SLD patients.

Figure 22. Boxplots of Tumor Growth Metrics by Baseline SLD Quartiles



Repository artifact ID FI-2191381.

Quantile values of baseline SLD are listed in red as minimum, 25th, 50th, 75th, and maximum values.

Time to tumor growth is presented up to 300 weeks.

Figure abbreviations: K_D = cell-kill rate constant, SLD = sum of the longest tumor diameters

Additionally, other efficacy endpoints of interest such as time to progression (TTP) and time to response (TTR) for partial or complete response (as defined by RECIST 1.1) can be determined based on the predicted tumor sizes from the final model for each individual patient. Predicted tumor sizes from the final model were based on time intervals consistent with scheduled study visits. Table 7 and Table 8 present the predicted TTP and TTR, respectively, by protocol and treatment.

Table 7. Summary of Predicted Time to Progression (weeks) by Study and Treatment

Protocol	Treatment	N	n (%)	Mean (SD)	Median (Min ; Max)
A4061051	Axitinib	175	16 (9.1%)	30.5 (23.23)	27.9 (5.3; 79.7)
A4061051	Sorafenib	83	21 (25.3%)	33.2 (15.51)	28.3 (6.0; 60.6)

Table 7. Summary of Predicted Time to Progression (weeks) by Study and Treatment

Protocol	Treatment	N	n (%)	Mean (SD)	Median (Min ; Max)
A6181034	IFN α	337	54 (16.0%)	17.6 (16.24)	11.3 (3.4; 71.0)
A6181034	Sunitinib	360	24 (6.7%)	36.5 (22.94)	34.6 (3.9; 81.1)
B9991002	Avelumab+Axitinib	54	9 (16.7%)	21.9 (12.26)	18.4 (6.1; 40.0)
B9991003	Avelumab+Axitinib	424	20 (4.7%)	22.0 (10.08)	24.1 (5.9; 42.1)
B9991003	Sunitinib	425	53 (12.5%)	24.3 (18.09)	18.1 (5.7; 79.6)

Repository artifact ID FI-2128549.

Time to progression defined by RECIST v1.1

Table abbreviations: N = total number of patients, n = number of patients with progression, SD = standard deviation

Table 8. Summary of Predicted Time to Response (weeks) by Study and Treatment

Protocol	Treatment	N	n (%)	Mean (SD)	Median (Min ; Max)
A4061051	Axitinib	175	77 (44.0%)	18.4 (12.06)	13.1 (5.7; 68.0)
A4061051	Sorafenib	83	17 (20.5%)	18.8 (12.86)	12.1 (5.9; 51.7)
A6181034	IFN α	337	35 (10.4%)	19.9 (15.73)	11.0 (3.4; 65.7)
A6181034	Sunitinib	360	157 (43.6%)	13.4 (7.77)	10.1 (3.6; 57.1)
B9991002	Avelumab+Axitinib	54	35 (64.8%)	10.9 (5.77)	7.0 (5.3; 25.4)
B9991003	Avelumab+Axitinib	424	258 (60.8%)	13.0 (8.45)	11.9 (4.9; 66.9)
B9991003	Sunitinib	425	153 (36.0%)	17.8 (9.75)	17.3 (5.1; 45.1)

Repository artifact ID FI-2128550.

Time to response includes partial response or complete response defined by RECIST v1.1

Table abbreviations: N = total number of patients, n = number of patients with partial or complete response, SD = standard deviation

Median TTP was reported for Study A6181034 as 49.1 weeks for the sunitinib arm and 22.4 weeks for the interferon- α arm. The model derived TTP were underpredicted compared to the observed data for this study at 34.6 and 11.3 weeks, respectively.

Median TTR were reported for Study B9991002 and Study B9991003. In Study B9991002, the median TTR was 1.6 months in all subjects, which is similar to the derived median 7.0 weeks from the model. The median TTR from Study B9991003 were 2.6 months and 3.2 months for combination avelumab+axitinib arm and sunitinib arm, respectively. The model derived median TTR were 11.9 and 17.3 weeks, respectively, which is similar for the combination therapy but longer for sunitinib, most likely due to sunitinib as a treatment covariate was present in two studies (A6181034 and B9991003) where study reported median PFS were different (11 months in A6181034 versus 7.2 months in B9991003).

6.10. Exploring Truncated Data

Subsequent analyses are based on this TGI model to explore whether early tumor metrics can predict clinical endpoints, such as PFS or OS. For future studies, it may be helpful to predict clinical endpoints during the early phases of the study. The final model was rerun after

empirically truncating the observed data to 24 weeks or to 12 weeks. The final model included 1839 patients with 12356 observations. After truncating the data to 24 weeks, the model included data from 1839 patients with 7435 observations. After truncating the data to 12 weeks, the model included data from 1839 patients with 4803 observations. Table 9 presents the estimates from the truncated datasets compared to the final model.

Table 9. Comparison of Model Estimates Using Truncated Dataset

Parameter	Final Model Estimate	Final Model RSE (%)	24 Weeks Model Estimate	24 Weeks Model RSE (%)	12 Weeks Model Estimate	12 Weeks Model RSE (%)
θ_{K_L} (years ⁻¹)	0.140	11.7	0.175	26.0	0.262	13.8
θ_{K_D} (years ⁻¹)	1.606	5.3	1.660	9.4	2.244	6.4
θ_{λ} (years ⁻¹)	3.976	9.2	4.460	17.1	8.414	14.5
$\theta_{\sigma;prop}$	0.081	6.6	0.057	9.6	0.033	0.8
$\theta_{\sigma;add}$	2.262	8.7	2.375	11.7	1.855	1.2
BSLD on θ_{K_D}	0.051	20.8	0.047	22.0	0.050	21.7
IFN α on θ_{K_D}	0.355	11.9	0.356	13.6	0.427	7.7
Sorafenib on θ_{K_D}	-0.077	-76.6	-0.185	-33.5	-0.167	-36.7
Axitinib on θ_{K_D}	0.010	324.3	-0.046	-74.4	0.032	99.3
Ave+axi on θ_{K_D}	-0.077	-26.1	-0.110	-20.0	-0.105	-23.1
IFN α on θ_{K_L}	-0.090	-26.9	-0.144	-19.4	-0.129	-19.0
Sorafenib on θ_{K_L}	-0.031	-112.3	-0.063	-70.4	0.012	429.5
Axitinib on θ_{K_L}	0.064	57.9	0.010	384.6	-0.031	-119.8
Ave+axi on θ_{K_L}	0.092	31.9	0.011	259.1	-0.013	-235.8
IFN α on λ	0.183	79.4	0.504	38.5	0.954	23.3
Sorafenib on λ	-0.413	-28.7	-0.568	-26.1	-0.554	-34.9
Axitinib on λ	0.053	137.4	-0.076	-122.8	0.560	30.4
Ave+axi on λ	0.062	83.7	0.042	170.5	0.173	64.0
ω_{K_L}	2.348	7.5	1.645	17.2	1.349	12.2
ω_{K_D}	0.842	7.4	0.822	6.9	0.754	7.8
ω_{λ}	1.681	15.2	1.385	104.2	2.058	16.6
OFV	65923.894	-	39889.762	-	22358.706	-

Repository artifact ID FI-2129857.

Table abbreviations: add = additive error, Ave+axi = avelumab plus axitinib combination treatment, BSLD = baseline sum of longest tumor diameters, CI = confidence interval, K_D = cell-kill rate constant, K_L = tumor growth rate constant, λ = drug-resistance rate constant, OFV = objective function value, prop = proportional error, RSE = relative standard error, SLD = sum of the longest tumor diameters

Compared with data truncated to 24 weeks, K_L and λ parameters changed by more than 15%. Compared with data truncated to 12 weeks, all TGI parameters increased by more than 15%.

Table 10 and Table 11 presents the geometric mean (% CV) of individual estimates for the TGI parameters and the derived metrics (TTG and TS_{ratio} at weeks 6 and 8) by study and treatment.

Table 10. Comparison of Individual Estimates of TGI Parameters Using Truncated Dataset by Study and Treatment

Protocol	Treatment	Parameter	12 weeks	24 weeks	Full data
A4061051	Axitinib	K_L	0.00878 (74.8%)	0.00471 (83.3%)	0.00301 (138.3%)
A4061051	Sorafenib	K_L	0.00649 (78.8%)	0.00726 (87.9%)	0.00501 (124.6%)
A6181034	IFN α	K_L	0.01389 (82.4%)	0.01107 (90.8%)	0.00771 (117.9%)
A6181034	Sunitinib	K_L	0.00656 (62.1%)	0.00475 (78.3%)	0.00462 (126.7%)
B9991002	Avelumab+Axitinib	K_L	0.00816 (94.8%)	0.00601 (134.1%)	0.00352 (262.4%)
B9991003	Avelumab+Axitinib	K_L	0.00715 (59.1%)	0.00449 (78.7%)	0.00241 (119.5%)
B9991003	Sunitinib	K_L	0.00766 (77.1%)	0.00553 (95.6%)	0.00469 (122.3%)
A4061051	Axitinib	K_D	0.0406 (70.6%)	0.0392 (75.5%)	0.0311 (81.5%)
A4061051	Sorafenib	K_D	0.0758 (52.1%)	0.0644 (54.4%)	0.0435 (63.0%)
A6181034	IFN α	K_D	0.0134 (68.5%)	0.0113 (70.8%)	0.0105 (74.9%)
A6181034	Sunitinib	K_D	0.0545 (76.4%)	0.0425 (81.4%)	0.0402 (81.5%)
B9991002	Avelumab+Axitinib	K_D	0.0718 (66.7%)	0.0579 (88.7%)	0.0505 (79.7%)
B9991003	Avelumab+Axitinib	K_D	0.0644 (63.9%)	0.0516 (78.2%)	0.0447 (81.6%)
B9991003	Sunitinib	K_D	0.0414 (62.4%)	0.0306 (74.3%)	0.0297 (74.2%)
A4061051	Axitinib	λ	0.0635 (72.7%)	0.1068 (58.5%)	0.0649 (94.6%)
A4061051	Sorafenib	λ	0.4378 (79.2%)	0.3127 (65.7%)	0.1939 (101.4%)
A6181034	IFN α	λ	0.0280 (39.3%)	0.0247 (34.5%)	0.0437 (42.5%)
A6181034	Sunitinib	λ	0.1629 (76.4%)	0.0980 (59.2%)	0.0795 (69.9%)
B9991002	Avelumab+Axitinib	λ	0.1589 (57.4%)	0.0901 (68.5%)	0.0719 (79.6%)
B9991003	Avelumab+Axitinib	λ	0.1350 (83.9%)	0.0825 (77.0%)	0.0672 (109.3%)
B9991003	Sunitinib	λ	0.1915 (79.1%)	0.0828 (63.8%)	0.0673 (103.0%)

Repository artifact ID FI-3035963.

Data are geometric mean (geometric % coefficient of variation (CV)).

Table abbreviations: CV = coefficient of variation, K_D = cell-kill rate constant, K_L = tumor growth rate constant, λ = drug-resistance rate constant, TGI = tumor growth inhibition

Table 11. Comparison of Individual Estimates of Derived TGI Metrics Using Truncated Dataset by Study and Treatment

Protocol	Treatment	Parameter	12 weeks	24 weeks	Full data
A4061051	Axitinib	TTG	3.6241 (136.4%)	3.7538 (199.8%)	5.0810 (248.7%)

Table 11. Comparison of Individual Estimates of Derived TGI Metrics Using Truncated Dataset by Study and Treatment

Protocol	Treatment	Parameter	12 weeks	24 weeks	Full data
A4061051	Sorafenib	TTG	3.4599 (75.8%)	3.0714 (92.5%)	3.6891 (108.5%)
A6181034	IFN α	TTG	1.2512 (383.4%)	3.2348 (NA%)	4.4156 (233.6%)
A6181034	Sunitinib	TTG	3.3918 (128.2%)	5.0154 (114.8%)	5.3349 (152.9%)
B9991002	Avelumab+Axitinib	TTG	3.8149 (116.2%)	8.0456 (98.4%)	12.6571 (109.7%)
B9991003	Avelumab+Axitinib	TTG	3.1506 (132.1%)	5.0698 (161.9%)	8.7311 (124.8%)
B9991003	Sunitinib	TTG	1.8710 (159.2%)	4.0833 (140.8%)	4.5108 (161.8%)
A4061051	Axitinib	Tumor Ratio Week 6	0.842 (30.8%)	0.837 (28.2%)	0.850 (27.2%)
A4061051	Sorafenib	Tumor Ratio Week 6	0.860 (17.5%)	0.864 (14.8%)	0.882 (13.3%)
A6181034	IFN α	Tumor Ratio Week 6	1.023 (18.4%)	1.016 (17.6%)	1.005 (17.2%)
A6181034	Sunitinib	Tumor Ratio Week 6	0.822 (20.0%)	0.825 (18.7%)	0.830 (17.9%)
B9991002	Avelumab+Axitinib	Tumor Ratio Week 6	0.776 (31.7%)	0.772 (26.8%)	0.793 (24.2%)
B9991003	Avelumab+Axitinib	Tumor Ratio Week 6	0.774 (24.9%)	0.777 (22.5%)	0.786 (21.5%)
B9991003	Sunitinib	Tumor Ratio Week 6	0.884 (25.4%)	0.875 (23.6%)	0.873 (23.4%)
A4061051	Axitinib	Tumor Ratio Week 8	0.812 (40.2%)	0.810 (35.9%)	0.820 (35.2%)
A4061051	Sorafenib	Tumor Ratio Week 8	0.862 (18.4%)	0.863 (17.1%)	0.874 (15.8%)
A6181034	IFN α	Tumor Ratio Week 8	1.035 (24.3%)	1.025 (23.2%)	1.012 (22.6%)
A6181034	Sunitinib	Tumor Ratio Week 8	0.801 (24.2%)	0.797 (22.8%)	0.800 (22.0%)
B9991002	Avelumab+Axitinib	Tumor Ratio Week 8	0.750 (40.5%)	0.738 (33.2%)	0.756 (30.8%)
B9991003	Avelumab+Axitinib	Tumor Ratio Week 8	0.741 (31.4%)	0.737 (28.1%)	0.744 (27.2%)
B9991003	Sunitinib	Tumor Ratio Week 8	0.874 (31.8%)	0.854 (28.8%)	0.848 (29.1%)

Repository artifact ID FI-3035962.

Data are median (min; max) for TTG. Data are geometric mean (geometric % CV) for tumor ratio.

Table abbreviations: CV = coefficient of variation, TGI = tumor growth inhibition, TTG = time to tumor growth

As can be seen from Table 11, TTG typically trended to be shorter with the 24 weeks or the 12 weeks models as compared to the model using full data, across all treatments and studies. On the other hand, the derived TS_{ratio} at weeks 6 and 8 are generally similar between the models with full data, data to 24 weeks, or even data to 12 weeks. Derivations of other clinical endpoints (eg., PFS) may be explored in subsequent analyses.

7. DISCUSSION

The tumor data from 4 clinical studies in patients with RCC: A4061051, A6181034, B9991002, and B9991003 with 5 different first-line treatments (1839 total patients with 12356 observations) were adequately characterized by the model previously reported by Claret et al in second line patients with RCC. Other TGI models with immunotherapy agents have been limited. Bruno et al presented data on a TGI model based on Phase 2 data with atezolizumab (an antibody against PD-L1) in non-small cell lung cancer and urothelial cancer [13], which concluded that TGI to OS modeling framework can predict the hazard ratios for OS in Phase 3 studies in these tumor types. In both tumor types, the modeling compared atezolizumab with traditional chemotherapy and showed a slower growth and deep and durable response with immunotherapy. Until now, TGI modeling with immunotherapy combination therapy in RCC has not been reported.

The typical values for the TGI parameters were 0.140 years⁻¹ for K_L , 1.606 years⁻¹ for K_D , and 3.976 years⁻¹ for λ for the reference treatment of sunitinib. Treatment was a statistically significant covariate on all 3 model parameters and baseline SLD was a statistically significant covariate on K_D . The VPC, after accounting for dropping out of the study with progressive disease per RECIST criteria, did not show any systematic bias or model misspecification.

In terms of the impact of treatment on model parameters and derived early tumor metrics, the trends were consistent with the clinical practice/knowledge of preferred therapy for first-line RCC. For the oldest regimen, interferon- α , the derived TS_{ratio} at weeks 6 and 8 were highest compared to the other oral TKIs (eg., sunitinib, axitinib, and sorafenib) and the immunotherapy combination treatment. For the most recently approved first-line therapy combination of avelumab+axitinib, the derived TS_{ratio} at weeks 6 and 8 were both below 1. For the TTG metric, combination avelumab+axitinib treatment demonstrated the longest median TTG at approximately 9 weeks over the single-agent oral TKIs and interferon- α treatments (TTG range approximately 3.7 to 5.1 weeks).

Baseline SLD was a statistically significant covariate on K_D , where, patients in the lower quartile of baseline SLD trended to have higher K_D . In other words, patients with smaller baseline tumors trended to have higher cell kill rate. In terms of early tumor metrics, smaller baseline tumors (lowest quartile for baseline SLD) trended to have longer TTG and lower TS_{ratio} at both weeks 6 and 8.

Other derived clinical endpoints (eg., TTP and TTR) were evaluated based on individual model parameter estimates and definitions per the currently used RECIST v 1.1 criteria [12]. For TTP, Study A6181034 reported median (95% CI) TTP was 49.1 (46.6 to 59.1) weeks for

sunitinib treatment and 22.4 (21.9 to 31.3) weeks for interferon- α treatment. This is longer than the derived median TTP of 34.6 weeks and 11.3 weeks for sunitinib and interferon- α , respectively. The discordance may be due to the use of different definitions of progression at the time of study conduct (study start in 2004), which used an older RECIST definition for progression of at least 20% increase in sum of diameters [14] versus the current RECIST v 1.1 definition of at least 20% increase and an absolute increase of 5 mm in sum of diameters [12]. TTR was reported for Study B9991002 and Study B9991003. The median derived TTG from the model in Study B9991002 were consistent with what was reported in the clinical study report (7.0 weeks versus 6.4 weeks) for the avelumab+axitinib combination treatment. The median derived TTR from the model for avelumab+axitinib treatment was similar (11.9 weeks) to the reported 2.6 months (or 10.4 weeks) in the study. As this analysis only evaluated two covariates, other factors may contribute to the clinical endpoints that were not accounted for in this tumor kinetics model.

One of the objectives of this analyses was to derive early TGI metrics that could be subsequently tested in future analyses to predict clinical outcomes (eg., PFS, OS). If the subsequent analyses find that early tumor metrics or the TGI parameters may be important predictors of survival, then it would be important to be able to utilize the model to inform on future studies. Thus, it is important to know whether observed data only at earlier time points (eg., up to 12 weeks or 24 weeks) to derive TGI metrics may be useful in predicting survival probabilities. This analysis evaluated the final model parameters and derived TGI metrics after truncating the observed data empirically to 12 and 24 weeks (as compared to the final model using full data). With fewer data (eg., 12 weeks of data), the model parameters K_L , K_D , and λ differed from the final model using full data by >15%. However, the derived TGI metric of TS_{ratio} at weeks 6 and 8 were similar between the final model using full data and the models using truncated data across studies and treatments, indicating this metric may have some utility when only observed data at early stages are available.

8. CONCLUSIONS

- The tumor kinetics from first-line patients with RCC from 4 clinical studies and 5 different treatments were well characterized by the Claret model;
- Treatment was a significant covariate for all three model parameters: K_L , K_D , and λ ;
- Baseline SLD was a significant covariate on K_D where smaller tumors at baseline trended to have higher K_D compared to patients with larger tumors at baseline;
- TTG was longest for the most recently approved first-line treatment of combination therapy of avelumab+axitinib and shortest for the oldest regimen: interferon- α . Similarly, TS_{ratio} at weeks 6 and 8 were below 1 for the combination immunotherapy regimen, and highest for interferon- α ;
- The typical values for K_L , K_D , and λ were different (>15% change) using truncated observed data as compared to full data. However, the derived early tumor metrics of TS_{ratio} at weeks 6 and 8 were similar.

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B999e
Avelumab, Axitinib, Sunitinib
ASR-EQDD-B999e-Other-994

Appendix 2. Data File Specifications

The next 52 pages are an external document with Repository artifact ID FI-637816.



AG-013736

Protocol: A4061051

Dataset type: PD

Version: Data set release

Final PK/PD Programming Plan, 01Nov2019

PK/PD Programming Plan

Reporting Event Version	Date	Author	Changes/Comments
1	20-Jun-2019	Zhang, Fangrong	Initial version
1.1	28-Jun-2019	Zhang, Fangrong	1. Removed second line patients per analyst's confirmation. 2. Added EVID, EVNT per analyst's request. 3. Updated ID per analyst's request.
1.2	11-Jul-2019	Zhang, Fangrong	Updated CENS for OS and PFS records.
1.3	30-Jul-2019	Zhang, Fangrong	1. LIVMET/LNGMET/BONEMET were set to 0 instead of "." for no baseline liver/lung/bone metastases records . 2. if baseline value was missing in source data, then we took the first value for the patient (even if post first dose) as baseline value per analyst's request. 3. Updated EVID to 0 for FLAGE=3 records per analyst's request.
1.4	20-Aug-2019	Zhang, Fangrong	1. Changed missing values ("." in last version) to -999 per analyst's request. 2. Set to -999 for LIVMET, LNGMET and BONEMET for the subjects without dose information.
1.5	25-Sep-2019	Zhang, Fangrong	Added DOSRED, DOSINT per analyst's request.

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**DMB09-GSOP-
RF06 2.0**

**PK/PD PROGRAMMING
PLAN TEMPLATE**

01-May-2019

AG-013736

Protocol: A4061051

Dataset type: PD

Version: Data set release

Final PK/PD Programming Plan, 01Nov2019

1.6	10-Oct-2019	Zhang, Fangrong	Updated MSKCC per analyst's request.
1.7	23-Oct-2019	Zhang, Fangrong	Added BLYM per analyst's request.
Final	01-Nov-2019	Zhang, Fangrong	Removed "Draft" in header and updated version date

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AG-013736

Protocol: A4061051

Dataset type: PD

Version: Data set release

Final PK/PD Programming Plan, 01Nov2019

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AG-013736

Protocol: A4061051

Dataset type: PD

Version: Data set release

Final PK/PD Programming Plan, 01Nov2019

1. Summary Request Information

Date of Request:	Wednesday, June 5, 2019 6:38 AM
Job ID:	NA

Note: In the table below, please include the names of all PK/PD programmers, PK/PD POCs and PK/PD analysts who perform a significant amount of work on this request.

	<i>Name</i>	<i>Start date*</i>	<i>Stop date**</i>	<i>e-mail address</i>
PK/PD Programmer, CRO name:	Zhang, Fangrong; Cai, Xiaoli	5-Jun-2019	1-Nov-2019	Fangrong.Zhang@pfizer.com ; Xiaoli.Cai@pfizer.com
CRO PK/PD Point of Contact	NA	NA	1-Nov-2019	NA
CPW PK/PD Support POC:	Salatka, Ken	5-Jun-2019	1-Nov-2019	Ken.Salatka@pfizer.com
Requesting Analyst:	Lin, Swan	5-Jun-2019	1-Nov-2019	Swan.Lin@pfizer.com

**Start date of work on this particular project.*

***Stop date is either the*

- date of the FINAL data file delivery*
- or the date that the colleague finished working on this project if they moved on before the FINAL was delivered.*

Approximate date is acceptable if the actual date is unknown. Indicate such in the above table.

2. Objectives

This request is to create a PD dataset for A4061051.

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Protocol: A4061051

Dataset type: PD

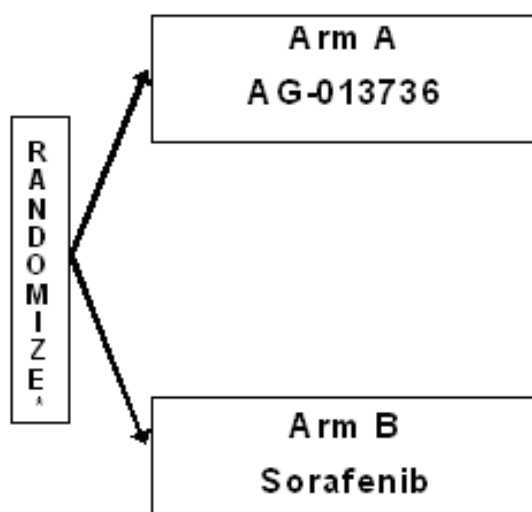
Version: Data set release

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3. Study Design

This is a 2-arm, randomized, open-label, multi-center Phase 3 study of AG-013736 vs sorafenib in patients with mRCC. A total of approximately 447 patients (approximately 247 treatment-naïve patients and approximately 200 previously-treated Asian patients) will be randomized in a 2:1 ratio between AG-013736 vs. sorafenib. Treatment-naïve patients will be stratified by ECOG performance status (0 vs 1). Previously-treated Asian patients will be stratified by ECOG performance status (0 vs 1) and by prior therapy (sunitinib-containing regimen vs cytokine-containing regimen). The on-study tumor assessment will be performed every 6 weeks X 2 then every 8 weeks by calendar to determine the PFS.

Study Schema:



*2:1 randomization, treatment-naïve patients will be stratified by ECOG performance status (0 vs 1). Previously-treated Asian patients will be stratified by ECOG performance status (0 vs 1) and by prior therapy (sunitinib-containing regimen vs cytokine-containing regimen).

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Protocol: A4061051
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4. Study File Reference

4.1 Name of CDARS SAS Data sets, Programs and Locations:

CDARS reporting system interface information

Site: groton
Project: A406
Submission: pkpd3
Protocol: A4061051_PD_2
Deliverable: PD VA Output Dataset Production with Laboratory Data
ToT: pd_2.tot

SAS data set:

/Volumes/app/cdars/prod/sites/groton/prjA406/pkpd3/A4061051_PD_2/saseng/pds1_0/data_vai/
pd_2.sas7bdat

SAS program:

/Volumes/app/cdars/prod/sites/groton/prjA406/pkpd3/A4061051_PD_2/saseng/pds1_0/macros/
pd_2.sas

4.2 Completed PK CSV Data set Name:

CDARS –

/Volumes/app/cdars/prod/sites/groton/prjA406/pkpd3/A4061051_PD_2/saseng/pds1_0/data_vai/
A4061051_PD_2_31OCT2019.csv

improve –

/root/_pkpd_star/A406 AG013736 Axitinib/A4061051/prod/output_data/
A4061051_PD_2_31OCT2019.csv

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4.3 Storage of Documents

Programming Plan Location:

/root/_pkpd_star/A406 AG013736 Axitinib/A4061051/prod/documents/
A4061051_PD_2_Programming_Plan.doc

Dataset Request Form Location:

/root/_pkpd_star/B999 MSB0010718C Avelumab/B9991003_restricted/prod/documents/
Global_Data_Request_Form_PMAR994_30MAY2019.xlsm

Issues Tracking Spreadsheet Location:

/root/_pkpd_star/B999 MSB0010718C Avelumab/B9991003_restricted/prod/documents/
B999e_Other_994_Combined_PD_2_Query.xls

Global PK/PD QC Checklist Location (Test Plan):

/root/_pkpd_star/A406 AG013736 Axitinib/A4061051/prod/documents/
A4061051_PD_2_QC.doc

Mail Messages:

/root/_pkpd_star/B999 MSB0010718C Avelumab/Mail Messages/
A4061051 A6181034 B9991002 1003 PD Finalization Confirmation.msg

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Protocol: A4061051

Dataset type: PD

Version: Data set release

Final PK/PD Programming Plan, 01Nov2019

5. Input Data Origin

OC data set release date: 25-Sep-2012

Note: DBR date was confirmed from analyst by email.



RE

EQDD-B999e-Oth

Table 1: Input Data set Origin

Data Set Name	Description of Data set	Date and Time that the source data set was extracted or created mm/dd/yyyy	Date that the data set was copied over to PK/PD Programming area from the source mm/dd/yyyy y HH:MM	Source Data Obtained and Verified From:	Folder location of source data set

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**DMB09-GSOP-RF06 2.0****PK/PD PROGRAMMING
PLAN TEMPLATE****01-May-2019**

AG-013736

Protocol: A4061051

Dataset type: PD

Version: Data set release

Final PK/PD Programming Plan, 01Nov2019

random	Randomization dataset	09/25/2012	06/19/2019 4:00 PM	Refer to A4061051_PD_Programming plan (improve Artifact ID: RA7590721)	/Volumes/app/cdars/prod/prjA406/nda3/A4061051_1stLine/saseng/pds1_0/data
testdrug	Dosing dataset	09/25/2012	06/19/2019 4:00 PM	Refer to A4061051_PD_Programming plan (improve Artifact ID: RA7590721)	/Volumes/app/cdars/prod/prjA406/nda3/A4061051_1stLine/saseng/pds1_0/data
cn_7_r	Prior Nephrectomy dataset	09/26/2012	06/19/2019 4:03 PM	Refer to A4061051_PD_Programming plan (improve Artifact ID: RA7590721)	/Volumes/app/cdars/prod/prjA406/nda3/A4061051_1stLine/saseng/pds1_0/data_vai
de1_1v	Demograp	09/25/2012	06/19/2019	Refer to	/Volumes/app/cdars/prod/prjA406/nda3/A4061051_1stLine/

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	hy value added dataset		4:04 PM	A4061051_P D_Programm ing plan (improve Artifact ID: RA7590721)	saseng/pds1_0/data_vai
eesrv_r	Overall response investigat or committee dataset	09/26/2012	06/19/2019 4:04 PM	Refer to A4061051_P D_Programm ing plan (improve Artifact ID: RA7590721)	/Volumes/app/cdars/prod/prjA 406/nda3/A4061051_1stLine/ saseng/pds1_0/data_vai
labs	Labs value added dataset	09/26/2012	06/19/2019 4:05 PM	Refer to A4061051_P D_Programm ing plan (improve Artifact ID: RA7590721)	/Volumes/app/cdars/prod/prjA 406/nda3/A4061051_1stLine/ saseng/pds1_0/data_vai
peedrsp_s a05_r	Overall response	10/12/2012	06/19/2019 4:03 PM	Refer to A4061051_P	/Volumes/app/cdars/prod/prjA 406/nda3/A4061051_1stLine/ saseng/pds1_0/data_vai

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Dataset type: PD

Version: Data set release

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	independent review committee dataset			D_Programming plan (improve Artifact ID: RA7590721)	
pfm_r	Time of Diagnosis dataset	09/26/2012	06/19/2019 4:04 PM	Refer to A4061051_P D_Programming plan (improve Artifact ID: RA7590721)	/Volumes/app/cdars/prod/prjA 406/nda3/A 4061051_1stLine/saseng/pds1_0/data_vai
primdiag	Primary Diagnosis dataset	09/25/2012	10/09/2019 3:07 PM	Refer to A4061051_P D_Programming plan (improve Artifact ID: RA7590721)	/Volumes/app/cdars/prod/prjA 406/nda3/A 4061051_1stLine/saseng/pds1_0/data
ptmm_r	Tumor Assessment for	09/26/2012	06/19/2019 4:03 PM	Refer to A4061051_P D_Programm	/Volumes/app/cdars/prod/prjA 406/nda3/A 4061051_1stLine/saseng/pds1_0/data_vai

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PLAN TEMPLATE****01-May-2019**

AG-013736

Protocol: A4061051

Dataset type: PD

Version: Data set release

Final PK/PD Programming Plan, 01Nov2019

	Independent Review committee			ing plan (improve Artifact ID: RA7590721)	
vs_v	Vitals value added dataset	09/28/2012	06/19/2019 4:04 PM	Refer to A4061051_PD_Programming plan (improve Artifact ID: RA7590721)	/Volumes/app/cdars/prod/prjA406/nda3/A4061051_1stLine/saseng/pds1_0/data_vai

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6. Variables and Description

Dataset Sort Order: NSID, TAFD, FLAGE, SURT

Table 2: Output Variable Descriptions

Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
C	Comment Column	01.01.01	Derived subjects without dosing information, but with PD data were set to C.	Analyst Input Not Required.	Default value is C. If requested, this is required to be the first column of a NONMEM data set	Char up to 1 alpha-numeric C	\$1.	Char
PROT	Protocol Number	02.01.02	DE1_1V/protno prot=input(substr(p rotno,5,4), best.);	Analyst Input Not Required.	Numeric conversion from PROTNO. If PROTNO=A5411003 then PROT=1003. Example: 1003	integer up to 5 digits 1,2,3 ... n	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
NSID	Subject Identification Number	02.01.04	ALL DATASET/ subjid nsid=input(subjid,8.);	Analyst Input Not Required.	Eight digit subject ID number typically derived from SID or PID. Used as a key variable for merging data. This data should be numeric as sorting and merging by this number. It should also be a unique number for each subject. E.g. If PID=A5411003-10021001 then SUBJ=10021001. Example: 10021015	integer upto 8 digits	8.	Num
ID	Sequential number ID	02.02.01	Derived ID = 751 for first subject and then ID = ID + 1 incrementing for every subject		Unique for each subject, incrementing by 1 for each new subject Default: Initial value = 1.	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
STID	Unique Subject ID for NONMEM	02.02.02	Derived from ID (Derivation listed in sort order 02.02.01) STID =51000+id;	Analyst Input Not Expected.	Related to protocol If protocol is A1281023 and patient number is 1 then ID is 23001. Exceptions made for large studied >1000 subjects or unusual protocol numbers. ID is directly mapped to subject ID such that they are comparable if subjects are excluded.	integer up to 5 digits 1,2,3 ... n.	5.	Num
DOSE	Actual Dose the subject received (for interferon alpha, sunitinib, sorafenib, or axitinib)	03.01.02	TESTDRUG/dostotr		Carried forward till next dose. It is not occasion-specific. Default: units = mg Default: Screening = -999 Default: Follow-up = -999 Default: If pre-dose records exist prior to	Up to 8 digits can include decimal places	BEST8.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
					first dose then = -999, else value will carry forward from previous dose.			
DOSEP	Planned First Dose the subject received (for interferon alpha, sunitinib, sorafenib, or axitinib)	03.01.02.01	Derived First planned dose that the subject received.			Up to 8 digits can include decimal places	BEST8.	Num
DOSIV	Actual avelumab dose received	03.01.03	No corresponding information collected in source data. All values of this field are missing.		Carried forward till next dose. It is not occasion-specific. Default: units = mg Default: Screening = -999 Default: Follow-up = -999	Up to 8 digits can include decimal places	BEST8.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
					Default: If pre-dose records exist prior to first dose then = -999, else value will carry forward from previous dose.			
DOS1VP	Planned First avelumab dose received	03.01.03.01	No corresponding information collected in source data. All values of this field are missing.			Up to 8 digits can include decimal places	BEST8.	Num
DOS2	Dose administered per kg of body weight (only for avelumab treatment)	03.02.01	No corresponding information collected in source data. All values of this field are missing.	Analyst Input Not Required.	Dose administered is in the units specified for DOSE.	Up to 8 digits can include decimal places	BEST8.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
DOS2P	Planned First Dose administered per kg of body weight (only for avelumab treatment)	03.02.010.01	No corresponding information collected in source data. All values of this field are missing.			Up to 8 digits can include decimal places	BEST8.	Num
TRT	Subject Treatment	03.07.01	TESTDRUG/drgname 3 = Sorafenib 4 = AG-013736		1 = interferon alpha from A6181034; 2 = sunitinib from A6181034, B9991002, or B9991003; 3 = sorafenib from A4061051; 4 = axitinib from A4061051; 5 = avelumab+axitinib from B9991002 or B9991003	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
TRTG	Treatment Group Label	03.10.02	TESTDRUG/drgname		Treatment Group (text description) is derived from CDARS actual treatment variable TREATTXT. Commas and hyphens will be removed. Spaces will be replaced with underscores (_). (or analyst defined).	Char up to 80 alpha-numeric	\$80.	Num
PERD	Period	05.03.01	Derived For SLD: PTMM_R/cpevent For OS & PFS: set to missing. Details please see section 8.2.		1 2 3 or 4 etc. Derived from CPEVENT or similar variable for each data type.	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
NTPD	Nominal Time Post Dose	05.05.01	Set to missing since no corresponding information collected.	Analyst Input Not Required.	Nominal Time Post Dose and is not OCC-specific. Default: units = hours (decimal)	Up to 5 digits can include decimal places	BEST5.	Num
DAY	Derived day	05.06.01	Derived If date<factdat then day=date-factdat; else day=date-factdat+1;	Analyst Input Not Required.	day=date-factdat+1	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
TAFD	Time After Subject's Very First Trt Dose	05.07.02	Derived Tafd = (date-factdat)/7; Round to 0.01 Unit: week	Please change the units from hours to weeks	Time After Subject's Very First Treatment Dose Does NOT reset at start of occasion. Default: units = hours Default: Pre-dose = 0 Default: Screening = -999 Default: Follow-up = -999	Up to 8 digits can include decimal places	BEST8.	Num
FLAGE	Flag efficacy	06.03.01	Derived 1 = OS; 2 = PFS; 3 = SLD (SLD = sum of longest diameter or	1 = OS; 2 = PFS; 3 = SLD (SLD = sum of longest diameter or tumors)	150-199 = Efficacy flags	integer up to 5 digits 150, 151, 152 ... 199.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			tumors)					
AGE	Age	07.01.01	DE1_1V/age If value is "." then set to -999.	Analyst Input Not Expected.	Default: units = years	integer up to 5 digits 1,2,3 ... n.	5.	Num
SEX	Gender Code	07.02.01	DE1_1V/sex if sex=1 then _sex=0; else if sex=2 then _sex=1; If value is "." then set to -999.	Use same coding as in popPK dataset which matched EMD coding. See as provided.	0 = Male 1 = Female	integer up to 5 digits 1,2,3 ... n.	5.	Num
RACE	Race	07.03.01	DE1_1V/races 1 = white 2 = black 3 = Asian	Use same coding as in popPK dataset which matched EMD	1=White 2=Black or African American 3=Asian 4=American Indian or	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			4 = other If value is "." then set to -999.	coding. See as provided.	Alaska native 5=Native Hawaiiin or other Pacific Islander 6=Other .=missing			
ETHN	Ethnicity	07.03.02	Derived DE1_1V/raciald If raciald=15 then ETHN=1 Else ETHN=2 Refer to A4061051_PD_Programming plan (improve Artifact ID: RA7590721). If value is "." then set to -999.	Analyst Input Not Required.	Use PDS codelist. 1 = HISPANIC/LATINO 2 = NOT HISPANIC/LATINO	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
RACD	Racial Designation	07.03.03	DE1_1V/raciald If value is "." then set to -999.	Analyst Input Not Required.	Use PDS codelist. 1 = INDIAN SUBCONTINENT ASIAN 2 = SOUTHEAST ASIAN 3 = FAR EAST ASIAN 4 = ALASKAN NATIVE 5 = PACIFIC ISLANDER 6 = NORTH AMERICAN INDIAN 7 = NATIVE HAWAIIAN	integer up to 5 digits 1,2,3 ... n.	5.	Num
BWT	Weight in Kg (Baseline)	07.05.02	VS_V/vsstres where vstestcd=20 and vsstres ne . and vsbflag="B"; if there is no baseline record, then take the first	Analyst Input Not Expected.	Default: unit = kg Baseline value of weight is used	Up to 5 digits can include decimal places	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			record after dose as baseline value per analyst's request. If value is "." then set to -999.					
SMOK	Smoking Classification	07.07.01	Set to missing since no corresponding information collected. If value is "." then set to -999.	Analyst Input Not Required.	Use PDS codelist. 1 = never smoked 2 = smoker 3 = ex-smoker	integer up to 5 digits 1,2,3 ... n.	5.	Num
BBMI	Body Mass Index (Baseline)	07.10.02	Derived bbmi=round(bwt/(bht**2),0.01); If value is "." then set to -999.	Analyst Input Not Required.		Up to 5 digits can include decimal places	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
BCCL	Creatinine Clearance (Baseline)	10.01.02	LABS/lab_std Where labcode=48 Men: $(140 - \text{age}) * \text{bwt} / (72 * \text{bscr})$ Women: $(140 - \text{age}) * \text{bwt} * 0.85 / (72 * \text{bscr})$ Baseline is the last record on or before first dose date If value is "." then set to -999.	Analyst Input Not Required.	Default for Subjects 13 years or older, uses Cockcroft & Gault formula for Subjects less than 13 years old, uses Schwartz formula Methods available: Cockcroft & Gault (subjects ≥ 13 yr) Schwartz (subjects < 13 yr) * Note all calculations use the Baseline value for input variables	Up to 8 digits can include decimal places	BEST8.	Num

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**PK/PD PROGRAMMING
PLAN TEMPLATE**

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AG-013736

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Dataset type: PD

Version: Data set release

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
BCAL	Corrected Calcium (Baseline)	10.02.02	LABS/lab_std BCAL- labcode=58 BALB- labcode=25 BCORCLA = BCAL - 0.707*(BALB - 3.4) Drop BCAL; Rename BCORCLA=BCAL Baseline is the last record on or before first dose date. if there is no baseline record, then take the first record after dose as baseline value	Analyst Input Not Required.	Standard units: mg/dL	Up to 5 digits can include decimal places	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			per analyst's request. If value is "." then set to -999. Unit: mg/dL					
BPLT	Platelets (Baseline)	10.04.02	LABS/lab_rslt where labcode=5 Baseline is the last record on or before first dose date. if there is no baseline record, then take the first record after dose as baseline value per analyst's request.	Analyst Input Not Required.	Units = 10^9 cells/L	Up to 5 digits can include decimal places	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			If value is "." then set to -999. Unit: 10 ⁹ /L					
BNEU	Normalised Neutrophils (Baseline)	10.05.02	LABS/lab_rslt where labcode=608 Baseline is the last record on or before first dose date. if there is no baseline record, then take the first record after dose as baseline value per analyst's request.	Analyst Input Not Required.	Units = 10 ⁹ /L	Up to 5 digits can include decimal places	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			If value is "." then set to -999. Unit: 10 ⁹ /L					
BHGB	Hemoglobin (Baseline)	10.10.02	LABS/lab_std where labcode=1 Baseline is the last record on or before first dose date. if there is no baseline record, then take the first record after dose as baseline value per analyst's request. If value is "." then	Analyst Input Not Required.	Standard units: g/dL	Up to 5 digits can include decimal places	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			set to -999. Unit: g/dL					
BALB	Normalised Albumin (Baseline)	10.10.03	LABS/lab_std where labcode=25 Baseline is the last record on or before first dose date. if there is no baseline record, then take the first record after dose as baseline value per analyst's request. Unit: g/dL	Analyst Input Not Required.	Units:g/dL	Up to 5 digits can include decimal places	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			If value is "." then set to -999.					
BLDH	Lactic Acid Dehydrogenase (baseline)	10.11.02	LABS/lab_std where labcode=32 Baseline is the last record on or before first dose date. if there is no baseline record, then take the first record after dose as baseline value per analyst's request. Unit: U/L	Analyst Input Not Required.	Units = U/L	Up to 5 digits can include decimal places	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			If value is "." then set to -999.					
BALT	Normalised ALT (Baseline)	10.12.02	LABS/lab_std where labcode=30 Baseline is the last record on or before first dose date. if there is no baseline record, then take the first record after dose as baseline value per analyst's request. Unit: U/L If value is "." then	Analyst Input Not Required.	Standard units: U/L	Up to 5 digits can include decimal places	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			set to -999.					
BAST	Normalised AST (Baseline)	10.13.02	LABS/lab_std where labcode=28 Baseline is the last record on or before first dose date. if there is no baseline record, then take the first record after dose as baseline value per analyst's request. Unit: U/L	Analyst Input Not Required.	Standard units: U/L	Up to 5 digits can include decimal places	BEST5.	Num

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Dataset type: PD

Version: Data set release

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			If value is "." then set to -999.					
BBIL	Normalised Bilirubin (Baseline)	10.14.02	LABS/lab_std where labcode=21 Baseline is the last record on or before first dose date. if there is no baseline record, then take the first record after dose as baseline value per analyst's request. Unit: mg/dL	Analyst Input Not Required.	Standard units: mg/dL	Up to 5 digits can include decimal places	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			If value is "." then set to -999.					
BSLD	Tumor burden at baseline (mm), sum of longest diameter	99.99.01	PTMM_R/curntsld where curntsld ne . and index(readtype,"ACCEPT")>0 and lestypen=1; Baseline is the last record on or before first dose date. if there is no baseline record, then take the first record after dose as baseline value	Tumor burden at baseline (mm), sum of diameter of target lesions	mm	e.g. 5	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			per analyst's request. Unit: mm					
SLD	Tumor burden (mm)	99.99.02	PTMM_R/curntslid where curntslid ne . and index(readtype,"A CCEPT")>0 and lestypen=1; Unit: mm	tumor burden at current time (mm)	LOCF	e.g. 5	5.	Num
SURT	Survival time	99.99.03	PEEDRSP_sa05_ R/evaluated EESRV_R/ evaluated Unit: Week	For OS or PFS, time of event (in weeks)		e.g. 5	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
CENS	Censoring	99.99.04	PEEDRSP_sa05_ R/event EESRV_R/event if event="Y" then cens=0; else cens=1;	For OS or PFS, censoring	0 = not censored; 1 = censored event	integer up to 5 digits 1,2,3 ... n.	5.	Num
ECOG	ECOG status at baseline	99.99.05	PFM_R/pfmecog If value is "." then set to -999.	ECOG status at baseline		0,1,2,etc.	5.	Num
METS	Metastatic disease site	99.99.06	PTMM_R/tmmdis If value is "." then set to -999.	Number of metastatic sites at baseline		e.g. 5	5.	Num
LIVMET	Presence of liver metastases	99.99.07	PTMM_R/tmmdis If index(tmmdis,"LIV			0 = absent ; 1 = present	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			ER")>0 then livmet=1; else set to 0. If value is "." then set to -999.					
LNGMET	Presence of lung metastases	99.99.08	PTMM_R/tmmdis If index(tmmdis,"LU NG")>0 then livmet=1; else set to 0. If value is "." then set to -999.			0 = absent ; 1 = present	5.	Num
BONMET	Presence of bone metastases	99.99.09	PTMM_R/tmmdis If index(tmmdis,"BO NE")>0 then livmet=1; else set to 0.			0 = absent ; 1 = present	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			If value is "." then set to -999.					
MSKCC	Memorial Sloan-Kettering Cancer Center (MSKCC/Motzer) Score for Metastatic Renal Cell Carcinoma (RCC)	99.99.10	Derived Details please see section 8.6: for draft#7.		0 = favorable risk; 1 = intermediate risk (1-2 factors); 2 = poor risk (3 or more factors) -999= no related information was collected to derive 5 risk factors	integer up to 5 digits 1,2,3 ... n.	5.	Num
HENG	Heng criteria	99.99.11	Set to missing since no corresponding information collected. If value is "." then		0 = favorable risk; 1 = intermediate risk (1-2 factors); 2 = poor risk (3 or more factors)	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			set to -999.					
EGFR	eGFR (baseline)	99.99.12	Derived eGFR (mL/min/1.73m ²) = 175 × (CREAT) 1.154 × (Age) 0.203 × (0.742 if female) × (1.212 if African American) Baseline is the last record on or before first dose date. if there is no baseline record, then take the first			0.1,2,etc.	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			record after dose as baseline value per analyst's request. age unit: year creatinine unit: mg/dl If value is "." then set to -999.					
EVID	Event identification	99.99.13	Derived For OS and PFS records, For start rows, evid=3; For end rows, evid=0; For SLD records, evid=0.	For FLAGE=1 and FLAGE=2 (OS and PFS), currently there is 1 occurrence (row) per patient. For the analysis, please duplicate this row so that		e.g. 5	5.	Num

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PLAN TEMPLATE****01-May-2019**

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
				there are 2 per patient. The 2 rows will represent the START and the END of OS or PFS. Then, we need to add two additional columns in order to identify START or END: EVID and EVNT, where EVID=3 for START of OS or PFS and EVID=0 for the END of OS or PFS. Then, for				

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
				EVID=3, please change SURT to 0 for the START time of 0 weeks.				
EVNT	Dependent variable event	99.99.14	Derived For OS and PFS, If evid=3 then evnt=0; If evid=0 and cens=0 then evnt=1; If evid=0 and cens=1 then evnt=0; For SLD records, evnt=0.	When EVID=3, EVNT=0; When EVID=0 and CENS=0, EVNT=1; When EVID=0 and CENS=1, EVNT=0; For FLAGE=3 (SLD), EVID=1 and EVNT=0.		e.g. 5	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
DOSRED	Dose Reduction Category	99.99.15	Derived If dose was reduced during treatment then 3 = dose reduced sorafenib 4 = dose reduced axitinib; Else dosred=0. We ignored all dose=0 recrds for dose reduction per analyst's confirmation.	Dose reduction category to indicate whether a patient had at least one dose reduction of a treatment	0 = no dose reductions 1 = dose reduced interferon-alpha from A6181034 2 = dose reduced sunitinib from A6181034, B9991002, or B9991003 3 = dose reduced sorafenib from A4061051 4 = dose reduced axitinib 5 = dose reduced avelumab from B9991002 or B9991003 45= dose reduced on both axitinib and avelumab	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
DOSINT	Dose Interruption Category	99.99.16	TESTDRUG/dosint If dosint = "Y" and trtg="SORAFENIB" then dosint=3; else if dosint="Y" and trtg="AG_013736" then dosint=4; else dosint=0. We took records of dose=0 into account when deriving DOSINT.	Dose interruption category to indicate whether a patient had at least one dose interruption of a treatment	0 = no dose interruption 1 = dose interruption interferon-alpha from A6181034 2 = dose interruption sunitinib from A6181034, B9991002, or B9991003 3 = dose interruption sorafenib from A4061051 4 = dose interruption axitinib 5 = dose interruption avelumab from B9991002 or B9991003 45 = dose interruption on both avelumab and axitinib	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
BLYM	Lymphocyte (Baseline)	99.99.17	LABS/lab_std where labcode=611 Baseline is the last record on or before first dose date. if there is no baseline record, then take the first record after dose as baseline value per analyst's request. If value is "." then set to -999. Unit: 10 ⁹ /L	Please add an additional variable – baseline lymphocyte from the CBC test	Standard units: 10 ⁹ /L	Up to 5 digits can include decimal places	BEST5.	Num

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7. Test Plan

The software will be tested by completing the Global PK/PD QC checklist and executing the global PK/PD QC automated checks macro in accordance with the PK/PD QC guidelines and OPD. The output PDF produced by the PK/PD QC automated checks macro will reside in CDARS in the location listed in the completed QC checklist. Additional checks for the non-standard variables/derivations can be added to the checklist section 20. This checklist is located in improve in the folder listed in section 4.3 Storage of Documents.

8. Programming Notes

8.1 Source data

There are two DBR dates for this study.

1. DBR date: 25-Sep-2012
2. DBR Suppl date: 28-Jun-2021

Per analyst's confirmation, we use the Sep 2012 DBR.

8.2 Derivation of PERD

For OS & PFS: set PERD to missing.

For SLD: We set PERD based on CPEVENT as below:

CPE Name	PERD
Screening	-999
Baseline	0
Week 6	1
Week 12	2
Week 20	3
Week 28	4
Week 36	5
Week 44	6
Week 52	7
Week 60	8
Week 68	9

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Week 76	10
Week 84	11
Week 92	12
Week 100	13
Confirmation Scan	996
Unscheduled -- 1	997
Unscheduled -- 12-Ap	997
Unscheduled -- 27-Se	997
Unscheduled -- BS	997
Unscheduled -- C17D1	997
Unscheduled -- CT	997
Unscheduled -- Chest	997
Unscheduled -- Disco	997
Unscheduled -- EOT	997
Unscheduled -- Follo	997
Unscheduled -- Week	997
Unscheduled -- end o	997
Unscheduled -- week	997
Unscheduled -- wk 24	997
Unscheduled -- wk 25	997
Unscheduled / Unplanned	997
End of Treatment	998
Follow Up	999

8.3 Derivation of MSKCC

We derived MSKCC based on method from A4061051_PD_Programming plan (improve Artifact ID: RA7590721)

For MSKCC same formula used for both 1st and 2nd line Therapy so have used same code as used by CPW in

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Volumes/app/cdars/prod/prjA406/nda3/A4061051_1stLine/saseng/pds1_0/macros/MSKCC.sas

```
*--- Hemoglobin ---*;
      if HMG_STD eq . then HMG_rsk=.;
    else if .<HMG_STD < HMG_SMIN then HMG_rsk=1;
    else if HMG_STD >= HMG_SMIN>. then HMG_rsk=0;

*--- LDH ---*;
      if LDH_STD eq . then LDH_rsk=.;
    else if .<LDH_STD <= 1.5*LDH_SMAX then LDH_rsk=0;
    else if LDH_STD > 1.5*LDH_SMAX>. then LDH_rsk=1;

*--- Corrected Serum Ca ---*;
CaCorrct = Ca_STD - 0.707*(ALB_STD - 3.4);

      if CaCorrct eq . then CaC_rsk=.;
    else if CaCorrct > 10 then CaC_rsk=1;
    else if .<CaCorrct <=10 then CaC_rsk=0;

*--- Check for lab ---*;
Sum_LAB=HMG_rsk + LDH_rsk + CaC_rsk;

*--- Check for collection date for albimin and calcium ---*;
if CA_DATE ne ALB_DATE then ca_alb_dt_diff=1;

*--- Number of risk factor ---*;
Num_RSK=HMG_rsk + LDH_rsk + CaC_rsk + neph;

      if Num_RSK= . then mskcat=99;
    else if Num_RSK= 0 then mskcat=0;
    else if 1<=Num_RSK<=2 then mskcat=1;
    else if 3<=Num_RSK then mskcat=2;
```

Please note: we updated MSKCC derivation method in draft#7, details please see section 8.6.

8.4 C column

There were 3 subjects without dosing information, but with PD data, and marked as C in the PD dataset.

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8.5 Dose Merge Algorithm

We merged PD endpoints to the most recent dosing records per analyst's confirmation based on rules as below:

1. If dosages are same on the day, we merged to each dosage.
2. If there are zero and non-zero dose on the same day, we merge to non-zero dose.
3. If two dosages are non-zero dose, we choose the most recent visit to merge.
4. If two dosages are non-zero dose and in the same visit, we merge to PM dose.

8.6 Differences in datafile versions

For draft#2:

- a. Removed second line patients per analyst's confirmation.
- b. Added EVID, EVNT per analyst's request.
- c. Updated ID per analyst's request.

For draft#3:

We updated CENS values (0=not censored 1=censored) for OS and PFS records.

For draft#4:

- a. LIVMET/LNGMET/BONEMET were set to 0 instead of "." for no baseline liver/lung/bone metastases records .
- b. if baseline value was missing in source data, then we took the first value for the patient (even if post first dose) as baseline value per analyst's request.
- c. Updated EVID to 0 for FLAGE=3 records per analyst's request.

For draft#5:

- a. Changed missing values (AGE SEX RACE ETHN RACD BWT SMOK BBMI BCCL BCAL BPLT BNEU BHGB BALB BLDH BALT BAST BBIL ECOG METS LIVMET LNGMET BONMET MSKCC HENG EGFR , "." in last version) to -999 per analyst's request.
- b. Set to -999 for LIVMET, LNGMET and BONEMET for the subjects without dose information.

For draft#6:

Added DOSRED, DOSINT per analyst's request.

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For draft#7:

We used following risk factors to derive the MSKCC scores per analyst's request.

1. ECOG PS \geq 2
2. LDH > 1.5 times the ULN
3. Serum hemoglobin < LLN
4. Corrected serum calcium > 10 mg/dL
5. Time from initial diagnosis to study treatment start less than one year

In the criteria, ECOG, LDH, Serum hemoglobin, Corrected serum calcium were baseline values. For the fifth risk, the date of histopathological diagnosis (PRIMHDT) was used.

- If PRIMHDT was missing, then the 5th risk is missing;
- If first active dose date (FACTDAT) was missing, then the 5th risk was missing.
- If PRIMHDT and FACTDAT were not missing, FACTDAT-PRIMHDT+1<365 were considered as the 5th risk.

If the risk factors were missing for a subject, then MSKCC was set to -999.

If the risk factor criteria were not met for a subject, then MSKCC was set to 0.

If there were 1-2 risk factor criteria were met for a subject, then MSKCC was set to 1.

If there were 3 or more risk factor criteria were met for a subject, then MSKCC was set to 2.

For draft#8:

We added baseline lymphocyte (BLYM) from the CBC test per analyst's request.

For final:

Removed "Draft" in header and updated version date.

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B999e
Avelumab, Axitinib, Sunitinib
ASR-EQDD-B999e-Other-994

The next 50 pages are an external document with Repository artifact ID FI-637817.



SU011248

Protocol: A6181034

Data set type: PD

Version: Data set release

Final PK/PD Programming Plan, 01Nov2019

PK/PD Programming Plan

Reporting Event Version	Date	Author	Changes/Comments
1	20-Jun-2019	Tao, Xi	Initial Version
1.1	01-Jul-2019	Tao, Xi	1. Duplicated OS and PFS records 2. Added variables EVID and EVNT 3. Changed SURT to 0 for EVID=3 records
1.2	30-Jul-2019	Tao, Xi	1. Updated LIVMET, LNGMET and BONOMET for subjects without dose information 2. Updated baseline demographics/lab variables 3. Changed EVID from 1 to 0 for FLAGE=3 (SLD) records
1.3	20-Aug-2019	Pan, Yanzhuo	1. Changed missing values to “-999” for some variables 2. LIVMET, LNGMET and BONMET changed to -999 from 0 for the subjects without dose information
1.4	29-Sep-2019	Tao, Xi	Added variables DOSRED and DOSINT
1.5	10-Oct-2019	Tao, Xi	Updated the derivation algorithm of MSKCC
1.6	22-Oct-2019	Tao, Xi	Added variable BLYM
Final	01-Nov-2019	Tao, Xi	Removed “Draft” in header and updated version date

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1. Summary Request Information

Date of Request:	Wed 6/5/2019 9:55 AM
Job ID:	NA

Note: In the table below, please include the names of all PK/PD programmers, PK/PD POCs and PK/PD analysts who perform a significant amount of work on this request.

	<i>Name</i>	<i>Start date*</i>	<i>Stop date**</i>	<i>e-mail address</i>
PK/PD Programmer, CRO name:	Tao, Xi; Yu, Panpan Pan, Yanzhuo	05-Jun-2019	01-Nov-2019	Xi.Tao@pfizer.com Panpan.Yu@pfizer.com Yanzhuo.pan@pfizer.com
CRO PK/PD Point of Contact	NA	NA	NA	NA
CPW PK/PD Support POC:	Salatka, Ken	05-Jun-2019	01-Nov-2019	Ken.Salatka@pfizer.com
Requesting Analyst:	Lin, Swan	05-Jun-2019	01-Nov-2019	Swan.Lin@pfizer.com

**Start date of work on this particular project.*

***Stop date is either the*

- date of the FINAL data file delivery*
- or the date that the colleague finished working on this project if they moved on before the FINAL was delivered.*

Approximate date is acceptable if the actual date is unknown. Indicate such in the above table.

2. Objectives

The objective is to provide PD dataset of study A6181034 for analysis.

3. Study Design

This study was a randomized, multi-center, international, Phase 3 comparison of

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sunitinib (Arm A) vs IFN- α (Arm B) as first-line therapy in subjects with MRCC. Subjects received treatment with either sunitinib in repeated 6-week cycles, consisting of 4 weeks of 50 mg daily sunitinib administration followed by 2 weeks off treatment (Schedule 4/2), or IFN- α , administered as a subcutaneous injection on 3 non-consecutive days each week.

Diagnosis and Main Criteria for Inclusion: Subjects with MRCC (with a component of clear cell histology) that had not previously been treated with systemic therapy were eligible to participate in the study if they had unidimensionally measurable disease, were at least 18 years of age, had adequate organ function, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Study Treatment: Subjects received either sunitinib or IFN- α . Sunitinib was administered as an oral capsule at 50 mg daily for 4 weeks followed by 2 weeks off treatment in repeated 6-week cycles of treatment. IFN- α (Roferon α -A, Roche) was administered as a subcutaneous injection in 6-week cycles on 3 non-consecutive days per week; Subjects received 3 MU per dose during the first week, 6 MU per dose the second week, and 9 MU per dose thereafter. Dose modifications were allowed for toxicity management on both arms. Sunitinib was approved by the US FDA for treatment of patients with advanced RCC in January 2006; following a protocol amendment in February 2006, subjects randomized to the IFN- α arm with documented disease progression were given an option to be treated with sunitinib on study.

Efficacy Evaluations: The primary efficacy endpoint was PFS, based on an independent core radiology laboratory assessment, in the intent-to-treat (ITT) population (all subjects who were randomized to treatment); supportive analyses of the primary endpoint were performed in the astreated population (AT; all subjects with available drug dosing information, with treatment assigned as actual treatment received) and evaluating PFS in the ITT and AT populations based on investigator assessment. The primary endpoint was further analyzed for the effects of baseline and stratification factors.

Secondary efficacy endpoints were TTP, ORR, OS, duration of response (DR), and PROs, based upon the Functional Assessment of Cancer Therapy (FACT) - General (G), the FACT - Advanced Kidney Cancer Symptom Index (FKSI), and the EuroQol EQ-5D Self-Report Questionnaire (EQ-5D). PRO endpoints include FACT-G Total score and its four subscales (Physical Well Being (PWB), Social/Family Well Being (SWB), Emotional Well Being (EWB) and Functional Well Being (FWB), FKSI score and its disease related symptoms subscale (FKSIDRS),

EQ-5D's Health State Index (EQ-5D Index) and Visual Analog Scale (EQ-VAS). The

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FKSI-DRS was pre-specified as the primary PRO endpoint. For all tumor assessments, response and progression were defined by the Response Evaluation Criteria in Solid Tumors (RECIST) and evaluated by an independent, third-party core radiology laboratory.

4. Study File Reference

4.1 Name of CDARS SAS Data sets, Programs and Locations:

CDARS reporting system interface information

Site: groton
Project: A618
Submission: pkpd3
Protocol: A6181034_PD_2
Deliverable: PD VA Output Dataset Production with Laboratory Data
ToT: pd.tot

SAS data set:

/Volumes/app/cdars/prod/sites/groton/prjA618/pkpd3/A6181034_PD_2/saseng/pds1_0/data_vai/
pd.sas7bdat

SAS program:

/Volumes/app/cdars/prod/sites/groton/prjA618/pkpd3/A6181034_PD_2/saseng/pds1_0/macros/
pd.sas

4.2 Completed PK CSV Data set Name:

CDARS -

/Volumes/app/cdars/prod/sites/groton/prjA618/pkpd3/A6181034_PD_2/saseng/pds1_0/data_vai/
A6181034_PD_2_31OCT2019.csv

improve - /root/_pkpd_star/A618 SU011248 Sunitinib Sutent /A6181034/prod/output_data/
A6181034_PD_2_31OCT2019.csv

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4.3 Storage of Documents

Programming Plan Location:

/root/_pkpd_star/A618 SU011248 Sunitinib Sutent /A6181034/prod/documents/
A6181034_PD_2_Programming_Plan.doc

Data set Request Form Location:

/root/_pkpd_star/B999 MSB0010718C Avelumab/B9991003_restricted/prod/documents/
Global_Data_Request_Form_PMAR994_30MAY2019.xlsm

Issues Tracking Spreadsheet Location:

/root/_pkpd_star/B999 MSB0010718C Avelumab/B9991003_restricted/prod/documents/
B999e_Other_994_Combined_PD_2_Query.xls

Global PK/PD QC Checklist Location (Test Plan):

/root/_pkpd_star/A618 SU011248 Sunitinib Sutent /A6181034/prod/documents/
A6181034_PD_2_QC.doc

Mail Messages:

/root/_pkpd_star/B999 MSB0010718C Avelumab/Mail Messages/A4061051 A6181034
B9991002 1003 PD Finalization Confirmation.msg

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5. Input Data Origin

External data base release date: NA

Note: As this is an old external study, we couldn't get the DBR notification email and DBR date is unknown.

Table 1: Input Data set Origin

Dataset Name	Description of Dataset	Date that the source data set was extracted or created mm/dd/yy yy HH:MM	Date that the data set was copied over to PK/PD Programming area from the source mm/dd/yyyy HH:MM	Source Data Obtained and Verified From:	Folder location of source data set
CONVLAB	Lab VA Dataset	07/07/2009	06/20/2019 10:12 AM	Analyst-Lin, Swan	/Volumes/app/cdars/prod/sites/lj/prjA618/ctc_csr1/A6181034/saseng/pds1_0/data/PRA_DATA/repository/data/withxover

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				 RE EQDD-8999e-Oth	
DER_TIME	Prior Radiation Therapy INV VA Dataset	07/07/2009	06/20/2019 10:12 AM	Same as above	/Volumes/app/cdars/prod/sites/lj/prjA618/ctc_csr1/A6181034/saseng/pds1_0/data/PRA_DATA/repository/d ata/withxover
DERDRUG	Doing VA Dataset	07/07/2009	06/20/2019 10:12 AM	Same as above	/Volumes/app/cdars/prod/sites/lj/prjA618/ctc_csr1/A6181034/saseng/pds1_0/data/PRA_DATA/repository/d ata/withxover
DERRADTIME	Efficacy IRX VA Dataset	07/07/2009	06/20/2019 10:12 AM	Same as above	/Volumes/app/cdars/prod/sites/lj/prjA618/ctc_csr1/A6181034/saseng/pds1_0/data/PRA_DATA/repository/d ata/withxover
MALHX	Malignancy History for RCC VA Dataset	07/07/2009	10/09/2019 02:40 PM	Same as above	/Volumes/app/cdars/prod/sites/lj/prjA618/ctc_csr1/A6181034/saseng/pds1_0/data/PRA_DATA/repository/d ata/withxover
POP_GEN	Demographics VA Dataset	07/07/2009	06/20/2019 10:12 AM	Same as above	/Volumes/app/cdars/prod/sites/lj/prjA618/ctc_csr1/A6181034/saseng/pds1_0/data/PRA_DATA/repository/d ata/withxover
RAD_LESION	Efficacy IRC Dataset	07/07/2009	06/20/2019 10:12 AM	Same as above	/Volumes/app/cdars/prod/sites/lj/prjA618/ctc_csr1/A6181034/saseng/pds1_0/data/PRA_DATA/repository/d ata/withxover
VITALS	Vital Signs VA	07/07/2009	06/20/2019	Same as	/Volumes/app/cdars/prod/sites/lj/prjA618/ctc_csr1/A6

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	Dataset		10:12 AM	above	181034/saseng/pds1_0/data/PRA_DATA/repository/d ata/withxover
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6. Variables and Description

Data set Sort Order: NSID, DATE, FLAGE, EVID, EVNT**Table 2: Output Variable Descriptions**

Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
C	Comment Column	01.01.01	Derived Subjects with PD data but without dosing information were commented out.	Analyst Input Not Required.	Default value is C. If requested, this is required to be the first column of a NONMEM data set	Char up to 1 alpha-numeric C	\$1.	Char
PROT	Protocol Number	02.01.02	POP_GEN/prot	Analyst Input Not Required.	Numeric conversion from PROTNO. If PROTNO=A5411003 then PROT=1003. Example: 1003	integer up to 5 digits 1,2,3 ... n	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
NSID	Subject Identification Number	02.01.04	All datasets/ptno	Analyst Input Not Required.	Eight digit subject ID number typically derived from SID or PID. Used as a key variable for merging data. This data should be numeric as sorting and merging by this number. It should also be a unique number for each subject. E.g. If PID=A5411003-10021001 then SUBJ=10021001. Example: 10021015	integer upto 8 digits	8.	Num
ID	Sequential number ID	02.02.01	Derived ID = 1 for first subject and then ID = ID + 1 incrementing for every subject		Unique for each subject, incrementing by 1 for each new subject Default: Initial value = 1.	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
STID	Unique Subject ID for NONMEM	02.02.02	Derived from ID (Derivation listed in sort order 02.02.01) STID =34000+id;	Analyst Input Not Expected.	Related to protocol If protocol is A1281023 and patient number is 1 then ID is 23001. Exceptions made for large studied >1000 subjects or unusual protocol numbers. ID is directly mapped to subject ID such that they are comparable if subjects are excluded.	integer up to 5 digits 1,2,3 ... n.	5.	Num
DOSE	Actual Dose the subject received (for interferon alpha, sunitinib, sorafenib, or axitinib)	03.01.02	DERDRUG/avgddose		Carried forward till next dose. It is not occasion-specific. Default: units = mg Default: Screening = -999 Default: Follow-up = -999 Default: If pre-dose records exist prior to	Up to 8 digits can include decimal places	BEST8.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
					first dose then = -999, else value will carry forward from previous dose.			
DOSE P	Planned First Dose the subject received (for interferon alpha, sunitinib, sorafenib, or axitinib)	03.01.02.01	Derived No planned dose was collected in source data. First dose the subjects received was used.			Up to 8 digits can include decimal places	BEST8.	Num
DOSIV	Actual avelumab dose received	03.01.03	No avelumab dose for this study, so set it as missing.		Carried forward till next dose. It is not occasion-specific. Default: units = mg Default: Screening = -999 Default: Follow-up = -999 Default: If pre-dose	Up to 8 digits can include decimal places	BEST8.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
					records exist prior to first dose then = -999, else value will carry forward from previous dose.			
DOSIVP	Planned First avelumab dose received	03.01.03.01	No avelumab dose for this study, so set it as missing.			Up to 8 digits can include decimal places	BEST8.	Num
DOS2	Dose administered per kg of body weight (only for avelumab treatment)	03.02.01	No avelumab dose for this study, so set it as missing.	Analyst Input Not Required.	Dose administered is in the units specified for DOSE.	Up to 8 digits can include decimal places	BEST8.	Num
DOS2P	Planned First Dose administered per kg of body weight (only for avelumab)	03.02.010.01	No avelumab dose for this study, so set it as missing.			Up to 8 digits can include decimal places	BEST8.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
	treatment)							
TRT	Subject Treatment	03.07.01	DERDRUG/tmtregtx 1 = interferon alpha from A6181034; 2 = sunitinib from A6181034		1 = interferon alpha from A6181034; 2 = sunitinib from A6181034, B9991002, or B9991003; 3 = sorafenib from A4061051; 4 = axitinib from A4061051; 5 = avelumab+axitinib from B9991002 or B9991003	integer up to 5 digits 1,2,3 ... n.	5.	Num
TRTG	Treatment Group Label	03.10.02	DERDRUG/tmtregtx		Treatment Group (text description) is derived from CDARS actual treatment variable TREATTXT. Commas and hyphens will be removed. Spaces will be replaced with underscores (_). (or	Char up to 80 alpha-numeric	\$80.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
					analyst defined).			
PERD	Period	05.03.01	Derived For SLD: RAD_LESION/cycle Cycle1-20-1-20; SCREENING- -999; WITHDRAWAL-995; UNSCHED-997; END OF TREATMENT-998. For OS & PFS: set to missing		1 2 3 or 4 etc. Derived from CPEVENT or similar variable for each data type.	integer up to 5 digits 1,2,3 ... n.	5.	Num
NTPD	Nominal Time Post Dose	05.05.01	Set to missing since no corresponding information collected.	Analyst Input Not Required.	Nominal Time Post Dose and is not OCC-specific. Default: units = hours (decimal)	Up to 5 digits can include decimal places	BEST5.	Num
DAY	Derived day	05.06.01	Derived	Analyst Input Not Required.	day=date-factdat+1	integer up to 5 digits	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			If date<factdat then day=date-factdat; else day=date-factdat+1			1,2,3 ... n.		
TAFD	Time After Subject's Very First Trt Dose	05.07.02	Derived OS: DER_TIME/dth_d PFS: DERRADTIME/pfs_d t SLD: RAD_LESION/exam_date Derived from event date and first dosing date tafd = (event date – first dosing date)/7; set to 0 if	Please change the units from hours to weeks	Time After Subject's Very First Treatment Dose Does NOT reset at start of occasion. Default: units = hours Default: Pre-dose = 0 Default: Screening = -999 Default: Follow-up = -999	Up to 8 digits can include decimal places	BEST8.	Num

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			date<factdat; if date is missing then tafd is missing. Rounded to 0.01 Reported in weeks.					
FLAGE	Flag efficacy	06.03.01	Derived 1 = OS; 2 = PFS; 3 = SLD (SLD = sum of longest diameter or tumors)	1 = OS; 2 = PFS; 3 = SLD (SLD = sum of longest diameter or tumors)	150-199 = Efficacy flags	integer up to 5 digits 150, 151, 152 ... 199.	5.	Num
AGE	Age	07.01.01	POP_GEN/age Set to -999 if there are any missing records.	Analyst Input Not Expected.	Default: units = years	integer up to 5 digits 1,2,3 ... n.	5.	Num
SEX	Gender Code	07.02.01	POP_GEN/sex 0 = Male 1 = Female	Use same coding as in popPK dataset which	0 = Male 1 = Female	integer up to 5 digits 1,2,3 ... n.	5.	Num

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			Set to -999 if there are any missing records.	matched EMD coding. See as provided.				
RACE	Race	07.03.01	POP_GEN/raceshow 1=White 2=Black 3=Asian 6= Other ("Not Allowed to Ask" and "Not Listed" in source data) Set to -999 if there are any missing records.	Use same coding as in popPK dataset which matched EMD coding. See as provided.	1=White 2=Black or African American 3=Asian 4=American Indian or Alaska native 5=Native Hawaiiin or other Pacific Islander 6=Other . =missing	integer up to 5 digits 1,2,3 ... n.	5.	Num
ETHN	Ethnicity	07.03.02	No corresponding information collected. Set to -999	Analyst Input Not Required.	Use PDS codelist. 1 = HISPANIC/LATINO 2 = NOT HISPANIC/LATINO	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
RACD	Racial Designation	07.03.03	No corresponding information collected. Set to -999	Analyst Input Not Required.	Use PDS codelist. 1 = INDIAN SUBCONTINENT ASIAN 2 = SOUTHEAST ASIAN 3 = FAR EAST ASIAN 4 = ALASKAN NATIVE 5 = PACIFIC ISLANDER 6 = NORTH AMERICAN INDIAN 7 = NATIVE HAWAIIAN	integer up to 5 digits 1,2,3 ... n.	5.	Num
BWT	Weight in Kg (Baseline)	07.05.02	POP_GEN/bs_wt VITALS/wt If bs_wt is missing in POP_GEN, chose wt from VITALS. if baseline is not available, we used	Analyst Input Not Expected.	Default: unit = kg Baseline value of weight is used	Up to 5 digits can include decimal places	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			first valid value recorded for the patient instead of leaving it as missing. Set to -999 if there are any missing records.					
SMOK	Smoking Classification	07.07.01	No corresponding information collected. Set to -999	Analyst Input Not Required.	Use PDS codelist. 1 = never smoked 2 = smoker 3 = ex-smoker	integer up to 5 digits 1,2,3 ... n.	5.	Num
BBMI	Body Mass Index (Baseline)	07.10.02	Derived if bwt ne . and bht ne . then bbmi=round((bwt/(bht*0.01)**2),0.01) Set to -999 if there are any missing records.	Analyst Input Not Required.		Up to 5 digits can include decimal places	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
BCCL	Creatinine Clearance (Baseline)	10.01.02	Derived from age, sex and bscr Bscr derived from CONVLAB/lvalue Where lparm='CREAT' and LABDTS le DAY1DTS if baseline is not available, we used first valid value recorded for the patient instead of leaving it as missing. if age ne . and bwt ne . and bscr ne . then do; if age >= 13 and sex = 0 then bccl = round((140-age)*bwt/(72*bscr),0.	Analyst Input Not Expected.	Default for Subjects 13 years or older, uses Cockcroft & Gault formula for Subjects less than 13 years old, uses Schwartz formula Methods available: Cockcroft & Gault (subjects >= 13 yr) Schwartz (subjects < 13 yr) * Note all calculations use the Baseline value for input variables	Up to 8 digits can include decimal places	BEST8.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			01); if age >= 13 and sex = 1 then bccl = round(((140-age)*bwt*0.85/(72*bscr),0.01); if age < 13 and age >= 1 then bccl =round(0.55*bht/bscr ,0.01); if age < 1 and age >= 0 then bccl =round(0.45*bht/bscr ,0.01); end; Set to -999 if there are any missing records.					
BCAL	Corrected Calcium (Baseline)	10.02.02	CONVLAB/lvalue Where lparm=' CA' and LABDTS le	Analyst Input Not Required.	Standard units: mg/dL	Up to 5 digits can include decimal	BEST5.	Num

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			DAY1DTS if baseline is not available, we used first valid value recorded for the patient instead of leaving it as missing. bcal=round(bcal-0.707*(balb-3.4),0.01) Units: mg/dL Set to -999 if there are any missing records.			places		
BPLT	Platelets (Baseline)	10.04.02	CONVLAB/lvalue Where lparm=' PLT' and LABDTS le DAY1DTS	Analyst Input Not Required.	Units = 10 ⁹ cells/L	Up to 5 digits can include decimal places	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			if baseline is not available, we used first valid value recorded for the patient instead of leaving it as missing. Units: 10 ⁹ cells/L Set to -999 if there are any missing records.					
BNEU	Normalised Neutrophils (Baseline)	10.05.02	CONVLAB/lvalue Where lparm=' ANC' and LABDTS le DAY1DTS if baseline is not available, we used first valid value recorded for the patient instead of leaving it as missing.	Analyst Input Not Required.	Units = 10 ⁹ /L	Up to 5 digits can include decimal places	BEST5.	Num

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Version: Data set release

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			Units: 10 ⁹ /L Set to -999 if there are any missing records.					
BHGB	Hemoglobin (Baseline)	10.10.02	CONVLAB/lvalue Where lparm=' HGB' and LABDTS le DAY1DTS if baseline is not available, we used first valid value recorded for the patient instead of leaving it as missing. Units: g/dL Set to -999 if there are any missing records.	Analyst Input Not Required.	Standard units: g/dL	Up to 5 digits can include decimal places	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
BALB	Normalised Albumin (Baseline)	10.10.03	CONVLAB/Ivalue Where Iparm=' ALBUM' and LABDTS le DAY1DTS if baseline is not available, we used first valid value recorded for the patient instead of leaving it as missing. Units:g/dL Set to -999 if there are any missing records.	Analyst Input Not Required.	Units:g/dL	Up to 5 digits can include decimal places	BEST5.	Num
BLDH	Lactic Acid Dehydrogenase (baseline)	10.11.02	CONVLAB/Ivalue Where Iparm=' LDH' and LABDTS le	Analyst Input Not Required.	Units = U/L	Up to 5 digits can include decimal	BEST5.	Num

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			DAY1DTS if baseline is not available, we used first valid value recorded for the patient instead of leaving it as missing. Units: U/L Set to -999 if there are any missing records.			places		
BALT	Normalised ALT (Baseline)	10.12.02	CONVLAB/lvalue Where lparm=' ALT' and LABDTS le DAY1DTS if baseline is not available, we used first valid value	Analyst Input Not Required.	Standard units: U/L	Up to 5 digits can include decimal places	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			recorded for the patient instead of leaving it as missing. standard units U/L Set to -999 if there are any missing records.					
BAST	Normalised AST (Baseline)	10.13.02	CONVLAB/lvalue Where lparm=' AST' and LABDTS le DAY1DTS if baseline is not available, we used first valid value recorded for the patient instead of leaving it as missing. standard units U/L	Analyst Input Not Required.	Standard units: U/L	Up to 5 digits can include decimal places	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			Set to -999 if there are any missing records.					
BBIL	Normalised Bilirubin (Baseline)	10.14.02	CONVLAB/lvalue Where lparm='TBILI' and LABDTS le DAY1DTS if baseline is not available, we used first valid value recorded for the patient instead of leaving it as missing. Units: mg/dL Set to -999 if there are any missing records.	Analyst Input Not Required.	Standard units: mg/dL	Up to 5 digits can include decimal places	BEST5.	Num
BSLD	Tumor burden at baseline	99.99.01	RAD_LESION/les_su m	Tumor burden at baseline	mm	e.g. 5	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
	(mm), sum of longest diameter		Where EXAM_DATE ne . and Id not in ("","NA","ND","UE","TSTM") and les_sum not in ("NA","UE","UTD") and exam_date le firstdts (first dosing date)	(mm), sum of diameter of target lesions				
SLD	Tumor burden (mm)	99.99.02	RAD_LESION/les_sum Where EXAM_DATE ne . and Id not in ("","NA","ND","UE","TSTM") and les_sum not in ("NA","UE","UTD")	tumor burden at current time (mm)	LOCF	e.g. 5	BEST5.	Num
SURT	Survival time	99.99.03	PFS: DERRADTIME/ PFS_V OS: DER_TIME/ DTH_V Update in draft#2:	For OS or PFS, time of event (in weeks)		e.g. 5	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			Changed SURT to 0 for EVID=3 records					
CENS	Censoring	99.99.04	PFS: DERRADTIME/ PFS_C OS: DER_TIME/ DTH_C	For OS or PFS, censoring	0 = not censored; 1 = censored event	integer up to 5 digits 1,2,3 ... n.	5.	Num
ECOG	ECOG status at baseline	99.99.05	POP_GEN/bs_ecog Set to -999 if there are any missing records.	ECOG status at baseline		0.1,2,etc.	5.	Num
METS	Metastatic disease site	99.99.06	Derived RAD_LESION/SITE_DESCRIPTION RAD_LESION/EXAM_DATE POP_GEN/FIRSTDT S Where EXAM_DATE	Number of metastatic sites at baseline		e.g. 5	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			le firstdts and new_lesions='F' Chose records with EXAM_DATE le firstdts and new_lesions='F' and then count all unique site code number regardless of the letters. Set to -999 if there are any missing records.					
LIVMET	Presence of liver metastases	99.99.07	Derived RAD_LESION/SITE_CODE RAD_LESION/SITE_DESCRIPTION RAD_LESION/EXAM_DATE			0 = absent ; 1 = present	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			POP_GEN/FIRSTDT S Chose records with exam_date<=firstdts and NEW_LESIONS='F' and site_code in ('33') Changed missing to -999 for records without dosing information.					
LNGM ET	Presence of lung metastases	99.99.08	Derived RAD_LESION/SITE_CODE RAD_LESION/SITE_DESCRIPTION RAD_LESION/EXAM_DATE POP_GEN/FIRSTDT S			0 = absent ; 1 = present	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			<p>Chose records with exam_date<=firstdts and NEW_LESIONS='F' and site_code in ('29', 'L29', 'R29', '30', '47') or (site_code in ('42') and site_description in ('OTHER (SPECIFY) LEFT PLEURAL MASS', 'OTHER (SPECIFY) OTHER PLEURAL MASSES', 'OTHER (SPECIFY) RIGHT PLEURAL MASS'))</p> <p>Changed missing to -999 for records without dosing information.</p>					

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
BONMET	Presence of bone metastases	99.99.09	Derived RAD_LESION/SITE_CODE RAD_LESION/SITE_DESCRIPTION RAD_LESION/EXAM_DATE POP_GEN/FIRSTDT S Chose records with exam_date<=firstdts and NEW_LESIONS='F' and site_code in ('36', '48', '49') or (site_code in ('42') and site_description in ('OTHER (SPECIFY) LEFT FEMORAL HEAD', 'OTHER (SPECIFY) LEFT ILIUM',			0 = absent ; 1 = present	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			'OTHER (SPECIFY) RIGHT ILIUM', 'OTHER (SPECIFY)BASE OF SKULL MASS') Changed missing to -999 for records without dosing information.					
MSKCC	Memorial Sloan-Kettering Cancer Center (MSKCC/Motzer) Score for Metastatic Renal Cell Carcinoma (RCC)	99.99.10	Derived POP_GEN/bs_ecog POP_GEN/firstdts MALHX/diagdts CONVLAB/LVALUE Where LPARM in ('ALBUM', 'CA', 'HGB', 'LDH') and LABDTS le DAY1DTS		0 = favorable risk; 1 = intermediate risk (1-2 factors); 2 = poor risk (3 or more factors)	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			Details please see section 8.3.6. Set to -999 if there are any missing records.					
HENG	Heng criteria	99.99.11	No corresponding information collected, set to -999.		0 = favorable risk; 1 = intermediate risk (1-2 factors); 2 = poor risk (3 or more factors)	integer up to 5 digits 1,2,3 ... n.	5.	Num
EGFR	eGFR (baseline)	99.99.12	Derived CREAT is not collected in umol/L and is in mg/dL. if sex ne 1 and race ne 2 then eGFR=175*bscr**(-1.154)*age**(-0.203); if sex = 1 and race ne 2 then			0.1,2,etc.	BEST5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			eGFR=175*bscr**(-1.154)*age**(-0.203)*0.742; if sex ne 1 and race = 2 then eGFR=175*bscr**(-1.154)*age**(-0.203)*1.212; if sex = 1 and race = 2 then eGFR=175*bscr**(-1.154)*age**(-0.203)*0.742*1.212; Set to -999 if there are any missing records.					
EVID	Event identification	99.99.13	Derived For FLAGE=1(OS) and FLAGE= 2(PFS), EVID=3 for START of OS or PFS and			integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			EVID=0 for the END of OS or PFS; For FLAGE=3 (SLD), EVID=0					
EVNT	Dependent variable event	99.99.14	Derived For FLAGE=1(OS) and FLAGE= 2(PFS), when EVID=3, EVNT=0; when EVID=0 and CENS=0, EVNT=1; when EVID=0 and CENS=1, EVNT=0; For FLAGE=3 (SLD), EVNT=0			integer up to 5 digits 1,2,3 ... n.	5.	Num
DOSRED	Dose Reduction Category	99.99.15	DERDRUG/dosered 0 = no dose reductions	Dose reduction category to indicate	0 = no dose reductions 1 = dose reduced interferon-alpha from A6181034	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			1 = dose reduced interferon-alpha from A6181034 2 = dose reduced sunitinib from A6181034, B9991002, or B9991003	whether a patient had at least one dose reduction of a treatment	2 = dose reduced sunitinib from A6181034, B9991002, or B9991003 3 = dose reduced sorafenib from A4061051 4 = dose reduced axitinib 5 = dose reduced avelumab from B9991002 or B9991003 45= dose reduced on both axitinib and avelumab			
DOSINT	Dose Interruption Category	99.99.16	DERDRUG/interrupt 0 = no dose interruption 1 = dose interruption interferon-alpha from A6181034	Dose interruption category to indicate whether a patient had at least one dose	0 = no dose interruption 1 = dose interruption interferon-alpha from A6181034 2 = dose interruption sunitinib from A6181034, B9991002,	integer up to 5 digits 1,2,3 ... n	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			2 = dose interruption sunitinib from A6181034, B9991002, or B9991003	interruption of a treatment	or B9991003 3 = dose interruption sorafenib from A4061051 4 = dose interruption axitinib 5 = dose interruption avelumab from B9991002 or B9991003 45 = dose interruption on both avelumab and axitinib			
BLYM	Lymphocyte (Baseline)	99.99.17	CONVLAB/lvalue Where lparm='LYMPH' and LABDTS le DAY1DTS if baseline is not available, we used first valid value	Analyst Input Not Required.	Standard units: 10 ⁹ /L	Up to 8 digits can include decimal places	BEST5.	Num

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			<p>recorded for the patient instead of leaving it as missing.</p> <p>Units 10⁹/L</p> <p>Set to -999 if there are any missing records.</p>					

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7. Test Plan

The software will be tested by completing the Global PK/PD QC checklist and executing the global PK/PD QC automated checks macro in accordance with the PK/PD QC guidelines and OPD. The output PDF produced by the PK/PD QC automated checks macro will reside in CDARS in the location listed in the completed QC checklist. Additional checks for the non-standard variables/derivations can be added to the checklist section 20. This checklist is located in improve in the folder listed in section 4.3 *Storage of Documents*.

8. Programming Notes

8.1 *Alphanumeric PK Values*

NA. No PK data included.

8.2 *Screening, Follow-Up and Unplanned Events*

Screening, unplanned and withdraw assessments were supplied in the output data set.

8.3 *Other Data*

8.3.1 **C Column**

There were 15 subjects without dosing information, but with PD data, and marked as C in the PD dataset.

8.3.2 **Missing Dose**

AVGDDOSE (Average Daily Dose Administered) was used to derive the variable DOSE. Per analyst's confirmation, missing dose was kept to merge with PD data.

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8.3.3 Baseline Definition

Same as the previous PD file for A6181034, baseline for all lab tests was defined as the last lab record on or before first dose date. If baseline is not available, first valid value recorded for the patient was used as baseline per analyst's requirement.

8.3.4 Duplicated Lab Baseline Records on the Same Date

There are some duplicated lab records on the same date. Analyst suggested us to use the average value to derive baseline lab value. Here are some examples.

Subject ID	Visit Sequence	period	Day	Date of sample	Time of sample	Lab parameter	Lab values	Average
124	0	SCREEN	.	12/30/2004	7:30	HGB	13.2	13.15
124	210	C1	1	12/30/2004	8:10	HGB	13.1	
574	220	C2	28	9/21/2005	5:10	HGB	12.4	12.45
574	230	C3	1	9/21/2005	5:10	HGB	12.5	

8.3.5 SLD Values

As analyst confirmed, the SLD records with NA values were removed first. For duplicated values in column "Sum of the longest diameters (mm)" of the same date for each visit in source data, the sum was chose to derive SLD value.

8.3.6 MSKCC

Per analyst's comments, we used the following 5 risk factors to derive MSKCC scores.

- 1) ECOG BS ≥ 2
- 2) LDH > 1.5 times the ULN
- 3) Serum hemoglobin < LLN
- 4) Corrected serum calcium > 10 mg/dL
- 5) Time from initial diagnosis to study treatment start less than one year.

Following is the part of code.
data ecog;

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```
set datvprot.pop_gen;  
nsid=ptno;  
ecog=bs_ecog;  
keep nsid ecog firstdts;  
proc sort nodupkey; by nsid;  
run;
```

```
data diagdts;  
set datvprot.malhx;  
nsid=ptno;  
keep nsid diagdts;  
run;
```

```
data MSKCCb;  
merge ecog diagdts bhgb bALB bLDH bcal;  
by nsid;  
*--- ECOG ---*;  
    if ECOG eq . then ECOG_rsk=.;  
    else if .<ECOG <2 then ECOG_rsk=0;  
    else if ECOG >=2 then ECOG_rsk=1;
```

```
*--- Hemoglobin ---*;  
    if bhgb eq . then HMG_rsk=.;  
    else if .<bhgb < hgb_MIN then HMG_rsk=1;  
    else if bhgb >= hgb_MIN then HMG_rsk=0;
```

```
*--- LDH ---*;  
    if bLDH eq . then LDH_rsk=.;  
    else if .<bLDH <= 1.5*LDH_MAX then LDH_rsk=0;  
    else if bLDH > 1.5*LDH_MAX then LDH_rsk=1;
```

```
*--- Corrected Serum Ca ---*;  
if bcal^=. and balb^=. then CaCorrct = bcal - 0.707*(bALB - 3.4);
```

```
if CaCorrct eq . then CaC_rsk=.;
```

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```
else if CaCorrct > 10 then CaC_rsk=1;
else if .<CaCorrct <=10 then CaC_rsk=0;
```

```
*--- time from initial diagnosis to study treatment start less than one year ---*;
format diagdts date9. ;
if firstdts=. or diagdts=. then date_rsk=.;
else if . < firstdts-diaqdts+1<365 then date_rsk=1;
else date_rsk=0;
```

```
*--- Number of risk factor ---*;
Num_RSK=SUM(ECOG_RSK, HMG_rsk, LDH_rsk, CaC_rsk, date_rsk);
```

```
if Num_RSK= . then mskcat=.;
else if Num_RSK= 0 then mskcat=0;
else if 1<=Num_RSK<=2 then mskcat=1;
else if 3<=Num_RSK then mskcat=2;
attrib mskcat format=MSKCCN.;
run;
```

```
data mskcc(keep=nsid mskcc) ;
set mskccb;
mskcc=mskcat;
run;
```

Notes:

- 1) If subjects without any dose records, their baseline lab values were missing. The above three risk factors for lab tests – LDH, serum hemoglobin and corrected serum calcium were missing.
- 2) If all five risk factors were missing, MSKCC was set as -999.

8.4 Population of SS, II and ADDL

NA

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8.5 Programming or Data Issues

Dosing data issue

In dosing dataset DERDRUG, it is found a dosing date issue as shown below.

For the earliest date of drug consumption of cycle 9, it seems to be 23JUN2006 instead of 23JUN2004. Fortunately we can get the correct first dosing date and dose in another way without hard coding. No impact on this data file.

ptno	cycle	avgddose	dayson	dosefst	doselst
Patient Number	Cycle Number (0=all cycles)	Average Daily Dose Administered	Days on Drug	Earliest date of drug consumption	Latest date of drug consumption
23 Unique	23 Distinct	23	23	23	23
655	0	22.4439411099	883	23JUN2004	08SEP2008
655	1	7.41176470588	17	05JUL2005	15AUG2005
655	2	9	18	17AUG2005	27SEP2005
655	3	9	18	28SEP2005	08NOV2005
655	4	9	18	09NOV2005	20DEC2005
655	5	9	6	21DEC2005	01JAN2006
655	6	9	18	01FEB2006	14MAR2006
655	7	9	18	15MAR2006	25APR2006
655	8	9	18	11MAY2006	21JUN2006
655	9	9	331	23JUN2004	02AUG2006
655	10	9	18	16AUG2006	26SEP2006
655	11	9	18	27SEP2006	07NOV2006
655	12	9	18	08NOV2006	19DEC2006
655	13	9	16	22DEC2006	01FEB2007
655	14	9	18	02FEB2007	15MAR2007
655	15	8.64705882353	17	16MAR2007	26APR2007
655	16	7.57894736842	19	27APR2007	07JUN2007
655	17	9	6	08JUN2007	21JUN2007
655	18	50	28	26JUN2007	23JUL2007
655	19	50	19	07AUG2007	03SEP2007
655	20	50	28	18SEP2007	15OCT2007
655	21	50	28	02NOV2007	29NOV2007
655	22	50	28	13DEC2007	09JAN2008
655	23	50	28	24JAN2008	20FEB2008
655	24	50	28	06MAR2008	02APR2008
655	25	50	28	17APR2008	14MAY2008
655	26	50	28	29MAY2008	25JUN2008
655	27	50	28	09JUL2008	05AUG2008
655	28	50	20	20AUG2008	08SEP2008

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SU011248
Protocol: A6181034
Data set type: PD
Version: Data set release
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8.6 Differences in data file versions

8.6.1 Update in Draft #2 Delivery

1. Duplicated OS and PFS records.
2. Added variables EVID and EVNT.
3. Changed SURT to 0 for EVID=3 records.

8.6.2 Update in Draft #3 Delivery

1. Changed LIVMET, LNGMET and BONEMET from missing to 0 for subjects without dose information.
2. Updated baseline demographics/lab variables (if baseline is not available, we used first valid value recorded for the patient instead of leaving it as missing).
3. Changed EVID from 1 to 0 for FLAGE=3 (SLD) records.

8.6.3 Update in Draft #4 Delivery

1. Changed missing values to “-999” for following variables: AGE SEX RACE ETHN RACD BWT SMOK BBMI BCCL BCAL BPLT BNEU BHGB BALB BLDH BALT BAST BBIL ECOG METS MSKCC HENG EGFR.
2. Changed 0 to -999 for subjects without dosing information for LIVMET LNGMET BONMET.

8.6.4 Update in Draft #5 Delivery

Added variables DOSRED and DOSINT.

8.6.5 Update in Draft #6 Delivery

Updated the derivation algorithm of MSKCC.

- 1) For the three risk factors for lab tests – LDH, serum hemoglobin and corrected serum calcium, we used the same baseline value which is defined as the last lab record on or prior to the first dose date instead of randomization date.
- 2) Added two risk factors-ECOG PS ≥ 2 and time from initial diagnosis to study treatment start less than one year and dropped NEPH risk factor.

8.6.6 Update in Draft #7 Delivery

Added variable BLYM (Lymphocyte (Baseline)).

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SU011248

Protocol: A6181034

Data set type: PD

Version: Data set release

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8.6.7 Update in Final Delivery

The data file was not changed, and we just re-run it to remove the “_draft” suffix.

We also finalized the supporting documents to removed “Draft” in header and updated version date for all documents.

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B999e
Avelumab, Axitinib, Sunitinib
ASR-EQDD-B999e-Other-994

The next 30 pages are an external document with Repository artifact ID FI-637818.



MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991002

Dataset type: PD

Version: Data set release

Final PK/PD Programming Plan, 01NOV2019

PK/PD Programming Plan

Reporting Event Version	Date	Author	Changes/Comments
1	20-Jun-2019	Gao, Mochao	Initial version
1.1	03-Jul-2019	Gao, Mochao	1. Updated ID 2. Additional records were added for FLAGE=1 and FLAGE=2 (OS and PFS) 3. Added two new columns EVID and EVNT as per analyst's request.
1.2	31-Jul-2019	Gao, Mochao	1. Updated missing values of BCCL and BCAL; 2. Set EVID to 0 for FLAGE=3 (SLD); 3. Updated missing values of LIVMET, LNGMET & BONEMET to 0.
1.3	20-Aug-2019	Gao, Mochao	Change missing values to -999 for AGE SEX RACE ETHN RACD BWT SMOK BBMI BCCL BCAL BPLT BNEU BHGB BALB BLDH BALT BAST BBIL ECOG METS MSKCC HENG EGFR.
1.4	24-Sep-2019	Gao, Mochao	Add two new variables DOSRED & DOSINT.
1.5	23-Oct-2019	Gao, Mochao	Add a new variable BLYM.
Final	01-Nov-2019	Gao, Mochao	Removed "Draft" in header and updated version date

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991002

Dataset type: PD

Version: Data set release

Final PK/PD Programming Plan, 01NOV2019

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991002

Dataset type: PD

Version: Data set release

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1. Summary Request Information

Date of Request:	May 29, 2019
Job ID:	EQDD-B999e-Other-994

Note: In the table below, please include the names of all PK/PD programmers, PK/PD POCs and PK/PD analysts who perform a significant amount of work on this request.

	<i>Name</i>	<i>Start date*</i>	<i>Stop date**</i>	<i>e-mail address</i>
PK/PD Programmer, CRO name:	Gao, Mochao Zhang, Zhongling	20-Jun-2019	01-Nov-2019	Mochao.Gao@pfizer.com zhongling.Zhang@pfizer.com
CRO PK/PD Point of Contact	NA	NA	NA	NA
CPW PK/PD Support POC:	Salatka, Ken	20-Jun-2019	01-Nov-2019	Ken.Salatka@pfizer.com
Requesting Analyst:	Lin, Swan	20-Jun-2019	01-Nov-2019	Swan.Lin@pfizer.com

**Start date of work on this particular project.*

***Stop date is either the*

- date of the FINAL data file delivery*
- or the date that the colleague finished working on this project if they moved on before the FINAL was delivered.*

Approximate date is acceptable if the actual date is unknown. Indicate such in the above table.

2. Objectives

The objective is to provide PD dataset of study B9991002 for analysis.

3. Study Design

This is a Phase 1b, open-label, multi-center, multiple-dose, safety, PK and pharmacodynamics study of avelumab in combination with axitinib in adult patients with previously untreated aRCC. This clinical study will be composed of a Dose Finding Phase and a Dose Expansion Phase.

The Dose Finding Phase will estimate the MTD and RP2D in patients with aRCC with clear cell histology who did not receive prior systemic therapy for advanced disease, using the modified

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toxicity probability interval (mTPI) method.²⁹ Dose finding will follow an Mpi design, with up to 3 potential dose levels (DL) to be tested:

- (DL1) avelumab 10 mg/kg Q2W + axitinib 5 mg BID.
- (DL-1A) avelumab 5 mg/kg Q2W + axitinib 5 mg BID.
- (DL-1B) avelumab 10 mg/kg Q2W + axitinib 3 mg BID.

DL-1A and DL-1B will be explored concurrently in a randomized fashion only if the MTD is exceeded in DL1.

The Dose Finding Phase will lead to the identification of an Expansion Test Dose for avelumab in combination with axitinib in patients with aRCC who did not receive prior systemic therapy for their advanced disease. The Expansion Test Dose will either be the MTD (ie, the highest dose of avelumab and axitinib associated with the occurrence of DLTs in <33% of patients) or the RP2D, ie, the highest tested dose that is declared safe and tolerable by the investigators and sponsor. Once the Expansion Test Dose is identified, the Dose Expansion Phase will be opened, and avelumab in combination with axitinib will be evaluated in up to approximately 40 patients with previously untreated aRCC.

Axitinib will be given orally (PO) twice daily (BID), with or without food, on a continuous dosing schedule. Avelumab will be given as a 1-hour IV infusion Q2W. All patients will continue treatment with study drugs until confirmed disease progression, patient refusal, patient lost to follow up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first.

Schedule of Activities

Visit Identifiers ¹	Screening	Study Treatment (1 cycle = 14 days)		
		Cycle 1		Cycles ≥2
	≤28 Days Prior to Enrollment or Randomization	Day 1	Day 8 (±1 day)	Day 1 (±3 days)
Other Clinical Assessments				
Follow-up for Axitinib Dosing Compliance ¹⁷		X (D5 ± 3 days)		X ¹⁷ (D5 ± 3 days)
Adverse Events ¹⁸			X	
Concomitant Medications/Treatments ¹⁹	X	X	X	X
Enrollment by Study Treatment ²⁰				
Avelumab ²¹		X ²¹		X ²¹
Axitinib ²¹			X	
Other Samplings				
Pharmacokinetics ²²		X	X	X (Cycles 2, 3, 4, 6, 8, then Q12W)
Banked Blood Biospecimens ²³	X	X		X (Cycles 2, 3, 4, and 6)
Mandatory Archival FFPE Tumor Tissue ²⁴	X			
Mandatory Recent <i>De Novo</i> FFPE Tumor Block ²⁵	X			
Anti-Avelumab Antibodies and Neutralizing Antibodies ²⁶		X		X (Cycles 2, 3, 4, 6, 8, then Q12W)

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18. Adverse Events: Adverse events should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving study treatment, through and including 90 calendar days after the last administration of study treatment. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to the study drug are to be reported to the sponsor. AEs (serious and non serious) should be recorded on the Case Report Form (CRF) from the time the patient has taken at least 1 dose of study treatment through and including 90 calendar days after the last of study treatment. If a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study drug, irrespective of any intervening treatment.
19. Concomitant Medications/Treatments: Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).

4. Study File Reference

4.1 Name of CDARS SAS Data sets, Programs and Locations:

CDARS reporting system interface information

Site: groton

Project: B999

Submission: pkpd

Protocol: B9991002_PD_2

Deliverable: PD VA Output Dataset Production_

ToT: pd.tot

SAS dataset:

/Volumes/app/cdars/prod/sites/groton/prjB999/pkpd/B9991002_PD_2/saseng/pds1_0/data_vai/
pd.sas7bdat

SAS program:

/Volumes/app/cdars/prod/sites/groton/prjB999/pkpd/B9991002_PD_2/saseng/pds1_0/macros/
pd.sas

4.2 Completed PK CSV Data set Name:

CDARS -

/Volumes/app/cdars/prod/sites/groton/prjB999/pkpd/B9991002_PD_2/saseng/pds1_0/data_vai/
B9991002_PD_2_31OCT2019.csv

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Improve –

/root/_pkpd_star/B999 MSB0010718C

Avelumab/B9991002/prod/output_data/B9991002_PD_2_31OCT2019.csv

4.3 Storage of Documents

Programming Plan Location:

/root/_pkpd_star/B999 MSB0010718C Avelumab/B9991002/prod/documents/
B9991002_PD_2_Programming_Plan.doc

Dataset Request Form Location:

/root/_pkpd_star/ B999 MSB0010718C Avelumab/B9991003_restricted/prod/documents/
Global_Data_Request_Form_PMAR994_30MAY2019.xlsm

Issues Tracking Spreadsheet Location:

/root/_pkpd_star/B999 MSB0010718C Avelumab/B9991003_restricted/prod/documents/
B999e_Other_994_Combined_PD_2_Query.xls

Global PK/PD QC Checklist Location (Test Plan):

/root/_pkpd_star/B999 MSB0010718C Avelumab/B9991002/prod/documents/
B9991002_PD_2_QC.doc

Mail Messages:

/root/_pkpd_star/B999 MSB0010718C Avelumab/Mail Messages/A4061051 A6181034
B9991002 1003 PD Finalization Confirmation.msg

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5. Input Data Origin

e_FINAL_B999100
2_Released Study

OC Database release date: 17May2018

Table 1: Input Data set Origin

Dataset Name	Description of Dataset	Date and Time that the source data set was extracted or created mm/dd/yyyy HH:MM	Date that the data set was copied over to PK/PD Programming area from the source mm/dd/yyyy HH:MM	Source Data Obtained and Verified From(Attach email message, if available):	Folder location of source data set
ex	Exposure SDTM Dataset	05/18/2018	06/13/2019 15:18	Chen, Yan	Copied from: /Volumes/app/cdars/prod/sites/groton/prjB999/b9991002_csr/B9991002_BDR/saseng/cdisc3_0/data
suppdm	Supplemental Demographic SDTM Dataset	05/17/2018	06/13/2019 15:18	Chen, Yan	Copied from: /Volumes/app/cdars/prod/sites/groton/prjB999/b9991002_csr/B9991002_BDR/saseng/cdisc3_0/data

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Dataset type: PD

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tr	Tumor Results SDTM Dataset	05/18/2018	06/13/2019 15:18	Chen, Yan	Copied from: /Volumes/app/cdars/prod/sites/groton/prjB999/b9991002_csr/B9991002_BDR/saseng/cdisc3_0/data
tu	Tumor Identification SDTM Dataset	05/18/2018	06/13/2019 15:18	Chen, Yan	Copied from: /Volumes/app/cdars/prod/sites/groton/prjB999/b9991002_csr/B9991002_BDR/saseng/cdisc3_0/data
adsl	Subject Level ADAM Dataset	11/27/2018	06/13/2019 15:18	Chen, Yan	Copied from: /Volumes/app/cdars/prod/sites/groton/prjB999/b9991002_csr/B9991002_BDR/saseng/cdisc3_0/data_vai
adlb	Lab ADAM Dataset	11/27/2018	06/13/2019 15:18	Chen, Yan	Copied from: /Volumes/app/cdars/prod/sites/groton/prjB999/b9991002_csr/B9991002_BDR/saseng/cdisc3_0/data_vai
advs	Vital Signs ADAM Dataset	09/07/2018	06/13/2019 15:18	Chen, Yan	Copied from: /Volumes/app/cdars/prod/sites/groton/prjB999/b9991002_csr/B9991002_BDR/saseng/cdisc3_0/data_vai
adex2	Exposure ADAM Dataset	10/02/2018	06/13/2019 15:18	Chen, Yan	Copied from: /Volumes/app/cdars/prod/sites/groton/prjB999/b9991002_csr/B9991002_BDR/saseng/cdisc3_0/data_vai

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adtr	Tumor Results ADAM Dataset	09/08/2018 04:22	06/13/2019 15:18	Chen, Yan	Copied from: /Volumes/app/cdars/prod/sites/groton/prjB999/b9991002 _csr/B9991002_BDR/saseng/cdisc3_0/data_vai
adsu	Substance Use ADAM Dataset	09/18/2018 04:03	06/13/2019 16:17	Chen, Yan	Copied from: /Volumes/app/cdars/prod/sites/groton/prjB999/b9991002 _csr/B9991002_BDR/saseng/cdisc3_0/data_vai
adtte	Investigator Response ADAM Dataset	11/29/2018 03:41	06/13/2019 16:17	Chen, Yan	Copied from: /Volumes/app/cdars/prod/sites/groton/prjB999/b9991002 _csr/B9991002_BDR/saseng/cdisc3_0/data_vai

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Protocol: B9991002

Dataset type: PD

Version: Data set release

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6. Variables and Description

Data set Sort Order: NSID, FLAGE, PERD, descending EVID**Table 2: Output Variable Descriptions**

Global Variable Name	Variable Description	Sort order	SAS Dataset or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
C	Comment Column	01.01.01	No record was commented out.	Analyst Input Not Required.	Default value is C. If requested, this is required to be the first column of a NONMEM dataset.	Char up to 1 alpha-numeric C	\$1.	Char
PROT	Protocol Number	02.01.02	Set to 1002	Analyst Input Not Required.	Numeric conversion from PROTNO. If PROTNO=A5411003 then PROT=1003. Example: 1003	integer up to 5 digits 1,2,3 ... n.	5.	Num
NSID	Subject Identification Number	02.01.04	All datasets/usubjid subjid nsid=input(scan(USUBJID,3,' '),best.) or nsid=input(compress(SUBJID,'-'),best.);	Analyst Input Not Required.	Eight digit subject ID number typically derived from SID or PID. Used as a key variable for merging data. This data should be numeric	integer up to 8 digits	8.	Num

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					as sorting and merging by this number. It should also be a unique number for each subject. E.g. If PID=A5411003-10021001 then SUBJ=10021001. Example: 10021015			
ID	Sequential number ID	02.02.01	Derived ID = 1039 for first subject and then ID = ID + 1 incrementing for every subject		Unique for each subject, incrementing by 1 for each new subject Default: Initial value = 1.	integer up to 5 digits 1,2,3 ... n.	5.	Num
STID	Unique Subject ID for NONMEM	02.02.02	stid=2000+id	Analyst Input Not Expected.	last 2 digits of study number + NSID. e.g. protocol number= A4091014 and NSID=10261021 then STID=1410261021. protocol number = A4091018 and	integer up to 10 digits 1,2,3 ... n.	5.	Num

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					NSID=10031005 then STID=1810031005			
DOSE	Actual Dose the subject received (for interferon alpha, sunitinib, sorafenib, or axitinib)	03.01.01	EX/exdose where EXTRT='AXITINIB';		Carried forward till next dose. It is not occasion-specific. Default: units = mg Default: Screening = -999 Default: Follow-up = -999 Default: If pre-dose records exist prior to first dose then = -999, else value will carry forward from previous dose.	Up to 8 digits can include decimal places	BEST8.	Num
DOSEP	Planned First Dose the subject received (for interferon alpha, sunitinib, sorafenib, or axitinib)	03.01.02	ADEX2/expdose where PARCAT1='AXITINIB' and PARAM='Actual Dose Level (mg)' Administered at first Axitinib treatment.			Up to 8 digits can include decimal places	BEST8.	Num
DOSIV	Actual avelumab	03.01.03	EX/exdose		Carried forward till next dose. It is not	Up to 8 digits can	BEST8.	Num

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	dose received		where EXTRT='MSB0010718C';		occasion-specific. Default: units = mg Default: Screening = -999 Default: Follow-up = -999 Default: If pre-dose records exist prior to first dose then = - 999, else value will carry forward from previous dose.	include decimal places		
DOS1P	Planned First avelumab dose received	03.01.04	ADEX2/expdose where PARCAT1='AVELUMAB' and PARAM='Actual Dose Level (mg/kg)' Administered at first Avelumab treatment.			Up to 8 digits can include decimal places	BEST8.	Num
DOS2	Dose administered per kg of body weight (only for avelumab treatment)	03.01.05	ADEX2/aval where PARCAT1='AVELUMAB' and PARAM='Actual Dose Level (mg/kg)'		Dose administered is in the units specified for DOSE.	Up to 8 digits can include decimal places	BEST8.	Num

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DOS2P	Planned First Dose administered per kg of body weight (only for avelumab treatment)	03.01.06	Set to 10 mg/kg for 1002.			Up to 8 digits can include decimal places	BEST8.	Num
TRT	Subject Treatment	03.04.01	ADSL/trt01a 2 = sunitinib from A6181034, B9991002, or B9991003 ; 5 = avelumab+axitinib from B9991002 or B9991003		1 = interferon alpha from A6181034; 2 = sunitinib from A6181034, B9991002, or B9991003 ; 3 = sorafenib from A4061051 ; 4 = axitinib from A4061051; 5 = avelumab+axitinib from B9991002 or B9991003	integer up to 5 digits 1,2,3 ... n.	5.	Num
TRTG	Treatment Group Label	03.04.02	ADSL/trt01a Commas and hyphens will be removed. Spaces will be replaced with underscores (_).		Treatment Group (text description) is derived from CDARS actual treatment variable TREATTXT. Commas and hyphens will be removed. Spaces	Char up to 80 alpha-numeric	\$80.	Char

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					will be replaced with underscores (_). (or analyst defined).			
PERD	Period	05.01.01	Flage 3: ADTR/avisit where PARAMCD='SUMDIAM'; Flage 1 and Flage 2 Set to missing	Analyst Input Not Required.	1 2 3 or 4 etc. Derived from CPEVENT or similar variable for each data type.	integer up to 5 digits 1,2,3 & n.	5.	Num
NTPD	Nominal Time Post Dose	05.02.01	No corresponding information, leave as missing.	Analyst Input Not Required.	Nominal Time Post Dose and is not OCC-specific. Default: units = hours (decimal)	Up to 5 digits can include decimal places	BEST5.	Num
DAY	Derived day	05.04.01	Derived if date >= factdat then day=date-factdat+1; else day=date-factdat	Analyst Input Not Required.	day=date-factdat+1	integer up to 5 digits 1,2,3 & n.	5.	Num
TAFD	Time After Subject's Very First Trt Dose	05.07.02	Derived Reported in weeks tafd=day/7	Please change the units from hours to weeks	Time After Subject's Very First Treatment Dose Does NOT reset at	Up to 8 digits can include decimal places	BEST8.	Num

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991002

Dataset type: PD

Version: Data set release

Final PK/PD Programming Plan, 01NOV2019

					start of occasion. Default: units = hours Default: Pre-dose = 0 Default: Screening = -999 Default: Follow-up = -999			
FLAGE	Flag efficacy	06.01.01	Derived 1 = OS; 2 = PFS; 3 = SLD (SLD = sum of longest diameter or tumors)	1 = OS; 2 = PFS; 3 = SLD (SLD = sum of longest diameter or tumors)	150-199 = Efficacy flags	integer up to 5 digits 0,1,2,3, ... 29.	5.	Num
AGE	Age	07.01.01	ADSL/age	Analyst Input Not Expected.	Default: units = years	integer up to 5 digits 1,2,3 ... n.	5.	Num
SEX	Gender Code	07.02.01	ADSL/sex	Use same coding as in popPK dataset which matched EMD coding. See	0 = Male 1 = Female	integer up to 5 digits 1,2,3 ... n.	5.	Num

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991002

Dataset type: PD

Version: Data set release

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				as provided.				
RACE	Race	07.03.01	ADSL/race Set missing value to -99	Use same coding as in popPK dataset which matched EMD coding. See as provided.	1=White 2=Black or African American 3=Asian 4=American Indian or Alaska native 5=Native Hawaiiin or other Pacific Islander 6=Other -99=missing	integer up to 5 digits 1,2,3 ... n.	5.	Num
ETHN	Ethnicity	07.03.02	ADSL/ethnic 1 = HISPANIC/LATINO 2 = NOT HISPANIC/LATINO Set missing value to -99	Analyst Input Not Required.	Use PDS codelist. 1 = HISPANIC/LATINO 2 = NOT HISPANIC/LATINO	integer up to 5 digits 1,2,3 ... n.	5.	Num
RACD	Racial Designation	07.03.03	SUPPDM/qvall where qnam=" (RACIALD"; 5 = JAPANESE 6 = KOREAN 7 = CHINESE 8 = OTHER Set missing value to -999	Analyst Input Not Expected.	Use PDS codelist. 1 = INDIAN SUBCONTINENT ASIAN 2 = SOUTHEAST ASIAN 3 = FAR EAST ASIAN 4 = ALASKAN NATIVE	Up to 5 digits can include decimal places	BEST5.	Num

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991002

Dataset type: PD

Version: Data set release

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					5 = PACIFIC ISLANDER 6 = NORTH AMERICAN INDIAN 7 = NATIVE HAWAIIAN			
BWT	Weight in Kg (Baseline)	07.05.02	ADVS/aval where param="WEIGHT (KG)" and abfl="Y";	Analyst Input Not Expected.	Default: unit = kg Baseline value of weight is used	Up to 5 digits can include decimal places	BEST5.	Num
SMOK	Smoking Classification	07.07.01	ADSU/avalc where PARAM='SMOKING HISTORY' 1 = NEVER 2 = CURRENT 3 = FORMER	Analyst Input Not Required.	Use PDS codelist. 1 = never smoked 2 = smoker 3 = ex-smoker	integer up to 5 digits 1,2,3 ... n.	5.	Num
BBMI	Body Mass Index (Baseline)	07.10.02	ADLS/bmibl	Analyst Input Not Required.		Up to 5 digits can include decimal places	BEST5.	Num
BCCL	Creatinine Clearance (Baseline)	10.01.02	ADLB/aval if paramn=40076 and abfl="Y"	Analyst Input Not Expected.	Default for Subjects 13 years or older, uses	Up to 8 digits can include decimal	BEST8.	Num

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991002

Dataset type: PD

Version: Data set release

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			if baseline is not available, then if sex = 1 then do; bctl=round((140 - AGE) * bwt/(bscr1*72),0.01); end; else if sex = 2 then do; bctl=round((140 - AGE) * bwt* 0.85/(bscr1 * 72),0.01); end;		Cockroft & Gault formula for Subjects less than 13 years old, uses Schwartz formula Methods available: Cockroft & Gault (subjects >= 13 yr) Schwartz (subjects < 13 yr) * Note all calculations use the Baseline value for input variables	places		
BCAL	Corrected Calcium (Baseline)	10.02.02	ADLB/aval if paramn=40101 and abfl='Y' bcal-0.707*(balb-3.4) if baseline is not available, take the first values for the patient (even if post first dose)	Analyst Input Not Expected.	Standard units: mg/dL	Up to 5 digits can include decimal places	BEST5.	Num

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991002

Dataset type: PD

Version: Data set release

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BPLT	Platelets (Baseline)	10.04.02	ADLB/aval if paramn=40009 and ablfl='Y'	Analyst Input Not Required.	Units = 10 ⁹ cells/L	Up to 5 digits can include decimal places	BEST5.	Num
BNEU	Normalised Neutrophils (Baseline)	10.05.02	ADLB/aval if paramn=40020 and ablfl='Y'	Analyst Input Not Expected.	Units = mm ³	Up to 5 digits can include decimal places	BEST5.	Num
BHGB	Hemoglobin (Baseline)	10.10.02	ADLB/aval if paramn=40001 and ablfl='Y'	Analyst Input Not Required.	Standard units: g/dL	Up to 5 digits can include decimal places	BEST5.	Num
BALB	Normalised Albumin (Baseline)	10.10.03	ADLB/aval if paramn=40053 and ablfl='Y'	Analyst Input Not Required.	Standard units: g/dL	Up to 5 digits can include decimal places	BEST5.	Num
BLDH	Lactic Acid	10.11.02	ADLB/aval	Analyst	Units = U/L	Up to 5	BEST5.	Num

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991002

Dataset type: PD

Version: Data set release

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	Dehydrogenase (baseline)		if paramn=40055 and ablfl='Y'	Input Not Required.		digits can include decimal places		
BALT	Normalised ALT (Baseline)	10.12.02	ADLB/aval if paramn=40053 and ablfl='Y' Multiply ADLB/aval by 60 to convert unit from microkat/L to standard units U/L	Analyst Input Not Required.	Standard units: U/L	Up to 5 digits can include decimal places	BEST5.	Num
BAST	Normalised AST (Baseline)	10.13.02	ADLB/aval if paramn=40052 and ablfl='Y' Multiply ADLB/aval by 60 to convert unit from microkat/L to standard units U/L	Analyst Input Not Required.	Standard units: U/L	Up to 5 digits can include decimal places	BEST5.	Num
BBIL	Normalised Bilirubin (Baseline)	10.14.02	ADLB/aval if paramn=40049 and ablfl='Y' Multiply ADLB/aval by 1/17 to convert unit from micromol/L	Analyst Input Not Required.	Standard units: mg/dL	Up to 5 digits can include decimal places	BEST5.	Num

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Protocol: B9991002

Dataset type: PD

Version: Data set release

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			to standard units mg/dL					
BSLD	Tumor burden at baseline (mm), sum of longest diameter	99.99.01	ADTR/aval where PARAMCD='SUMDIAM' and AVISIT='Baseline'	Tumor burden at baseline (mm), sum of diameter of target lesions	mm	integer up to 5 digits 1,2,3 ... n.	BEST5.	Num
SLD	Tumor burden (mm)	99.99.02	ADTR/aval where PARAMCD='SUMDIAM'	tumor burden at current time (mm)	LOCF	Up to 5 digits can include decimal places	BEST5.	Num
SURT	Survival time	99.99.03	ADTTE/aval where param in ("PFS Primary (Months)","Overall Survival (Months)") Multiply 4.3482 to convert unit from weeks to months	For OS or PFS, time of event (in weeks)		integer up to 5 digits 1,2,3 ... n.	5.	Num
CENS	Censoring	99.99.04	ADTTE/cnsr where param in ("PFS Primary (Months)","Overall Survival (Months)")	For OS or PFS, censoring	0 = not censored; 1 = censored event	integer up to 5 digits 0,1,2,3 ... n.	5.	Num
ECOG	ECOG status at baseline	99.99.05	ADSL/ecogbl	ECOG status at baseline		0,1,2,etc.	5.	Num

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Dataset type: PD

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METS	Metastatic disease site	99.99.06	TU/tuloc where tudy < 1	Number of metastatic sites at baseline		e.g. 5	5.	Num
LIVMET	Presence of liver metastases	99.99.07	TR/torres where TRLOC='LIVER' and TRTEST='Tumor State' and TRDY<=1 set to 0 for missing value.	Only baseline is needed		0 = absent ; 1 = present	5.	Num
LNGMET	Presence of lung metastases	99.99.08	TR/torres where TRLOC='LUNG' and TRTEST='Tumor State' and TRDY<=1 set to 0 for missing value.	Only baseline is needed		0 = absent ; 1 = present	5.	Num
BONMET	Presence of bone metastases	99.99.09	TR/torres where TRLOC='BONE' and TRTEST='Tumor State' and TRDY<=1 set to 0 for missing value.	Only baseline is needed		0 = absent ; 1 = present	5.	Num
MSKCC	Memorial Sloan-Kettering Cancer Center (MSKCC/Motzer) Score for Metastatic Renal Cell Carcinoma (RCC)	99.99.10	ADLB/mskcc 0=Favorable 1=Intermediate 2=Poor Set missing value to -999	Only baseline is needed	0 = favorable risk; 1 = intermediate risk (1-2 factors); 2 = poor risk (3 or more factors)	integer up to 5 digits 1,2,3 ... n.	5.	Num

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PK/PD PROGRAMMING PLAN TEMPLATE

01-May-2019

MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991002

Dataset type: PD

Version: Data set release

Final PK/PD Programming Plan, 01NOV2019

HENG	Heng criteria	99.99.11	ADLB/heng 0=Favorable 1=Intermediate 2=Poor Set missing value to -999	Only baseline is needed	0 = favorable risk; 1 = intermediate risk (1-2 factors); 2 = poor risk (3 or more factors)	integer up to 5 digits 1,2,3 ... n.	5.	Num
EGFR	eGFR (baseline)	99.99.12	Derived Male, not Black or African American: EGFR (mL/min/1.73 m2) = 32788 * CREAT(μmol/L)-1.154 * AGE(y)-0.203 Male, Black or African American: EGFR (mL/min/1.73 m2) = 32788 * CREAT(μmol/L)-1.154 * AGE(y)-0.203 * 1.210 Female, not Black or African American: EGFR (mL/min/1.73 m2) = 32788 * CREAT(μmol/L)-1.154 * AGE(y)-0.203 * 0.742 Female, Black or African American: EGFR (mL/min/1.73 m2) = 32788 * CREAT(μmol/L)-1.154 * AGE(y)-0.203 * 1.210 * 0.742			0.1,2,etc.	BEST5.	Num
EVID	Event	99.99.13	Derived			integer up	5.	Num

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991002

Dataset type: PD

Version: Data set release

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	identification		For FLAGE=1 and FLAGE=2 (OS and PFS), there were 2 rows representing the START and the END of OS or PFS. Then, we need to add two additional columns in order to identify START or END: EVID and EVNT, where EVID=3 for START of OS or PFS and EVID=0 for the END of OS or PFS. Then, for EVID=3, please change SURT to 0 for the START time of 0 weeks. For FLAGE=3 (SLD), set to 0.			to 5 digits 1,2,3 ... n.		
EVNT	Dependent variable event	99.99.14	Derived o when EVID=3, EVNT=0 o when EVID=0 and CENS=0, EVNT=1 o when EVID=0 and CENS=1, EVNT=0 o For FLAGE=3 (SLD), EVID=1 and EVNT=0			integer up to 5 digits 1,2,3 ... n.	5.	Num
DOSRED	Dose Reduction Category	99.99.15	ADEX2/avalc where PARAM= 'Subject with At Least 1 Dose Reduction' 0 = no dose reductions	Dose reduction category to indicate whether a	0 = no dose reductions 1 = dose reduced interferon-alpha from A6181034	integer up to 5 digits 1,2,3 ... n.	5.	Num

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991002

Dataset type: PD

Version: Data set release

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			4 = dose reduced axitinib 5 = dose reduced avelumab from B9991002 or B9991003 45= dose reduced on both axitinib and avelumab	patient had at least one dose reduction of a treatment	2 = dose reduced sunitinib from A6181034, B9991002, or B9991003 3 = dose reduced sorafenib from A4061051 4 = dose reduced axitinib 5 = dose reduced avelumab from B9991002 or B9991003 45= dose reduced on both axitinib and avelumab			
DOSINT	Dose Interruption Category	99.99.16	ADEX2/avalc 0 = no dose interruption 4 = dose interruption axitinib 5 = dose interruption avelumab from B9991002 or B9991003 45= dose reduced on both axitinib and avelumab	Dose interruption category to indicate whether a patient had at least one dose interruption of a treatment	0 = no dose interruption 1 = dose interruption interferon-alpha from A6181034 2 = dose interruption sunitinib from A6181034, B9991002, or B9991003 3 = dose interruption sorafenib from	integer up to 5 digits 1,2,3 ... n.	5.	Num

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991002

Dataset type: PD

Version: Data set release

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					A4061051 4 = dose interruption axitinib 5 = dose interruption avelumab from B9991002 or B9991003 45= dose interruption on both axitinib and avelumab			
BLYM	Lymphocyte (Baseline)	99.99.17	ADLB/aval if paramn=40016 and ablfl='Y'	Analyst Input Not Expected.	Units = 10 ⁹ /L	Up to 5 digits can include decimal places	BEST5.	Num

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991002

Dataset type: PD

Version: Data set release

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7. Test Plan

The software will be tested by completing the Global PK/PD QC checklist and executing the global PK/PD QC automated checks macro in accordance with the PK/PD QC guidelines and OPD. The output PDF produced by the PK/PD QC automated checks macro will reside in CDARS in the location listed in the completed QC checklist. Additional checks for the non-standard variables/derivations can be added to the checklist section 20. This checklist is located in Improve in the folder listed in section 4.3 *Storage of Documents*.

8. Programming Notes

8.1 *Alphanumeric PK Values*

NA. No PK data included.

8.2 *Screening, Follow-Up and Unplanned Events*

Screening assessments will be supplied in the output data set.

8.3 *Inclusion and Exclusion*

The patients who were "Screen Failure" "Not Assigned" or "Not Treated" were excluded from the data file.

8.4 *METS, LIVMET, LNGMET and BONMET*

There are two source data for metastases. One is TU; other is TR. Here is some description about those two sources data.

- TU domain contains the details of each target, non-target, and new lesion's location and methods used for its identification.
- TR domain captures all the results associated with the scans.

In TU, only metastatic disease site information collected in TULOC.

In TR, both Metastatic disease site & Presence of liver, lung and bone metastases are collected in TULOC & TRSTRESC.

Therefore, we just can derive LIVMET, LNGMET and BONMET from TR. But for METS, we can derive it from TU.

TRSTRESC in source data (Character Result/Finding in Std Format)	LIVMET, LNGMET / BONMET
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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991002

Dataset type: PD

Version: Data set release

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ABSENT LESION OR NORMAL LYMPH NODE	0 = absent
INCREASED PRESENT PRESENT (FIRST APPEARANCE) PRESENT/NOT INCREASED	1 = present
INDETERMINATE Missing	0

8.5 DAY & TAFD derivation

The first dosing date for axitinib was used to derive DAY & TAFD, which is confirmed with analyst.

8.6 Programming or Data Issues

NA

8.7 Differences in data file versions

8.7.1 Updated on 03Jul2019 for draft#2 delivery

- For FLAGE=1 and FLAGE=2 (OS and PFS), currently there is 1 occurrence (row) per patient. For the analysis, we duplicated this row so that there are 2 per patient. The 2 rows will represent the START and the END of OS or PFS. Then, we need to add two additional columns in order to identify START or END: EVID and EVNT, where EVID=3 for START of OS or PFS and EVID=0 for the END of OS or PFS. Then, for EVID=3, we changed SURT to 0 for the START time of 0 weeks. For EVNT, we defined as follows:
 - when EVID=3, EVNT=0;
 - when EVID=0 and CENS=0, EVNT=1
 - when EVID=0 and CENS=1, EVNT=0
- For FLAGE=3 (SLD), EVID=1 and EVNT=0.

FLAGE	SURT	CENS	EVID	EVNT
1	0	1	3	0
1	44.14	1	0	0
2	0	0	3	0
2	6	0	0	1

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Protocol: B9991002

Dataset type: PD

Version: Data set release

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- For the variable ID, we used numbers 1-750 for A6181034, then use 751-1038 for A4061051 (N=288), 1039-1093 for B9991002 (N=55), and 1094-1979 for B9991003 per analyst's request.

8.7.2 Updated on 31Jul2019 for draft#3 delivery

- Updated missing values of BCCL and BCAL;
- Set EVID to 0 for FLAGE=3 (SLD)
- Updated missing values of LIVMET, LNGMET & BONEMET to 0.

8.7.3 Updated on 20Aug2019 for draft#4 delivery

Change missing values to -999 for AGE SEX RACE ETHN RACD BWT SMOK BBMI BCCL BCAL BPLT BNEU BHGB BALB BLDH BALT BAST BBIL ECOG METS MSKCC HENG EGFR.

8.7.4 Updated on 24Sep2019 for draft#5 delivery

Add two new variables DOSRED & DOSINT per analyst's request.

8.7.5 Updated on 23Oct2019 for draft#6 delivery

Add a new variable BLYM per analyst's request.

8.7.6 Updated on 01Nov2019 for final delivery

The data file was not changed, and just be re-run to remove the “_draft” suffix.

We also finalized the supporting documents to removed “Draft” in header and updated version date for all documents.

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B999e
Avelumab, Axitinib, Sunitinib
ASR-EQDD-B999e-Other-994

The next 42 pages are an external document with Repository artifact ID FI-637819.



MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991003

Data set type: PD

Version: Data set release

Final PK/PD Programming Plan, 01 Nov 2019

PK/PD Programming Plan

Reporting Event Version	Date	Author	Changes/Comments
1	20-Jun-2019	Wang, Ke	Initial Version
1.1	03-Jul-2019	Wang, Ke	1. Updated ID 2. Additional records were added for FLAGE=1 and FLAGE=2 (OS and PFS)
1.2	31-Jul-2019	Wang, Ke	1. Updated BCCL to missing; 2. Set EVID to 0 for FLAGE=3 (SLD) 3. Updated missing values of LIVMET, LNGMET & BONMET to 0.
1.3	20-Aug-2019	Wang, Ke	Change missing value to -999 for AGE SEX RACE ETHN RACD BWT SMOK BBMI BCCL BCAL BPLT BNEU BHGB BALB BLDH BALT BAST BBIL ECOG METS LIVMET LNGMET BONMET MSKCC HENG EGFR.
1.4	25-Sep-2019	Liu, Jindi	Updated per analyst's comments: 2 new variables added – DOSRED & DOSINT
1.5	23-Oct-2019	Liu, Jindi	Added a new variable BLYM per analyst's comments.
Final	01-Nov-2019	Liu, Jindi	Removed "Draft" in header and updated version date

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991003

Data set type: PD

Version: Data set release

Final PK/PD Programming Plan, 01 Nov 2019

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991003

Data set type: PD

Version: Data set release

Final PK/PD Programming Plan, 01 Nov 2019

1. Summary Request Information

Date of Request:	May 29, 2019
Job ID:	EQDD-B999e-Other-994

Note: In the table below, please include the names of all PK/PD programmers, PK/PD POCs and PK/PD analysts who perform a significant amount of work on this request.

	<i>Name</i>	<i>Start date*</i>	<i>Stop date**</i>	<i>e-mail address</i>
PK/PD Programmer, CRO name:	Liu, Jindi Zhang, Anjing Wang, Ke	20-Jun-2019	01-Nov-2019	Jindi.Liu@pfizer.com Anjing.Zhang@pfizer.com Ke.Wang@pfizer.com
CRO PK/PD Point of Contact	NA	NA	NA	NA
CPW PK/PD Support POC:	Salatka, Ken	20-Jun-2019	01-Nov-2019	ken.salatka@pfizer.com
Requesting Analyst:	Lin, Swan	20-Jun-2019	01-Nov-2019	Swan.Lin@pfizer.com

**Start date of work on this particular project.*

***Stop date is either the*

- date of the FINAL data file delivery*
- or the date that the colleague finished working on this project if they moved on before the FINAL was delivered.*

Approximate date is acceptable if the actual date is unknown. Indicate such in the above table.

2. Objectives

The objective is to provide PD dataset of study B9991003 for analysis.

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3. Study Design

This is a Phase 3, multinational, multicenter, randomized (1:1), open-label, parallel 2-arm study in which approximately 830 patients, including a minimum of 580 PD-L1 positive patients, are planned to be randomized to receive either avelumab in combination with axitinib or sunitinib monotherapy.

Arm A: avelumab 10 mg/kg IV Q2W in a 6-week cycle + axitinib 5 mg PO BID.

Arm B: sunitinib 50 mg PO QD on Schedule 4/2.

Patients will be stratified according to ECOG PS (0 vs. 1) and region (United States vs Canada/Western Europe vs the rest of the world).

4. Study File Reference

4.1 Name of CDARS SAS Data sets, Programs and Locations:

CDARS reporting system interface information

Site:	Groton
Project:	B999
Submission:	b9991003_pkpd
Protocol:	B9991003_PD
Deliverable:	PD VA Output Dataset Production with Laboratory Data
ToT:	pd.tot

SAS data set:

/Volumes/app/cdars/prod/sites/groton/prjB999/b9991003_pkpd/B9991003_PD/saseng/pds1_0/data_vai/pd.sas7bdat

SAS program:

/Volumes/app/cdars/prod/sites/groton/prjB999/b9991003_pkpd/B9991003_PD/saseng/pds1_0/macos/pd.sas

4.2 Completed PK CSV Data set Name:

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CDARS -

/Volumes/app/cdars/prod/sites/groton/prjB999/b9991003_pkpd/B9991003_PD/saseng/pds1_0/data_vai/B9991003_PD_2_31OCT2019.csv

improve –

/root/_pkpd_star/B999 MSB0010718C Avelumab/B9991003_restricted/test/output_data/B9991003_PD_2_31OCT2019.csv

4.3 Storage of Documents

Programming Plan Location:

/root/_pkpd_star/B999 MSB0010718C Avelumab/B9991003_restricted/prod/documents/B9991003_PD_2_Programming_Plan.doc

Data set Request Form Location:

/root/_pkpd_star/B999 MSB0010718C Avelumab/B9991003_restricted/prod/documents/Global_Data_Request_Form_PMAR994_30MAY2019.xlsm

Issues Tracking Spreadsheet Location:

/root/_pkpd_star/B999 MSB0010718C Avelumab/B9991003_restricted/prod/documents/B999e_Other_994_Combined_PD_2_Query.xls

Global PK/PD QC Checklist Location (Test Plan):

/root/_pkpd_star/B999 MSB0010718C Avelumab/B9991003_restricted/prod/documents/B9991003_PD_2_QC.doc

Mail Messages:

/root/_pkpd_star/B999 MSB0010718C Avelumab/Mail Messages/A4061051 A6181034 B9991002 1003 PD Finalization Confirmation.msg

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991003

Data set type: PD

Version: Data set release

Final PK/PD Programming Plan, 01 Nov 2019

5. Input Data Origin

Data set Release dates for OC, P1MS, Non-compartmental analysis (NCA)

note: data set release dates not applicable for unplanned or interim PK/PD programming.

1. **OC data base release date: 15-Feb-2019**
2. **P1MS database release date: NA**
3. **Trigger for Blinded / Unblinded Interim Analysis: NA**

Please kindly note: database release notification is unavailable.

Table 1: Input Data set Origin

Dataset Name	Descripti on of Dataset	Date and Time that the source data set was extracted or created mm/dd/yyyy HH:MM	Date that the data set was copied over to PK/PD Programming area from the source mm/dd/yyyy HH:MM	Source Data Obtained and Verified From(Attac h email message, if available):	Folder location of source data set
SUPPDM	Suppleme	09/07/2018	06/17/2019	Comfirmed	/Volumes/app/cdars/prod/sites/groton/prjB999/b9991003/

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	nt Demograp hy dataset		01:46 PM	with Chen, Yan	B9991003_BDR1/saseng/cdisc3_0/data
TR	Tumor status Dataset	08/02/2018	06/17/2019 01:46 PM	Same as above	/Volumes/app/cdars/prod/sites/groton/prjB999/b9991003/ B9991003_BDR1/saseng/cdisc3_0/data
TU	Tumor identificati on Dataset	08/02/2018	06/17/2019 01:46 PM	Same as above	/Volumes/app/cdars/prod/sites/groton/prjB999/b9991003/ B9991003_BDR1/saseng/cdisc3_0/data
ADEX_L0 01A	Listing dataset of Axitinib for reporting	09/22/2018	06/17/2019 01:46 PM	Same as above	/Volumes/app/cdars/prod/sites/groton/prjB999/b9991003/ B9991003_BDR1/saseng/cdisc3_0/data_report
ADEX_L0 01B	Listing dataset of Axitinib for reporting	09/22/2018	06/17/2019 01:46 PM	Same as above	/Volumes/app/cdars/prod/sites/groton/prjB999/b9991003/ B9991003_BDR1/saseng/cdisc3_0/data_report
ADEX_L0 01C	Listing dataset of Axitinib for	09/22/2018	06/17/2019 01:46 PM	Same as above	/Volumes/app/cdars/prod/sites/groton/prjB999/b9991003/ B9991003_BDR1/saseng/cdisc3_0/data_report

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	reporting				
ADSL	Subject level dataset	10/08/2018	06/17/2019 01:56 PM	Same as above	/Volumes/app/cdars/prod/sites/groton/prjB999/b9991003/B9991003_BDR1/saseng/cdisc3_0/data_vai
ADSU	Substance Use dataset	09/17/2018	06/17/2019 01:56 PM	Same as above	Volumes/app/cdars/prod/sites/groton/prjB999/b9991003/B9991003_BDR1/saseng/cdisc3_0/data_vai
ADEX2	Exposure Adam dataset	10/02/2018	06/17/2019 01:56 PM	Same as above	/Volumes/app/cdars/prod/sites/groton/prjB999/b9991003/B9991003_BDR1/saseng/cdisc3_0/data_vai
ADLB	Lab Adam dataset	10/08/2018	06/17/2019 01:56 PM	Same as above	/Volumes/app/cdars/prod/sites/groton/prjB999/b9991003/B9991003_BDR1/saseng/cdisc3_0/data_vai
ADVS	Analysis Vital Signs dataset	09/17/2018	06/17/2019 01:56 PM	Same as above	/Volumes/app/cdars/prod/sites/groton/prjB999/b9991003/B9991003_BDR1/saseng/cdisc3_0/data_vai
ADMH	Medical History Analysis Dataset	10/08/2018	06/17/2019 01:56 PM	Same as above	/Volumes/app/cdars/prod/sites/groton/prjB999/b9991003/B9991003_BDR1/saseng/cdisc3_0/data_vai
ADTRB	Analysis BICR Tumor	10/08/2018	06/17/2019 01:56 PM	Same as above	/Volumes/app/cdars/prod/sites/groton/prjB999/b9991003/B9991003_BDR1/saseng/cdisc3_0/data_vai

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	Response Dataset				
ADTTEB	ADTTEB - RECIST - BICR Response	10/08/2018	06/17/2019 01:56 PM	Same as above	/Volumes/app/cdars/prod/sites/groton/prjB999/b9991003/ B9991003_BDR1/saseng/cdisc3_0/data_vai

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6. Variables and Description

Data set Sort Order: NSID, DATE, FLAGE**Table 2: Output Variable Descriptions**

Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
C	Comment Column	01.01.01	Derived subjects without dosing information, but with PD data.	Analyst Input Not Required.	Default value is C. If requested, this is required to be the first column of a NONMEM data set	Char up to 1 alpha-numeric C	\$1.	Char
PROT	Protocol Number	02.01.02	ADSL/studyid prot=input(substr(studyid,5,4),5.);	Analyst Input Not Required.	Numeric conversion from PROTNO. If PROTNO=A5411003 then PROT=1003. Example: 1003	integer up to 5 digits 1,2,3 ... n	5.	Num
NSID	Subject Identification Number	02.01.04	ADSL/subjid nsid=input(subjid,8.);	Analyst Input Not Required.	Eight digit subject ID number typically derived from SID or PID. Used as a key variable for	integer upto 8 digits	8.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
					merging data. This data should be numeric as sorting and merging by this number. It should also be a unique number for each subject. E.g. If PID=A5411003-10021001 then SUBJ=10021001. Example: 10021015			
ID	Sequential number ID	02.02.01	Derived ID = 1094 for first subject and then ID = ID + 1 incrementing for every subject		Unique for each subject, incrementing by 1 for each new subject Default: Initial value = 1.	integer up to 5 digits 1,2,3 ... n.	5.	Num
STID	Unique Subject ID for NONMEM	02.02.02	Derived from ID (Derivation listed in sort order 02.02.01)	Analyst Input Not Expected.	Related to protocol If protocol is A1281023 and patient number is 1 then ID is 23001. Exceptions made for	integer upto 8 digits	8.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			STID =30000+id;		large studied >1000 subjects or unusual protocol numbers. ID is directly mapped to subject ID such that they are comparable if subjects are excluded.			
DOSE	Actual Dose the subject received (for interferon alpha, sunitinib, sorafenib, or axitinib)	03.01.02	ADEX2/exdose where extrt NE "MSB0010718C"		Carried forward till next dose. It is not occasion-specific. Default: units = mg Default: Screening = -999 Default: Follow-up = -999 Default: If pre-dose records exist prior to first dose then = -999, else value will carry forward from previous dose.	Up to 8 digits can include decimal places	BEST8.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
DOSEP	Planned First Dose the subject received (for interferon alpha, sunitinib, sorafenib, or axitinib)	03.01.02.01	ADEX_L001B/du1 ADEX_L001C/du1			Up to 8 digits can include decimal places	BEST8.	Num
DOSIV	Actual avelumab dose received	03.01.03	ADEX2/exdose where extrt = "MSB0010718C"		Carried forward till next dose. It is not occasion-specific. Default: units = mg Default: Screening = -999 Default: Follow-up = -999 Default: If pre-dose records exist prior to first dose then = -999, else value will carry forward from previous dose.	Up to 8 digits can include decimal places	BEST8.	Num

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Protocol: B9991003

Data set type: PD

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
DOS1P	Planned First avelumab dose received	03.01.03.01	ADEX_L001A/du1			Up to 8 digits can include decimal places	BEST8.	Num
DOS2	Dose administered per kg of body weight (only for avelumab treatment)	03.02.01	ADEX2/aval WHERE PARAM= "Actual Dose Level (mg/kg)" AND PARCAT1 = "AVELUMAB";	Analyst Input Not Required.	Dose administered is in the units specified for DOSE.	Up to 8 digits can include decimal places	BEST8.	Num
DOS2P	Planned First Dose administered per kg of body weight (only for avelumab treatment)	03.02.010.01	ADEX_L001A/ exdosrgm 10 for this study			Up to 8 digits can include decimal places	BEST8.	Num
TRT	Subject Treatment	03.07.01	ADSL/trt01a 2 = sunitinib from A6181034, B9991002, or		1 = interferon alpha from A6181034; 2 = sunitinib from A6181034, B9991002, or B9991003;	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Protocol: B9991003

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			B9991003 ; 5 = avelumab+axitinib from B9991002 or B9991003		3 = sorafenib from A4061051 ; 4 = axitinib from A4061051; 5 = avelumab+axitinib from B9991002 or B9991003			
TRTG	Treatment Group Label	03.10.02	ADSL/trt01a		Treatment Group (text description) is derived from CDARS actual treatment variable TREATTXT. Commas and hyphens will be removed. Spaces will be replaced with underscores (_). (or analyst defined).	Char up to 80 alpha-numeric	\$80.	Num
PERD	Period	05.03.01	Derived For SLD: ADTRB/visit For OS & PFS: set to missing		1 2 3 or 4 etc. Derived from CPEVENT or similar variable for each data type.	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
NTPD	Nominal Time Post Dose	05.05.01	Set to missing since no corresponding information collected	Analyst Input Not Required.	Nominal Time Post Dose and is not OCC-specific. Default: units = hours (decimal)	Up to 5 digits can include decimal places	Best5.	Num
DAY	Derived day	05.06.01	Derived If date<factdat then day=date-factdat; else day=date-factdat+1; The dosing date for Sunitinib or axitinib to derive day	Analyst Input Not Required.	day=date-factdat+1	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
TAFD	Time After Subject's Very First Trt Dose	05.07.02	ADTRB/adt ADTTEB/adt ADEX2/astdt Derived from event date and first dosing date tafd = (event date – first dosing date + 1)/7 set to 0 if date < factdat Rounded to 0.01. The dosing date for Sunitinib or axitinib to derive day	Please change the units from hours to weeks	Time After Subject's Very First Treatment Dose Does NOT reset at start of occasion. Default: units = hours Default: Pre-dose = 0 Default: Screening = -999 Default: Follow-up = -999	Up to 8 digits can include decimal places	BEST8.	Num
FLAGE	Flag efficacy	06.03.01	Derived 1 = OS; 2 = PFS; 3 = SLD (SLD =	1 = OS; 2 = PFS; 3 = SLD (SLD = sum of longest	150-199 = Efficacy flags	integer up to 5 digits 150, 151, 152 ...	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			sum of longest diameter or tumors)	diameter or tumors)		199.		
AGE	Age	07.01.01	ADSL/aage Set missing value to -999	Analyst Input Not Expected.	Default: units = years	integer up to 5 digits 1,2,3 ... n.	5.	Num
SEX	Gender Code	07.02.01	ADSL/sex if sex='M' then _sex=0; else if sex='F' then _sex=1; Set missing value to -999	Use same coding as in popPK dataset which matched EMD coding. See as provided.	0 = Male 1 = Female	integer up to 5 digits 1,2,3 ... n.	5.	Num
RACE	Race	07.03.01	ADSL/race 1=White 2=Black or African American 3=Asian 4=American Indian or Alaska native	Use same coding as in popPK dataset which matched EMD coding. See as provided.	1=White 2=Black or African American 3=Asian 4=American Indian or Alaska native 5=Native Hawaiiin or other Pacific Islander	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			5=Native Hawaiian or other Pacific Islander 6=Other -999=missing		6=Other .=missing			
ETHN	Ethnicity	07.03.02	ADSL/ethnic Set missing value to -999	Analyst Input Not Required.	Use PDS codelist. 1 = HISPANIC/LATINO 2 = NOT HISPANIC/LATINO	integer up to 5 digits 1,2,3 ... n.	5.	Num
RACD	Racial Designation	07.03.03	SUPPDM/qval if qnam="RACIALD" 5=Japanese 6=KOREAN 7=Chinese 8=Other -999=missing	Analyst Input Not Required.	Use PDS codelist. 1 = INDIAN SUBCONTINENT ASIAN 2 = SOUTHEAST ASIAN 3 = FAR EAST ASIAN 4 = ALASKAN NATIVE 5 = PACIFIC ISLANDER 6 = NORTH AMERICAN	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
					INDIAN 7 = NATIVE HAWAIIAN			
BWT	Weight in Kg (Baseline)	07.05.02	ADVS/aval where param in (WEIGHT (KG)) and not missing(base) and abfl = "Y"; Set missing value to -999	Analyst Input Not Expected.	Default: unit = kg Baseline value of weight is used	Up to 5 digits can include decimal places	Best5.	Num
SMOK	Smoking Classification	07.07.01	ADSU/avalc where param = "SMOKING HISTORY" and armcd = "A" ; 1=NEVER 2=CURRENT 3=FORMER	Analyst Input Not Required.	Use PDS codelist. 1 = never smoked 2 = smoker 3 = ex-smoker	integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			Set missing value to -999					
BBMI	Body Mass Index (Baseline)	07.10.02	ADVS/aval where param in ("BODY MASS INDEX (KG/M**2)") AND ABLFL = "Y" ; Set missing value to -999	Analyst Input Not Required.		Up to 5 digits can include decimal places	BEST5.	Num
BCCL	Creatinine Clearance (Baseline)	10.01.02	Set to -999 to keep consistent with PopPK data file	Analyst Input Not Required.	Default for Subjects 13 years or older, uses Cockcroft & Gault formula for Subjects less than 13 years old, uses Schwartz formula Methods available:	Up to 8 digits can include decimal places	BEST8.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
					Cockcroft & Gault (subjects ≥ 13 yr) Schwartz (subjects < 13 yr) * Note all calculations use the Baseline value for input variables			
BCAL	Corrected Calcium (Baseline)	10.02.02	ADLB/aval Multiplied by 4 to convert unit Set missing value to -999 if param="Calcium Corrected (mmol/L)" and abfl='Y' Units: mg/dL	Analyst Input Not Required.	Standard units: mg/dL	Up to 5 digits can include decimal places	Best5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
BPLT	Platelets (Baseline)	10.04.02	ADLB/aval Set missing value to -999 if param= "Platelets (10 ⁹ /L)" and ablf='Y' Units: 10 ⁹ /L	Analyst Input Not Required.	Units = 10 ⁹ cells/L	Up to 5 digits can include decimal places	Best5.	Num
BNEU	Normalised Neutrophils (Baseline)	10.05.02	ADLB/aval Set missing value to -999 if param= "Neutrophils (10 ⁹ /L)" and ablf='Y' Units: 10 ⁹ /L	Analyst Input Not Required.	Units = 10 ⁹ /L	Up to 5 digits can include decimal places	Best5.	Num

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991003

Data set type: PD

Version: Data set release

Final PK/PD Programming Plan, 01 Nov 2019

Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
BHGB	Hemoglobin (Baseline)	10.10.02	ADLB/aval Set missing value to -999 Multiplied by 0.1 to convert unit if param="Hemoglobin (g/L)" and ablf='Y' Units: g/dL	Analyst Input Not Required.	Standard units: g/dL	Up to 5 digits can include decimal places	Best5.	Num
BALB	Normalised Albumin (Baseline)	10.10.03	ADLB/aval Multiplied by 0.1 to convert unit Set missing value to -999 if param="Albumin (g/L)" and ablf='Y' Units:g/dL	Analyst Input Not Required.	Units:g/dL	Up to 5 digits can include decimal places	Best5.	Num

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991003

Data set type: PD

Version: Data set release

Final PK/PD Programming Plan, 01 Nov 2019

Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
BLDH	Lactic Acid Dehydrogenase (baseline)	10.11.02	ADLB/aval Set missing value to -999 if param= "Lactate Dehydrogenase (U/L)" and abfl='Y' Units: U/L	Analyst Input Not Required.	Units = U/L	Up to 5 digits can include decimal places	Best5.	Num
BALT	Normalised ALT (Baseline)	10.12.02	ADLB/aval Set missing value to -999 if param= "Alanine Aminotransferase (microkat/L)" and abfl='Y' Multiply ADLB/aval by 60 to convert unit from microkat/L to standard units U/L	Analyst Input Not Required.	Standard units: U/L	Up to 5 digits can include decimal places	Best5.	Num

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991003

Data set type: PD

Version: Data set release

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
BAST	Normalised AST (Baseline)	10.13.02	ADLB/aval Set missing value to -999 if param= "Aspartate Aminotransferase (microkat/L)" and abfl='Y' Multiply ADLB/aval by 60 to convert unit from microkat/L to standard units U/L	Analyst Input Not Required.	Standard units: U/L	Up to 5 digits can include decimal places	Best5.	Num
BBIL	Normalised Bilirubin (Baseline)	10.14.02	ADLB/aval Multiplied by 1/17 to convert unit Set missing value to -999 if param= "Bilirubin (micromol/L)" and abfl='Y'	Analyst Input Not Required.	Standard units: mg/dL	Up to 5 digits can include decimal places	Best5.	Num

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991003

Data set type: PD

Version: Data set release

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			Units: mg/dL					
BSLD	Tumor burden at baseline (mm), sum of longest diameter	99.99.01	ADTRB/base where param = "Sum of Diameter" ;	Tumor burden at baseline (mm), sum of diameter of target lesions	mm	e.g. 5	5.	Num
SLD	Tumor burden (mm)	99.99.02	ADTRB/aval where param = "Sum of Diameter" ;	tumor burden at current time (mm)	LOCF	e.g. 5	5.	Num
SURT	Survival time	99.99.03	ADTTEB/aval where param in ("PFS Primary (Months)", "Overall Survival (Months)");	For OS or PFS, time of event (in weeks)		e.g. 5	5.	Num

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991003

Data set type: PD

Version: Data set release

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
CENS	Censoring	99.99.04	ADTTEB/cnsr where param in ("PFS Primary (Months)", "Overall Survival (Months)");	For OS or PFS, censoring	0 = not censored; 1 = censored event	integer up to 5 digits 1,2,3 ... n.	5.	Num
ECOG	ECOG status at baseline	99.99.05	ADSL/ecogbl Set missing value to -999	ECOG status at baseline		0,1,2,etc.	5.	Num
METS	Metastatic disease site	99.99.06	TU/tuloc where . < tudy < 1 Set missing value to -999	Number of metastatic sites at baseline		e.g. 5	5.	Num
LIVMET	Presence of liver metastases	99.99.07	TR/trloc where trtest = "Tumor State" and . < TRDY <= 1 and not index(TRSTAT,"N			0 = absent ; 1 = present	5.	Num

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**DMB09-GSOP-
RF06 2.0**

**PK/PD PROGRAMMING
PLAN TEMPLATE**

01-May-2019

MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991003

Data set type: PD

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			OT"); set to 0 for missing value.					
LNGME T	Presence of lung metastases	99.99.08	TR/trloc where trtest = "Tumor State" and . < TRDY <= 1 and not index(TRSTAT,"N OT"); set to 0 for missing value.			0 = absent ; 1 = present	5.	Num
BONME T	Presence of bone metastases	99.99.09	TR/trloc where trtest = "Tumor State" and . < TRDY <= 1 and not index(TRSTAT,"N OT"); set to 0 for missing			0 = absent ; 1 = present	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			value.					
MSKCC	Memorial Sloan-Kettering Cancer Center (MSKCC/Motzer) Score for Metastatic Renal Cell Carcinoma (RCC)	99.99.10	ADMH/mskccbl 0=Favorable 1=Intermediate 2=Poor Set missing value to -999		0 = favorable risk; 1 = intermediate risk (1-2 factors); 2 = poor risk (3 or more factors)	integer up to 5 digits 1,2,3 ... n.	5.	Num
HENG	Heng criteria	99.99.11	ADMH/hengbl 0=Favorable 1=Intermediate 2=Poor Set missing value to -999		0 = favorable risk; 1 = intermediate risk (1-2 factors); 2 = poor risk (3 or more factors)	integer up to 5 digits 1,2,3 ... n.	5.	Num

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
EGFR	eGFR (baseline)	99.99.12	Derived Male, not Black or African American: EGFR (mL/min/1.73 m2) = 32788 * CREAT(μmol/L)- 1.154 * AGE(y)- 0.203 Male, Black or African American: EGFR (mL/min/1.73 m2) = 32788 * CREAT(μmol/L)- 1.154 * AGE(y)- 0.203 * 1.210 Female, not Black or African American: EGFR (mL/min/1.73 m2) = 32788 * CREAT(μmol/L)-			0.1,2,etc.	Best5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			1.154 * AGE(y)- 0.203 * 0.742 Female, Black or African American: EGFR (mL/min/1.73 m2) = 32788 * CREAT(μmol/L)- 1.154 * AGE(y)- 0.203 * 1.210 * 0.742 Set missing value to -999					
EVID	Event identification	99.99.13	Derived For FLAGE=1 and FLAGE=2 (OS and PFS), there were 2 rows representing the START and the END of OS or PFS. Then, we need to add two additional columns			integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			in order to identify START or END: EVID and EVNT, where EVID=3 for START of OS or PFS and EVID=0 for the END of OS or PFS. Then, for EVID=3, please change SURT to 0 for the START time of 0 weeks. For FALGE=3, set to 0.					
EVNT	Dependent variable event	99.99.14	Derived <ul style="list-style-type: none">o when EVID=3, EVNT=0o when EVID=0 and CENS=0, EVNT=1o when EVID=0 and CENS=1, EVNT=0			integer up to 5 digits 1,2,3 ... n.	5.	Num

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			o For FLAGE=3 (SLD), EVID=1 and EVNT=0					
DOSRED	Dose Reduction Category	99.99.15	ADEX2/AVALC WHERE param='Subject with At Least 1 Dose Reduction' 0 = no dose reductions 2 = dose reduced sunitinib 4 = dose reduced axitinib 5 = dose reduced avelumab 45= dose reduced on both axitinib and avelumab					

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			set DOSRED to 0 for no-treated subjects					
DOSINT	Dose Interruption Category	99.99.16	ADEX2/AVALC WHERE param in ('Subject with At Least 1 Dose Interruption', 'Subject with At Least 1 Infusion Interruption') 0 = no dose interruption 2 = dose interruption sunitinib 4 = dose interruption axitinib 5 = dose interruption					

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			avelumab 45 = dose interruption on both avelumab and axitinib set DOSINT to 0 for no-treated subjects and subjects(110 subjects) without dose interruption information in dosing source data – ADEX2					
BLYM	Lymphocyte (Baseline)	99.99.17	ADLB/aval Set missing value to -999 if param= "Lymphocytes (10^9/L)" and			Up to 5 digits can include decimal places	Best5.	Num

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Data set type: PD

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Global Variable Name	Variable Description	Sort Order	SAS Data set or View/ Reference Variable	Analyst Input	Additional Information / Default Values	Required Format / Examples	SAS Format	SAS Type
			ablfl='Y' Units: 10^9/L					

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7. Test Plan

The software will be tested by completing the Global PK/PD QC checklist and executing the global PK/PD QC automated checks macro in accordance with the PK/PD QC guidelines and OPD. The output PDF produced by the PK/PD QC automated checks macro will reside in CDARS in the location listed in the completed QC checklist. Additional checks for the non-standard variables/derivations can be added to the checklist section 20. This checklist is located in improve in the folder listed in section 4.3 *Storage of Documents*.

8. Programming Notes

8.1 *Alphanumeric PK Values*

NA. No PK data is included.

8.2 *Screening, Follow-Up and Unplanned Events*

Screening assessments will be supplied in the output data set.

8.3 *Other Data*

8.3.1 **C column**

There were 13 subjects without dosing information, but with PD data, and marked as C in the PD dataset.

8.3.2 **METS, LIVMET, LNGMET and BONMET**

There are two source data for metastases. One is TU; other is TR. Here is some description about those two source data.

- TU domain contains the details of each target, non-target, and new lesion's location and methods used for its identification.
- TR domain captures all the results associated with the scans.

In TU, only metastatic disease site information collected in TULOC.

In TR, both Metastatic disease site & Presence of liver, lung and bone metastases are collected in TULOC & TRSTRESC.

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Therefore, we just can derive LIVMET, LNGMET and BONMET from TR. But for METS, we can derive it from TU.

For missing/ INDETERMINATE, set LIVMET, LNGMET and BONMET to 0.

TRSTRESC in source data (Character Result/Finding in Std Format)	LIVMET, LNGMET / BONMET
ABSENT LESION OR NORMAL LYMPH NODE	0 = absent
INCREASED PRESENT PRESENT (FIRST APPEARANCE) PRESENT/NOT INCREASED	1 = present
INDETERMINATE Missing	Missing

8.3.3 DAY & TAFD derivation

The first dosing date for Sunitinib or axitinib was used to derive DAY & TAFD, which is confirmed with analyst.

8.3.4 DOSRED & DOSINT derivation

1. DOSRED = Dose reduction category to indicate whether a patient had at least one dose reduction of a treatment
 - 0 = no dose reductions
 - 1 = dose reduced interferon-alpha from A6181034
 - 2 = dose reduced sunitinib from A6181034, B9991002, or B9991003
 - 3 = dose reduced sorafenib from A4061051
 - 4 = dose reduced axitinib
 - 5 = dose reduced avelumab from B9991002 or B9991003
 - 45= dose reduced on both axitinib and avelumab
2. DOSINT = Dose interruption category to indicate whether a patient had at least one dose interruption of a treatment
 - 0 = no dose interruption
 - 1 = dose interruption interferon-alpha from A6181034
 - 2 = dose interruption sunitinib from A6181034, B9991002, or B9991003
 - 3 = dose interruption sorafenib from A4061051
 - 4 = dose interruption axitinib

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- 5 = dose interruption avelumab from B9991002 or B9991003
- 45 = dose interruption on both avelumab and axitinib

For no-treated subjects but with some PK/PD records in datafile, set DOSRED and DOSINT to 0 per analyst's confirmation.

There are 110 of 886 subjects without dose interruption information in dosing source data – ADEX2, we will set DOSINT as 0 per analyst's confirmation.

8.4 Population of SS, II and ADDL

NA

8.5 Programming or Data Issues

8.5.1 DOSE derivation

Scenario 1: It is found that there are two QD AXI doses for subject 12001003 in study B9991003 as below.

For the following SLD record collected on 16AUG2017, we will derive DOSE to 3, instead of 0.

USUBJID	EXDOSFRQ	EXADJ	VISIT	EXSTDTC	EXENDTC	DOSE
B9991003 1200 12001003	QD	OTHER SPECIFY	CYCLE3_DOSE_AXI	2017-08-16	2017-08-16	0
B9991003 1200 12001003	QD	ADVERSE EVENT(S)	CYCLE3_DOSE_AXI	2017-08-16	2017-08-16	3

PARAM	VISIT	nsid	date	FLAGE	SLD	SURT	CENS
Sum of Diameter	SCREENING	12001003	26APR2017	3	65.2	.	.
Sum of Diameter	CYCLE1_IOTA	12001003	05JUL2017	3	70.3	.	.
Sum of Diameter	CYCLE2_IOTA	12001003	16AUG2017	3	48	.	.
Sum of Diameter	CYCLE3_IOTA	12001003	27SEP2017	3	47.8	.	.
Sum of Diameter	CYCLE4_IOTA	12001003	08NOV2017	3	42.6	.	.
Sum of Diameter	CYCLE5_IOTA	12001003	20DEC2017	3	40.9	.	.
Sum of Diameter	CYCLE6_IOTA	12001003	31JAN2018	3	41.6	.	.
Sum of Diameter	CYCLE7_IOTA	12001003	14MAR2018	3	36.3	.	.
Sum of Diameter	CYCLE8_IOTA	12001003	25APR2018	3	35.9	.	.
Sum of Diameter	CYCLE9_IOTA	12001003	06JUN2018	3	38.4	.	.
PFS Primary (Months)		12001003	06JUN2018	2	38.4	54.43	1
Overall Survival (Months)		12001003	20JUN2018	1	38.4	56.43	1

Scenario 2: For the subject 12121001, there are two different QD doses on 19FEB2018 for the following one SLD record on 19FEB2018 which highlight in black as below.

1. One is 37.5 with the dose end date - 19FEB2018
2. The other is 50 with the dose start date - 19FEB2018

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Since the SLD is for Cycle 11, we will use the DOSE on Cycle 11 of 37.5.

SLD data:

USUBJID	PARAM	VISIT	nsid	date	FLAGE	SLD	SURT	CENS
B9991003 1212 12121001	Sum of Diameter	SCREENING	12121001	27OCT2016	3	153.7	.	.
B9991003 1212 12121001	Sum of Diameter	CYCLE1_IOTA	12121001	08DEC2016	3	171.1	.	.
B9991003 1212 12121001	Sum of Diameter	CYCLE2_IOTA	12121001	06JAN2017	3	153.7	.	.
B9991003 1212 12121001	Sum of Diameter	CYCLE3_IOTA	12121001	03MAR2017	3	135.3	.	.
B9991003 1212 12121001	Sum of Diameter	CYCLE4_IOTA	12121001	14APR2017	3	119.2	.	.
B9991003 1212 12121001	Sum of Diameter	CYCLE5_IOTA	12121001	26MAY2017	3	117.5	.	.
B9991003 1212 12121001	Sum of Diameter	CYCLE6_IOTA	12121001	07JUL2017	3	92.8	.	.
B9991003 1212 12121001	Sum of Diameter	CYCLE7_IOTA	12121001	21AUG2017	3	97.2	.	.
B9991003 1212 12121001	Sum of Diameter	CYCLE8_IOTA	12121001	02OCT2017	3	100.6	.	.
B9991003 1212 12121001	Sum of Diameter	CYCLE9_IOTA	12121001	13NOV2017	3	106.5	.	.
B9991003 1212 12121001	Sum of Diameter	CYCLE10_IOTA	12121001	05JAN2018	3	102.7	.	.
B9991003 1212 12121001	Sum of Diameter	CYCLE11_IOTA	12121001	19FEB2018	3	95.3	.	.
B9991003 1212 12121001	Sum of Diameter	CYCLE12_IOTA	12121001	06APR2018	3	98.4	.	.
B9991003 1212 12121001	PFS Primary (Months)		12121001	06APR2018	2	.	75.14	0
B9991003 1212 12121001	Sum of Diameter	CYCLE13_IOTA	12121001	18MAY2018	3	87.2	.	.
B9991003 1212 12121001	Overall Survival (Months)		12121001	20JUN2018	1	.	85.86	1

Dosing data:

USUBJID	EXDOSFRQ	VISIT	EXSTDTC	EXENDTC	DOSE
B9991003 1212 12121001	QD	CYCLE1_DOSE_SUN	2016-10-28	2016-11-24	50
B9991003 1212 12121001	QD	CYCLE2_DOSE_SUN	2016-12-09	2017-01-05	50
B9991003 1212 12121001	QD	CYCLE3_DOSE_SUN	2017-01-20	2017-02-16	50
B9991003 1212 12121001	QD	CYCLE4_DOSE_SUN	2017-03-03	2017-03-30	37.5
B9991003 1212 12121001	QD	CYCLE5_DOSE_SUN	2017-04-14	2017-05-11	37.5
B9991003 1212 12121001	QD	CYCLE6_DOSE_SUN	2017-05-26	2017-06-22	37.5
B9991003 1212 12121001	QD	CYCLE7_DOSE_SUN	2017-07-07	2017-08-04	37.5
B9991003 1212 12121001	QD	CYCLE8_DOSE_SUN	2017-08-21	2017-09-17	37.5
B9991003 1212 12121001	QD	CYCLE9_DOSE_SUN	2017-10-02	2017-10-30	37.5
B9991003 1212 12121001	QD	CYCLE10_DOSE_SUN	2017-11-13	2017-12-11	37.5
B9991003 1212 12121001	QD	CYCLE11_DOSE_SUN	2018-01-05	2018-02-19	37.5
B9991003 1212 12121001	QD	CYCLE12_DOSE_SUN	2018-02-19	2018-03-01	50
B9991003 1212 12121001	QD	CYCLE12_DOSE_SUN	2018-03-01	2018-04-04	0
B9991003 1212 12121001	QD	CYCLE13_DOSE_SUN	2018-04-09	2018-05-06	50
B9991003 1212 12121001	QD	CYCLE14_DOSE_SUN	2018-05-18		50

8.6 Differences between versions of files

8.6.1 Updated on 03Jul2019 for draft#2 delivery

- For FLAGE=1 and FLAGE=2 (OS and PFS), currently there is 1 occurrence (row) per patient. For the analysis, please duplicate this row so that there are 2 per patient. The 2 rows will represent the START and the END of OS or PFS. Then, we need to add two additional columns in order to identify START or END: EVID and EVNT, where EVID=3 for START of OS or PFS and EVID=0 for the END of OS or PFS. Then, for EVID=3, please change SURT to 0 for the START time of 0 weeks. For EVNT, please define as follows:

- when EVID=3, EVNT=0;
- when EVID=0 and CENS=0, EVNT=1
- when EVID=0 and CENS=1, EVNT=0

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MSB0010718C (Avelumab), AG-013736 (Axitinib)

Protocol: B9991003

Data set type: PD

Version: Data set release

Final PK/PD Programming Plan, 01 Nov 2019

- For FLAGE=3 (SLD), EVID=1 and EVNT=0.

FLAGE	SURT	CENS	EVID	EVNT
1	0	1	3	0
1	44.14	1	0	0
2	0	0	3	0
2	6	0	0	1

- For the variable ID, please use numbers 1-750 for A6181034, then use 751-1038 for A4061051 (N=288), 1039-1093 for B9991002 (N=55), and 1094-1979 for B9991003 per analyst's request.

8.6.2 Updated on 31Jul2019 for draft#3 delivery

- Updated BCCL to missing;
- Set EVID to 0 for FLAGE=3 (SLD)
- Updated missing values of LIVMET, LNGMET & BONMET to 0.

8.6.3 Updated on 20Aug2019 for draft#4 delivery

- Change missing value to -999 for AGE SEX RACE ETHN RACD BWT SMOK BBMI BCCL BCAL BPLT BNEU BHGB BALB BLDH BALT BAST BBIL ECOG METS LIVMET LNGMET BONMET MSKCC HENG EGFR.

8.6.4 Updated on 25Sep2019 for draft#5 delivery

There were 2 variables – DOSRED & DOSINT added to the data file per analyst's comments.

8.6.5 Updated on 23Oct2019 for draft#6 delivery

The variable BLYM was added to the data file per analyst's comments.

8.6.6 Updated on 01Nov2019 for final delivery

The data file was not changed, and just be re-run to remove the “_draft” suffix.

We also finalized the supporting documents to removed “Draft” in header and updated version date for all documents.

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Appendix 3. Data Exclusions

```
1 #####
2 #
3 #   Pre-processing dataset for TGI modeling
4 #
5 #####
6
7 remove(list=ls())
8
9 library(tidyverse)
10 library(readxl)
11 library(magrittr)
12 library(lattice)
13 library(gridExtra)
14 library(GGally)
15 library(psych)
16 library(reshape2)
17 library(zoo)
18 library(survival)
19
20
21 as.num<-function(x){as.numeric(as.character(x))}
22 as.fac<-function(x){as.numeric(as.factor(x))}
23
24 # define equations for geometric mean, geometric cv%, and outliers
25 gm_mean<-function(x,na.rm=T){
26   a <- mean(log(x[x>0]),na.rm=T)
27   exp(a)
28 }
29
30 geocv<-function(x, na.rm = TRUE){
31   sdlog <- sd(log(x[x > 0]), na.rm = na.rm)
32   geosd <- exp(sdlog)
33   100*(sqrt(exp(log(geosd)^2)-1))
34 }
35
36 is_outlier <- function(x, na.rm=T) {
37   a<-quantile(x, 0.25,na.rm=T) - 1.5 * IQR(x,na.rm=T)
38   b<-quantile(x, 0.75,na.rm=T) + 1.5 * IQR(x,na.rm=T)
39   return(x < a | x > b)
40 }
41
42 `%!in%`=Negate(`%in%`)
43
44
45
46 #####
47 #
48 #---- Read in file
49 #
50 #####
51
52 #----Load in datafile
53 d1<-read.csv("RCC_COMBINED_PD_2_31OCT2019.csv",header=T,stringsAsFactors=F)
54
55
56 length(unique(d1$ID))
57 # [1] 1979
58
59
60 #####
61 #
62 # Explore SLD
63 #
64 #####
65
66
```

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```
67 # Subset FLAG = 3 for SLD
68 sld1<-d1 %>% subset (FLAG==3) %>% subset (C==".")
69
70 length(unique(sld1$ID)) # [1] 1842
71 # missing 85 patients compared to PFS
72
73
74 summary(as.numeric(sld1$BSLD))
75 # Min. 1st Qu. Median Mean 3rd Qu. Max. NA's
76 # 10.00 45.00 79.65 106.35 141.00 707.50 11
77
78
79 # 11 missing baseline SLD, remove for now
80 sld1$C<-ifelse(sld1$BSLD==".", "CBSLD", sld1$C)
81
82 sld2<-sld1 %>% subset (C==".")
83
84
85 sld2$DSLD<-as.numeric(sld2$SLD)-as.numeric(sld2$BSLD)
86 summary(sld2$DSLD)
87 # Min. 1st Qu. Median Mean 3rd Qu. Max.
88 # -257.00 -30.30 -10.90 -19.42 0.00 180.80
89
90 sld2$TAFD<-as.numeric(sld2$TAFD)
91 sld2$TREAT<-ifelse(sld2$TRT=="1", "INFa",
92 ifelse(sld2$TRT=="2", "Sunitinib",
93 ifelse(sld2$TRT=="3", "Sorafenib",
94 ifelse(sld2$TRT=="4", "Axitinib", "Avelumab+Axitinib"))))
95
96
97 sld2$TREAT2<-ifelse(sld2$TRT=="1", "Cytokine",
98 ifelse(sld2$TRT=="5", "IO+TKI", "TKI"))
99
100
101 #--- log transformation
102 sld2$LBSLD<-log(as.numeric(sld2$BSLD))
103 sld2$LSLD<-ifelse(as.numeric(sld2$SLD)!=0, log(as.numeric(sld2$SLD)), log(0.001))
104
105
106
107 write.csv(sld2, "RCC_COMBINED_PD2_SLD_31OCT2019.csv", quote=F, na=".",
108 row.names= F)
109
110
111
112 #--- See range of SLD
113 summary(as.numeric(sld2$SLD))
114 # Min. 1st Qu. Median Mean 3rd Qu. Max.
115 # 0.00 29.50 59.80 86.93 119.00 712.00
116
117 summary(as.numeric(sld2$BSLD))
118 # Min. 1st Qu. Median Mean 3rd Qu. Max.
119 # 10.00 45.00 79.65 106.35 141.00 707.50
120
121
122
123
124 # Plotting
125
126 p1<-ggplot()+
127 geom_line(data=sld2, aes(x=TAFD, y=DSLD, group=ID, color=TREAT))+
128 facet_wrap(~PROT, scales="free_y")+
129 xlab("Time after dose (weeks)")+
130 ylab("Change in Sum of Longest Diameter (mm)")+
131 theme_bw()+
132 theme(legend.title = element_blank())
133
134 p1
```

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```
135 png("RCC_SLD_changes_byStudy.png",height=600,width=600)
136 grid.arrange(p1, ncol=1)
137 dev.off()
138
139
140 p2<-ggplot()+
141   geom_line(data=sld2,aes(x=TAFD,y=DSLD,group=ID,color=as.character(PROT)))+
142   facet_wrap(~TREAT2, scales="free_y")+
143   xlab("Time after dose (weeks)")+
144   ylab("Change in Sum of Longest Diameter (mm)")+
145   theme_bw()+
146   theme(legend.title = element_blank())
147
148 p2
149 png("RCC_SLD_changes_byTreatmentType.png",height=600,width=1000)
150 grid.arrange(p2, ncol=1)
151 dev.off()
152
153
154 # truncate TAFD < 20 weeks
155 p2a<-ggplot()+
156   geom_line(data=sld2,aes(x=TAFD,y=DSLD,group=ID,color=as.character(PROT)))+
157   facet_wrap(~TREAT2, scales="free_y")+
158   xlab("Time after dose (weeks)")+
159   xlim(0,20)+
160   ylab("Change in Sum of Longest Diameter (mm)")+
161   theme_bw()+
162   theme(legend.title = element_blank())
163
164 p2a
165 png("RCC_SLD_changes_byTreatmentType_TAFD20w.png",height=600,width=1000)
166 grid.arrange(p2a, ncol=1)
167 dev.off()
168
169
170 # log SLD
171 p2b<-ggplot()+
172   geom_line(data=sld2,aes(x=TAFD,y=LSLD,group=ID,color=as.character(PROT)))+
173   facet_wrap(~TREAT2, scales="free_y")+
174   xlab("Time after dose (weeks)")+
175   xlim(0,20)+
176   ylab("log of Sum of Longest Diameter (mm)")+
177   theme_bw()+
178   theme(legend.title = element_blank())
179 p2b
180
181 # SLD
182 p2c<-ggplot()+
183   geom_line(data=sld2,aes(x=TAFD,y=as.numeric(SLD),group=ID,color=as.character(PROT)))+
184   facet_wrap(~TREAT2, scales="free_y")+
185   xlab("Time after dose (weeks)")+
186   xlim(0,20)+
187   ylab("Sum of Longest Diameter (mm)")+
188   theme_bw()+
189   theme(legend.title = element_blank())
190
191 p2c
192 png("RCC_SLD_rawlog_byTreatmentType_TAFD20w.png",height=600,width=1000)
193 grid.arrange(p2b,p2c, ncol=2)
194 dev.off()
195
196
197 ##### Individual plot of change in SLD
198
199 pdf("Change_SLD_individual_plots.pdf")
200 par(mfrow=c(3,4), mar=c(2,2,2,2))
201 for(i in sort(unique(sld2$ID))){
202   temp<-sld2 [sld2$ID==i,]
```

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```

203   plot(temp$TAFD, temp$DSDL, type="n", ylab="Change in Sum of Longest Diameter (mm)",
204         xlab="Time (hr)",
205         main=paste("ID=", i), cex=0.5)
206   lines(temp$TAFD, temp$DSDL, type="b", lty=3, cex=1.2, lwd=1.5, col="black")
207
208
209 }
210
211
212
213 dev.off()
214
215 pdf("logSLD_individual_plots.pdf")
216 par(mfrow=c(3,4), mar=c(2,2,2,2))
217 for(i in sort(unique(sld2$ID))) {
218   temp<-sld2 [sld2$ID==i,]
219   plot(temp$TAFD, temp$LSDL, type="n", ylab="log of Sum of Longest Diameter (mm)",
220         xlab="Time (hr)",
221         main=paste("ID=", i), cex=0.5)
222   lines(temp$TAFD, temp$LSDL, type="b", lty=3, cex=1.2, lwd=1.5, col="black")
223
224
225 }
226
227
228
229 dev.off()
230
231
232 #--- Histogram
233
234 p3<-ggplot(sld2, aes(x=as.numeric(BSLD))) +
235   geom_histogram(aes(y=..density..), # Histogram with density instead of count on y-axis
236                 colour="black", fill="#3399FF", binwidth = 20) +
237   geom_density(alpha=.2) + theme_bw() + xlab("Baseline SLD (mm)") + ylab("Density")
238
239 p3a<-ggplot(sld2, aes(x=log(as.numeric(BSLD)))) +
240   geom_histogram(aes(y=..density..), # Histogram with density instead of count on y-axis
241                 colour="black", fill="#3399FF", binwidth = 0.2) +
242   geom_density(alpha=.2) + theme_bw() + xlab("log of Baseline SLD (mm)") + ylab("Density")
243
244 png("RCC_BSLD_histogram.png", height=600, width=1200)
245 grid.arrange(p3, p3a, ncol=2)
246 dev.off()
247
248 p4<-ggplot(sld2, aes(x=as.numeric(SLD))) +
249   geom_histogram(aes(y=..density..), # Histogram with density instead of count on y-axis
250                 colour="black", fill="#3399FF", binwidth = 20) +
251   geom_density(alpha=.2) + theme_bw() + xlab("SLD (mm)") + ylab("Density")
252
253 p4a<-ggplot(sld2, aes(x=log(as.numeric(SLD)))) +
254   geom_histogram(aes(y=..density..), # Histogram with density instead of count on y-axis
255                 colour="black", fill="#3399FF", binwidth=0.2) +
256   geom_density(alpha=.2) + theme_bw() + xlab("log of SLD (mm)") + ylab("Density")
257
258 png("RCC_SLD_histogram.png", height=600, width=1200)
259 grid.arrange(p4, p4a, ncol=2)
260 dev.off()
261
262
263
264 #####
265 #
266 # Find time of min SLD
267 #
268 #####
269
270 min1<-aggregate(as.numeric(sld2$SLD), by=list(sld2$ID), min)

```

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```
271 names(min1) <-c("ID", "MINSLD")
272
273 sld3<-merge(sld2,min1,by=c("ID"),all.x=T)
274
275 sld3$SLD<-as.numeric(sld3$SLD)
276 sld3$MINTIME<-ifelse(sld3$MINSLD==sld3$SLD,sld3$TAFD,99999)
277
278
279 # get the first instance of min time
280 min2<-aggregate(sld3$MINTIME,by=list(sld3$ID),min)
281 names(min2) <-c("ID", "MINTIME1")
282
283
284 sld4<-merge(sld3,min2,by=c("ID"),all.x=T)
285
286 sld5<-sld4 %>% select(ID,PROT,TREAT,TREAT2,BSLD,MINSLD,MINTIME1) %>% distinct()
287 # remove MINTIME1=0 (which is when min SLD is baseline SLD)
288 sld6<-sld5 %>% subset(MINTIME1>0)
289
290 # Plot min SLD by time
291
292 p5<-ggplot()+
293   geom_boxplot(data=sld5,aes(x=TREAT,y=MINTIME1,group=TREAT,color=TREAT))+
294   #facet_wrap(~PROT, scales="free_y")+
295   ylab("Time to minimum SLD (weeks)") +
296   xlab("Includes those that progress (Min SLD=BSLD)") +
297   theme_bw()+
298   theme(legend.position = "none")
299
300 p6<-ggplot()+
301   geom_point(data=sld5,aes(x=MINTIME1,y=MINSLD,group=ID,color=TREAT))+
302   facet_wrap(~PROT, scales="free_y")+
303   xlab("Time to minimum SLD (weeks)") +
304   ylab("Minimum SLD (mm)") +
305   theme_bw()+
306   theme(legend.title = element_blank())
307
308 p7<-ggplot()+
309   geom_boxplot(data=sld6,aes(x=TREAT,y=MINTIME1,group=TREAT,color=TREAT))+
310   #facet_wrap(~PROT, scales="free_y")+
311   ylab("Time to minimum SLD (weeks)") +
312   xlab("Excludes Min SLD=BSLD") +
313   theme_bw()+
314   theme(legend.position = "none")
315
316 png("RCC_SLD_min_time_byPROTTRT.png",height=600,width=600)
317 grid.arrange(p6, ncol=1)
318 dev.off()
319
320 png("RCC_SLD_mintime_boxplots.png",height=600,width=1200)
321 grid.arrange(p5,p7, ncol=2)
322 dev.off()
323
324
325 #### Plotting by time block - histogram of SLD
326 sld2$TIMEBLOCK<-case_when(sld2$TAFD==0 ~"Baseline",
327                             sld2$TAFD>0 & sld2$TAFD<=6~"Block 1 - 6 wk",
328                             sld2$TAFD>6 & sld2$TAFD<=12~"Block 2 - 12 wk",
329                             sld2$TAFD>12 & sld2$TAFD<=18~"Block 3 - 18 wk",
330                             sld2$TAFD>18 & sld2$TAFD<=24~"Block 4 - 24 wk",
331                             sld2$TAFD>24 & sld2$TAFD<=36~"Block 5 - 36 wk",
332                             sld2$TAFD>36 & sld2$TAFD<=52~"Block 6 - 52 wk",
333                             TRUE~"Block 7 - over 1 yr")
334
335
336 # Plotting
337
338 tim1<-ggplot(sld2, aes(x=as.numeric(SLD))) +
```

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```
339   facet_wrap(~TIMEBLOCK) +
340   geom_histogram(aes(y=..density..),      # Histogram with density instead of count on y-axis
341                 colour="black", fill="#3399FF") +
342   geom_density(alpha=.2) + theme_bw() + xlab("SLD (mm)") + ylab("Density")
343
344 tim2<-ggplot(sld2, aes(x=LSLD)) +
345   facet_wrap(~TIMEBLOCK) +
346   geom_histogram(aes(y=..density..),      # Histogram with density instead of count on y-axis
347                 colour="black", fill="#3399FF") +
348   geom_density(alpha=.2) + theme_bw() + xlab("log of SLD (mm)") + ylab("Density")
349
350 png("RCC_SLD_histogram_timeblock.png",height=600,width=1200)
351 grid.arrange(tim1,tim2, ncol=2)
352 dev.off()
353
354
355 sessionInfo()
356 # R version 3.5.1 Patched (2018-11-18 r75627)
357 # Platform: x86_64-w64-mingw32/x64 (64-bit)
358 # Running under: Windows >= 8 x64 (build 9200)
359 #
360 # Matrix products: default
361 #
362 # locale:
363 #   [1] LC_COLLATE=English_United States.1252  LC_CTYPE=English_United States.1252
364 #   [3] LC_MONETARY=English_United States.1252 LC_NUMERIC=C
365 #   [5] LC_TIME=English_United States.1252
366 #
367 # attached base packages:
368 #   [1] stats      graphics  grDevices  utils      datasets  methods   base
369 #
370 # other attached packages:
371 #   [1] survival_2.43-1 zoo_1.8-6      reshape2_1.4.3 psych_1.7.8    GGally_1.4.0
372 #   [6] gridExtra_2.3  lattice_0.20-38 magrittr_1.5   readxl_1.3.1  forcats_0.2.0
373 #  [11] stringr_1.4.0  dplyr_0.8.3    purrr_0.3.2    readr_1.3.1   tidyr_0.8.3
374 #  [16] tibble_2.1.3   ggplot2_3.2.1  tidyverse_1.2.1
375 #
376 # loaded via a namespace (and not attached):
377 #   [1] tidyselect_0.2.5  splines_3.5.1    haven_2.1.1      colorspace_1.4-1
378 #   [5] vctrs_0.2.0      yaml_2.2.0       rlang_0.4.1      pillar_1.4.2
379 #   [9] foreign_0.8-71    glue_1.3.1       withr_2.1.2      RColorBrewer_1.1-2
380 #  [13] modelr_0.1.1     plyr_1.8.4       munsell_0.5.0    gtable_0.2.0
381 #  [17] cellranger_1.1.0 rvest_0.3.2      labeling_0.3     parallel_3.5.1
382 #  [21] broom_0.4.3      Rcpp_1.0.2       scales_1.0.0     backports_1.1.4
383 #  [25] jsonlite_1.6     mnormt_1.5-5     digest_0.6.20    hms_0.5.1
384 #  [29] stringi_1.4.3    grid_3.5.1       cli_1.1.0        tools_3.5.1
385 #  [33] lazyeval_0.2.2   crayon_1.3.4     pkgconfig_2.0.1  zeallot_0.1.0
386 #  [37] Matrix_1.2-15    xml2_1.2.2       lubridate_1.7.4  reshape_0.8.8
387 #  [41] assertthat_0.2.0 httr_1.3.1       rstudioapi_0.7   R6_2.2.2
388 #  [45] nlme_3.1-137     compiler_3.5.1
```

Repository artifact ID FI-432749.

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Appendix 4. Population Modeling Analysis Plan (PMAP)

The next 15 pages are an external document with Repository artifact ID RA16374921.
This document is the Population Modeling Analysis Plan (PMAP).

	POPULATION MODELING ANALYSIS PLAN (PMAP)
Report Title:	Tumor growth inhibition modeling in first line advanced renal cell carcinoma
Compound:	Avelumab, Axitinib, Sunitinib
Report Number:	PMAP-EQDD-B999e-Other-994
Date Issued:	02 OCT 2019
Study Protocol(s):	A6181034, A4061051, B9991002, B9991003
Author(s):	Swan Lin, PharmD Clinical Pharmacology/Pharmacometrics, GPD Pfizer Global Research and Development, La Jolla

DOCUMENT HISTORY:			
Version	Date	Author(s)	Summary of Changes/Comments
0.1	20 JUN 2019	Swan Lin	First version of document
0.2	27 JUN 2019	Swan Lin	Second version of document updating methods section
0.3	12 JUL 2019	Swan Lin	Third version of document incorporating team comments
1.0	02 OCT 2019	Swan Lin	Final version incorporating all comments

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POPULATION MODELING ANALYSIS PLAN (PMAP)
APPROVAL PAGE

Report Title:	Tumor growth inhibition modeling in first line advanced renal cell carcinoma
Report Number:	PMAP-EQDD-B999e-Other-994

REPORT APPROVAL:

Ana Ruiz-Garcia

a353a395-b283-48c6-9cdc-eb478224cc5a

02 Oct 2019
18:40:039-0400

Ana Ruiz, Senior Director
Clinical Pharmacology/Pharmacometrics, GPD
Pfizer Global Research and Development, La Jolla

APPROVAL DATE: 02 OCT 2019

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ABBREVIATION AND DEFINITION OF TERMS

Notation	Description
λ	Drug-resistance rate constant.
BICR	Blinded independent central review.
BID	Twice daily.
DRF	Data request form.
E-R	Exposure-response.
ECOG	Eastern Cooperative Oncology Group.
FDA	Food and Drug Administration.
GBDM	Global Biometrics and Data Management.
IRC	Independent review committee.
IV	Intravenous.
K_D	Cell-kill rate constant.
K_L	Tumor growth rate constant.
MTD	Maximum tolerated dose.
OFV	Objective function value.
ORR	Objective response rate.
OS	Overall survival.
PD-1	Programmed Death-1.
PD-L1	Programmed Death Ligand-1.
PFS	Progression-free survival.
PK	Pharmacokinetic.
PKPD	Pharmacokinetic-pharmacodynamic.
PO	Oral.
PS	Performance status.
Q2W	Every 2 weeks.
QD	Once daily.
RCC	Renal cell carcinoma.
RECIST	Response Evaluation Criteria in Solid Tumors.
RP2D	Recommended Phase 2 dose.
SCM	Stepwise covariate model building procedure.
SLD	Sum of the longest tumor diameters.
TGI	Tumor growth inhibition.
TKI	Tyrosine kinase inhibitor.
TMS	Time to maximum tumor shrinkage.
TS _{ratio}	Tumor size ratio.
VEGFR	Vascular endothelial growth factor receptor.

1. INTRODUCTION

Renal cell carcinoma (RCC) is the most common kidney cancer and constitutes about 3% of all malignant tumors in adults [1]. Renal cell carcinoma (RCC) is often first detected at an advanced stage, with 25-30% of patients with metastatic disease at diagnosis.

There has been significant progress in the treatment of patients with advanced RCC with the use of targeted oral therapies and immunotherapies [2]. Prior to the introduction of targeted therapies, cytokines, including high-dose interleukin 2 and interferon- α were the standard of care for advanced RCC [3]. With the introduction of tyrosine kinase inhibitors (TKIs), the use of cytokines have been largely diminished. For many years, the TKIs sunitinib and pazopanib were considered the preferred first line treatments based on improvements in progression-free survival (PFS) in their pivotal studies [3].

Monoclonal antibodies that block the Programmed Death-1 (PD-1)/Programmed Death Ligand-1 (PD-L1) interaction are novel immunotherapeutic approaches for advanced RCC, which have shown single-agent efficacy in patients whose disease has progressed following vascular endothelial growth factor receptor (VEGFR) pathway inhibitor therapy. Avelumab is a human immunoglobulin G1 monoclonal antibody directed against PD-L1. Axitinib is a TKI targeted against VEGFR and is approved as monotherapy treatment of second line RCC. Recently, the Food and Drug Administration (FDA) approved the use of avelumab in combination with axitinib for the treatment of first-line advanced RCC. The efficacy and safety of avelumab in combination with axitinib was demonstrated in the JAVELIN Renal 101 trial (Study B9991003). In this study, the median PFS for this combination was 13.8 months compared to 8.4 months with sunitinib monotherapy.

Early tumor shrinkage, as well as other tumor growth inhibition (TGI) metrics, have been shown to be good predictors of the probability of survival in cancer patients [4, 5, 6]. The use of these metrics to predict clinical outcomes has the potential to support early decision making in phase 1b/2 studies [7]. Several longitudinal TGI models have been described in patients with first and second line RCC who were treated with traditional cytokine therapy or TKIs [8, 9]. Currently, the time course of tumor size has not been characterized in patients receiving immunotherapy or combination therapies.

2. OBJECTIVE(S)

- Develop a longitudinal model for the time course of tumor size in first line RCC patients.
- Evaluate treatment effect on the time course of tumor size with interferon- α , sunitinib, sorafenib, axitinib, or combination therapy with avelumab + axitinib.
- Summarize tumor growth inhibition metrics that could be subsequently tested in future analyses to predict clinical outcomes.

3. STUDY OVERVIEW

3.1. Study Design

3.1.1. Study A6181034

Study A6181034 (N=750) was a randomized, multi-center, international, Phase 3 study of sunitinib (Arm A) vs interferon- α (Arm B) as first-line therapy in subjects with metastatic RCC. The primary objective of the study was to compare PFS in sunitinib treated arm versus the interferon- α arm.

Patients received treatment with either sunitinib in repeated 6 week cycles, consisting of 4 weeks of 50 mg daily administration followed by 2 weeks off treatment (Schedule 4/2), or interferon- α , 9 million units, administered as a subcutaneous injection on 3 non-consecutive days each week.

3.1.2. Study A4061051

The first line portion of Study A4061051 (N=288) was a 2-arm, randomized, open-label, multicenter study to evaluate the efficacy and safety of axitinib versus sorafenib in treatment-naïve patients with metastatic RCC. The primary objective of this first line portion of the study was to compare the PFS between the two treatments. A total of approximately 247 treatment-naïve patients were randomized in a 2:1 ratio between axitinib vs sorafenib, and stratified by Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 vs 1.

Patients received axitinib at the starting dose of 5 mg twice daily (BID) with continuous dosing. Dose adjustments, including axitinib dose increase or dose reduction, were to be based on tolerability in the individual patient to levels of 2, 3, 5, 7, or 10 mg BID. The active comparator was sorafenib, dosed at 400 mg BID continuously. Dose adjustments of sorafenib was allowed to 400 mg once daily (QD) or 400 mg every other day.

3.1.3. Study B9991002

Study B9991002 (N=55) was a Phase 1b, open label, multi-center, multiple dose, safety, pharmacokinetic (PK), and pharmacodynamic study of avelumab in combination with axitinib in adult treatment-naïve patients with advanced RCC. The primary objective of this study was to assess the safety and tolerability of avelumab in combination with axitinib to estimate the maximum tolerated dose (MTD) and select the recommended Phase 2 dose (RP2D). Evaluating antitumor activity and survival were secondary endpoints. This clinical study was composed of two phases. The dose finding phase was in patients with RCC with clear cell histology who did not receive prior systemic therapy for advanced disease. From this phase, the MTD and RP2D of avelumab was determined to be 10 mg/kg every 2 weeks (Q2W) and the dose for axitinib was determined to be 5 mg BID. The dose expansion phase evaluated this combination dosing regimen in a cohort of treatment-naïve patients.

Axitinib was given orally 5 mg BID, with or without food, on a continuous dosing schedule, as according to the approved prescribing information. Avelumab was given as a 1-hour

intravenous (IV) infusion Q2W. All patients were to be continued on treatment with study drugs until confirmed disease progression, patient refusal, patient lost to follow up, unacceptable toxicity, or the study was terminated by the Sponsor, whichever occurred first.

3.1.4. Study B9991003

Study B9991003 (N=886) is an ongoing Phase 3, multinational, multicenter, randomized, open-label, parallel 2-arm study in which 442 patients have been randomized to the avelumab in combination with axitinib arm (Arm A) and 444 patients have been randomized to the sunitinib arm (Arm B).

- Arm A: avelumab 10 mg/kg IV Q2W in a 6-week cycle + axitinib 5 mg oral (PO) BID
- Arm B: sunitinib 50 mg PO QD on Schedule 4/2 (4 weeks on treatment followed by 2 weeks off treatment)

The primary objective of this study is to demonstrate that avelumab in combination with axitinib is superior to sunitinib monotherapy in prolonging PFS or overall survival (OS) in treatment-naïve patients with advanced RCC with PD-L1-positive tumors. Additional objectives include assessment of safety and PK and evaluation of efficacy in first-line treatment irrespective of PD-L1 expression. The data included in this analysis report are from an interim analysis of this ongoing study.

Patients were stratified according to ECOG PS (0 versus 1) and region (United States versus Canada/Western Europe versus the rest of the world). Treatment with study drugs continues until confirmed disease progression assessed by blinded independent central review (BICR) as per the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1, patient refusal, patient lost to follow up, unacceptable toxicity, or if the study is terminated by the Sponsor, whichever comes first. Crossover between treatment arms was not permitted.

3.2. Study Assessments

3.2.1. Study A6181034

The primary efficacy endpoint was PFS. Tumor assessments were performed both by the local study site and by a blinded, third-party, core imaging laboratory. The primary analysis of efficacy endpoints was based on the central radiology assessment. Tumor assessments were made by using RECIST at baseline, Day 28 of cycles 1-4, and Day 28 every 2 cycles thereafter.

3.2.2. Study A4061051

The primary endpoint was PFS by independent review committee (IRC). Tumor assessments were made by using RECIST at baseline, Weeks 6 and 12, and every 8 weeks thereafter.

3.2.3. Study B9991002

Anti-tumor activity was assessed by radiological tumor assessments and was based on RECIST. Tumor assessments included all known or suspected disease sites. Tumor

assessments were made at baseline, every 6 weeks up to 12 months, and every 12 weeks thereafter.

3.2.4. Study B9991003

Anti-tumor activity was assessed through radiological tumor assessments conducted at screening, at 6 weeks from randomization, then every 6 weeks up to 18 months after randomization and every 12 weeks thereafter until documented confirmed disease progression by BICR assessment regardless of initiation of subsequent anti-cancer therapy. In addition, radiological tumor assessments were conducted whenever disease progression was suspected (e.g., symptomatic deterioration).

4. DATA FOR ANALYSIS

4.1. Analysis Data Files

The pharmacokinetic-pharmacodynamic (PKPD) Programming group within Global Biometrics and Data Management (GBDM) will be responsible for generating the analysis data file using a validated process. Global processes and procedures will be followed. Programming plans, data request forms (DRFs), and quality control documentations can be found in each respective study folders in ePharmacology (Pfizer's internal population PK repository; source data are referenced in this report by a unique numeric locator).

4.2. Data Exclusions

Patients who did not have dosing records (eg., in other words, never received treatment) or patients who do not have tumor assessments for determination of sum of the longest tumor diameters (SLD) will be excluded in the analysis.

4.3. Missing Data and Imputations

No imputations will be made for missing dosing or SLD.

5. METHODS

5.1. Prior Knowledge/Modeling Experience

Anti-tumor activity is commonly evaluated in early development studies using objective response rate (ORR), where achievement of a predefined ORR is often the main decision criteria to inform about drug efficacy. The relative change in tumor size was recorded according to RECIST as the SLDs across specific targeted lesions. Using SLD-time data, TGI models could be used to characterize the tumor dynamics, which includes several processes occurring simultaneously; tumor growth kinetics, treatment-related shrinkage as well as potential tumor resistant development.

Longitudinal exposure-response (E-R) TGI models have been used to evaluate the anti-tumor effect of a drug based on continuous tumor size measurements and key parameters derived from these TGI have been successfully used to predict survival outcomes and evaluate the influence of drug exposure in key efficacy endpoints. A thorough review of tumor models that

have been developed since 2008 is provided in Ribba et al. [10].

A nonlinear TGI model was previously developed by Claret et al. in first line RCC patients using Studies A6181034 and A4061051 [9]. In the Claret model, it was found that there was a linkage between early tumor shrinkage (at week 8) to PFS. Using an external validation dataset, this model was qualified in predicting risk of PFS in the first line RCC.

5.2. Modeling: Software and Strategy

In this analysis, NONMEM version 7.4.3 or higher, PsN version 4.8.0 or higher, and R version 3.4.1 or higher (R Foundation for Statistical Computing, Vienna, Austria) will be used during the modeling. NONMEM will be used for the nonlinear mixed effects modeling of the tumor size over time. PsN will be used for stepwise covariate model building procedure (SCM). R will be used for all data manipulation, graphics, and table creation.

5.3. Base Model Description

The primary tumor dynamic model presented in this report takes the general form described by Claret et al [9]. This model utilizes longitudinal tumor size data to estimate drug-specific (cell-kill rate constant (K_D) and drug-resistance rate constant (λ)) and disease-specific parameters such as baseline tumor size (y_0) and tumor growth rate constant (K_L). The equation is provided below:

$$y(t) = y_0 \cdot e^{[K_L \cdot t - \frac{K_D}{\lambda} \cdot (1 - e^{-\lambda \cdot t})]} \quad (1)$$

In this model, the tumor growth rate constant (K_L) is proportional to the size of the tumor at time t . It also includes a cell-kill rate constant (K_D) that is proportional to the size of the tumor at time t . The growth rate is assumed to be linear and the drug effect is the result of the cell kill and tumor resistance to treatment. The cell kill follows an exponential decrease over time driven by the parameter λ . The rate of decay characterizes the tumor resistance over time to cell-killing.

Using this model, the time to maximum tumor shrinkage (TMS) can be obtained using the derivative of the differential equation as follows:

$$TMS = \frac{\ln(K_D) - \ln(K_L)}{\lambda} \quad (2)$$

where K_L , K_D , and λ are defined as before. The time units are the same as the time used in the model estimation. The TMS is presented in the primary analysis and calculated using the post hoc estimates from the model. Another informative metric often used as early predictor of efficacy outcomes is the tumor size ratio (TS_{ratio}) for a pre-defined period of time, this ratio is calculated as the tumor size at a given time over the tumor size at baseline:

$$TS_{ratio} = \frac{TS_t}{TS_{t=0}}. \quad (3)$$

5.4. Random Effects Model Development

Random effects will be added to the parameters to account for inter-individual differences in the rate of the tumor growth (K_L), rate of the cell-kill decay (K_D), and the drug-resistance parameter (λ). The specific parameterization of these random effects is as follows:

$$\begin{aligned}K_{D,TV} &= \theta_1 \\K_{L,TV} &= \theta_2 \\\lambda_{TV} &= \theta_3\end{aligned}$$

where $K_{D,TV}$, $K_{L,TV}$, and λ_{TV} are the typical values for the population, and the individual post hoc estimates for subjects $i = 1, \dots, N$ are:

$$\begin{aligned}K_{Di} &= K_{D,TV} + \eta_{1i} \\K_{Li} &= K_{L,TV} + \eta_{2i} \\\lambda_i &= \lambda_{TV} + \eta_{3i}\end{aligned}$$

where η_1 , η_2 , and η_3 are assumed to follow a multivariate normal distribution with mean 0 and a diagonal variance-covariance matrix Ω . To evaluate if the random effects were accounting for variation across individuals, the shrinkage and η significance (p-values) will be evaluated. The p-values will be evaluated to see if the η mean is significantly different than 0 and the shrinkage was evaluated using a maximum acceptable value of 20% to determine if individual parameter estimates are appropriate.

5.5. Inclusion of Covariates

Selected covariates will be tested for significance using SCM application in PsN with statistical criteria of $\alpha=0.05$ for forward inclusion, which corresponds to an objective function value (OFV) change of 3.84 based on a Chi-square distribution with df=1. The effect of treatment will be modeled by adding a parameter linearly as $1 + \theta \cdot (\text{Treatment})$. For example, to evaluate the potential effect of different treatments on cell killing (eg. K_D), the differential equation is described as:

$$K_{D,TV} = \theta_1 \cdot (1 + \theta \cdot \text{Treatment}) \quad (4)$$

where θ is an estimated parameter to characterize the effect of treatment on the cell death.

The effect of treatment may also be tested on other parameters (eg. K_L and λ).

Baseline SLD will also be assessed on model parameters as a linear, exponential or power function. No other covariates will be evaluated in this model.

5.6. Final Model Development

The final model development will start with a full model containing the parameters from the base model along with the covariates that were included from SCM through forward inclusion. This full model will then be subjected to stepwise backward elimination. The significance threshold for retaining covariates in the final model will be determined using the

likelihood ratio test to assess the significance of a covariate in the model when eliminated from the full model. The test for elimination of an individual covariate parameter, given the others were kept in the model, will be performed at a pre-specified significance level of $\alpha=0.001$, which corresponds to an OFV change of 10.84 based on a Chi-square distribution with $df=1$.

A covariate will be removed from the full model in a stepwise fashion, and the change in OFV will be calculated. If removal of any covariate results in a statistically significant increase (worsening) in OFV with $p<0.001$, the covariate giving the smallest insignificant increase will be removed from the full model, and a next round of elimination of a covariate will be performed. This process will be repeated until all remaining covariates are statistically significant. The final model will be obtained from the last stage of the elimination algorithm, in which all of the remaining covariate parameters, when tested 1 at a time, results in statistically significant likelihood ratio tests (ie, $p<0.001$).

In order to obtain the most parsimonious and stable final model, the candidate covariate model resulting from the backward elimination step in SCM will be subjected to a separate NONMEM run with \$COV step executed to examine any sign of model over parameterization and poorly estimated parameters.

TGI metrics will be defined from the output of the final model in the subsequent linkage to survival modeling, which will be described separately.

6. REFERENCES

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LIST OF ARTIFACTS

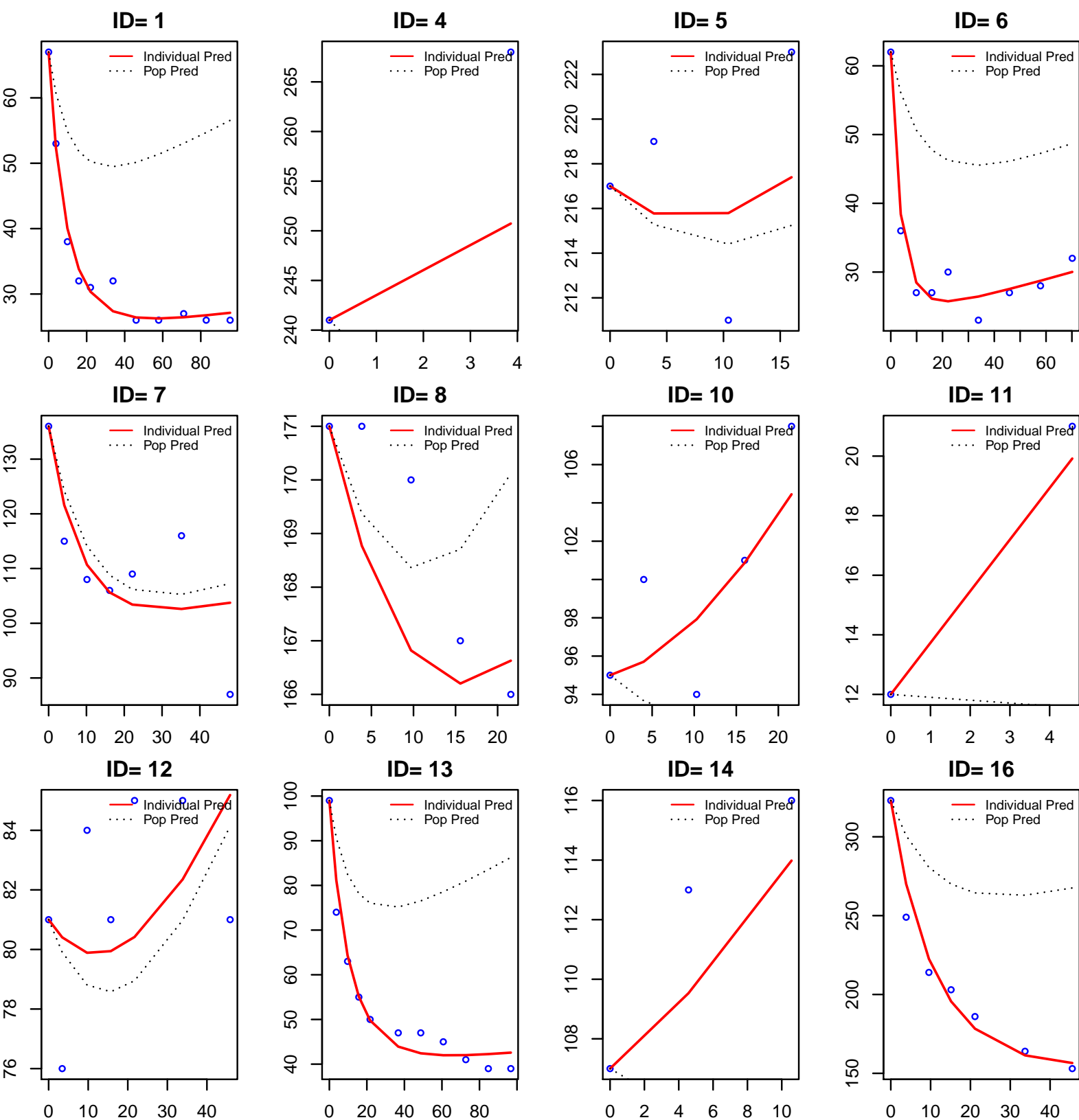
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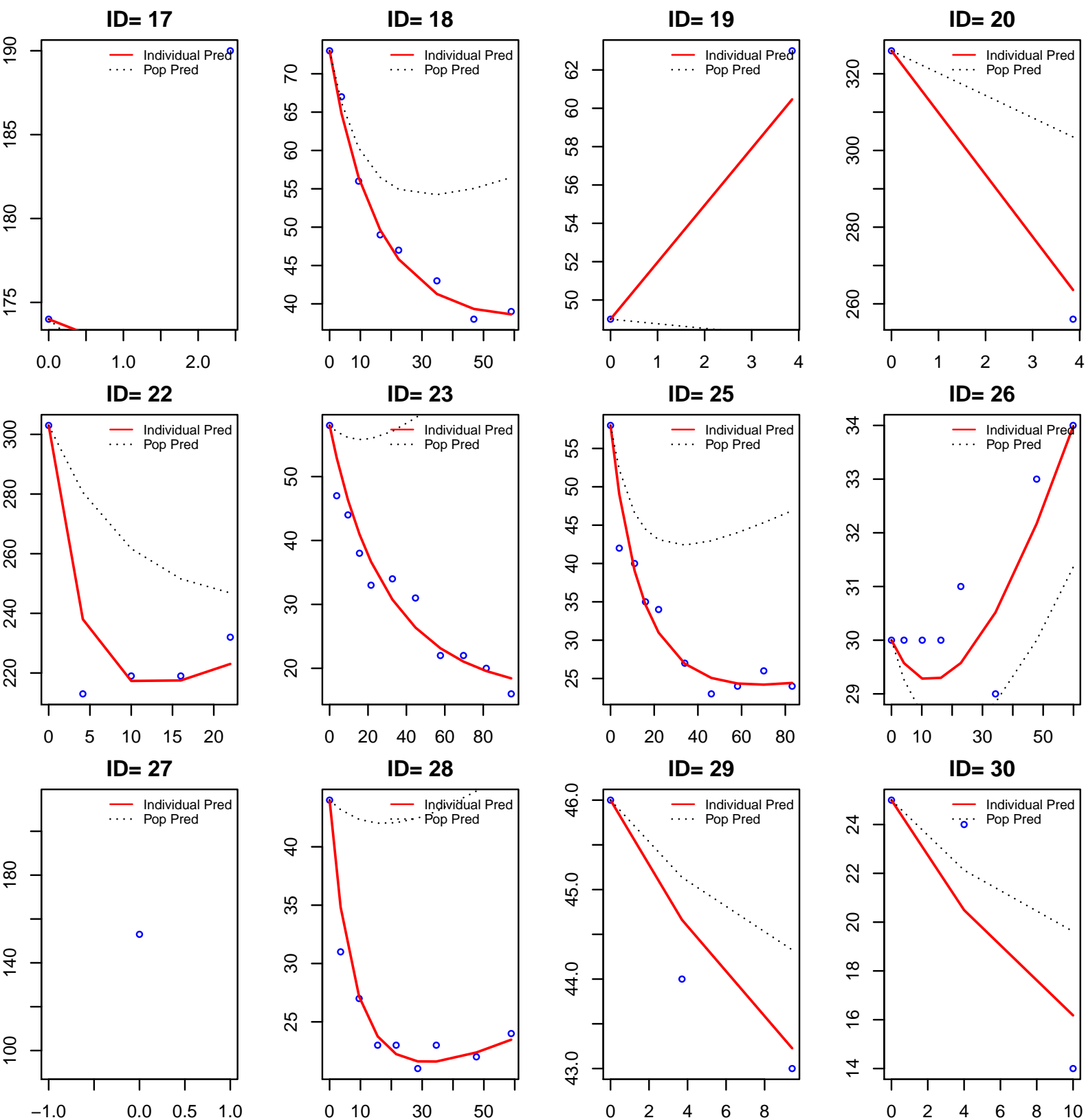
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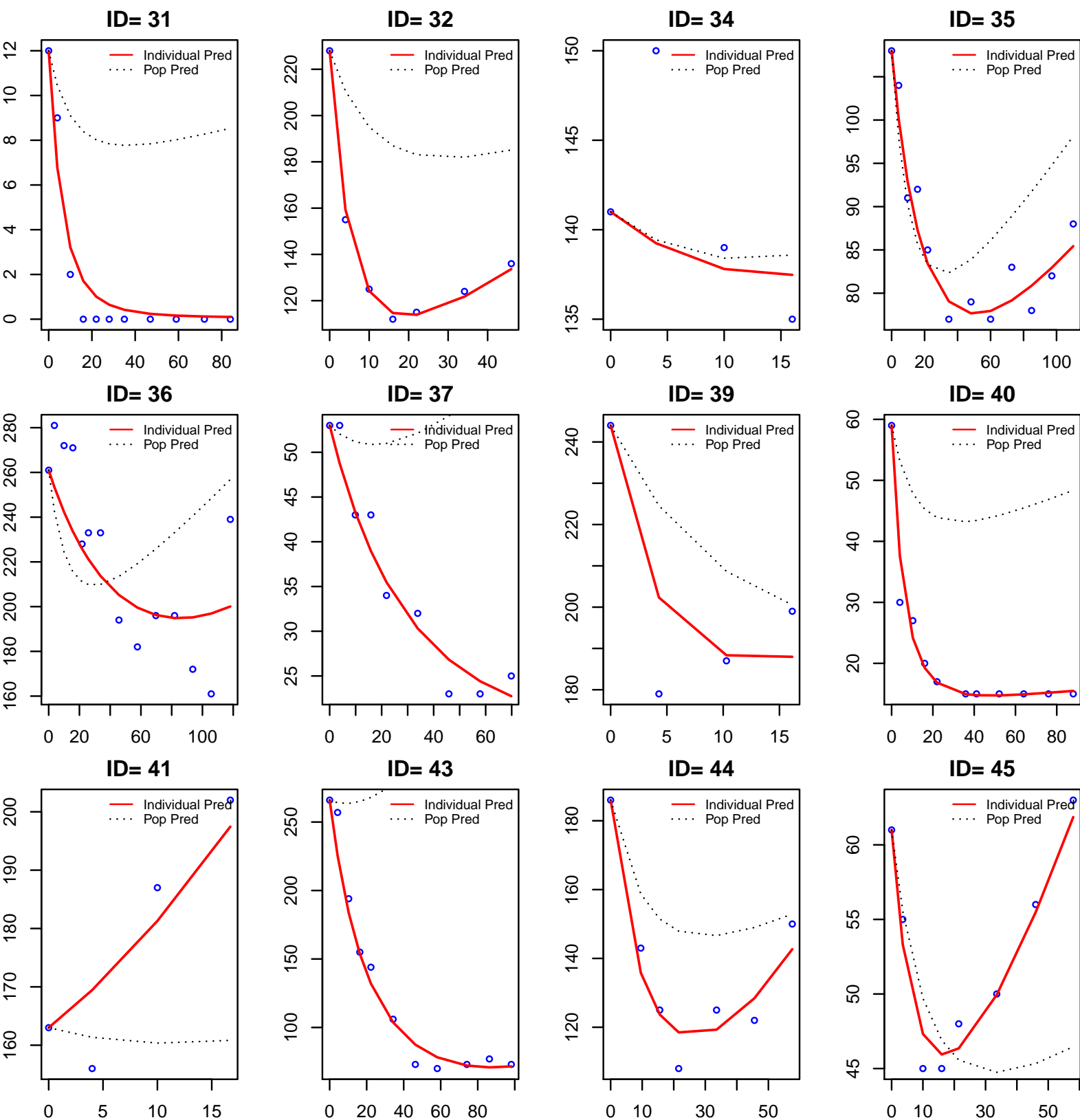
Appendix 5. Key Diagnostic Plots

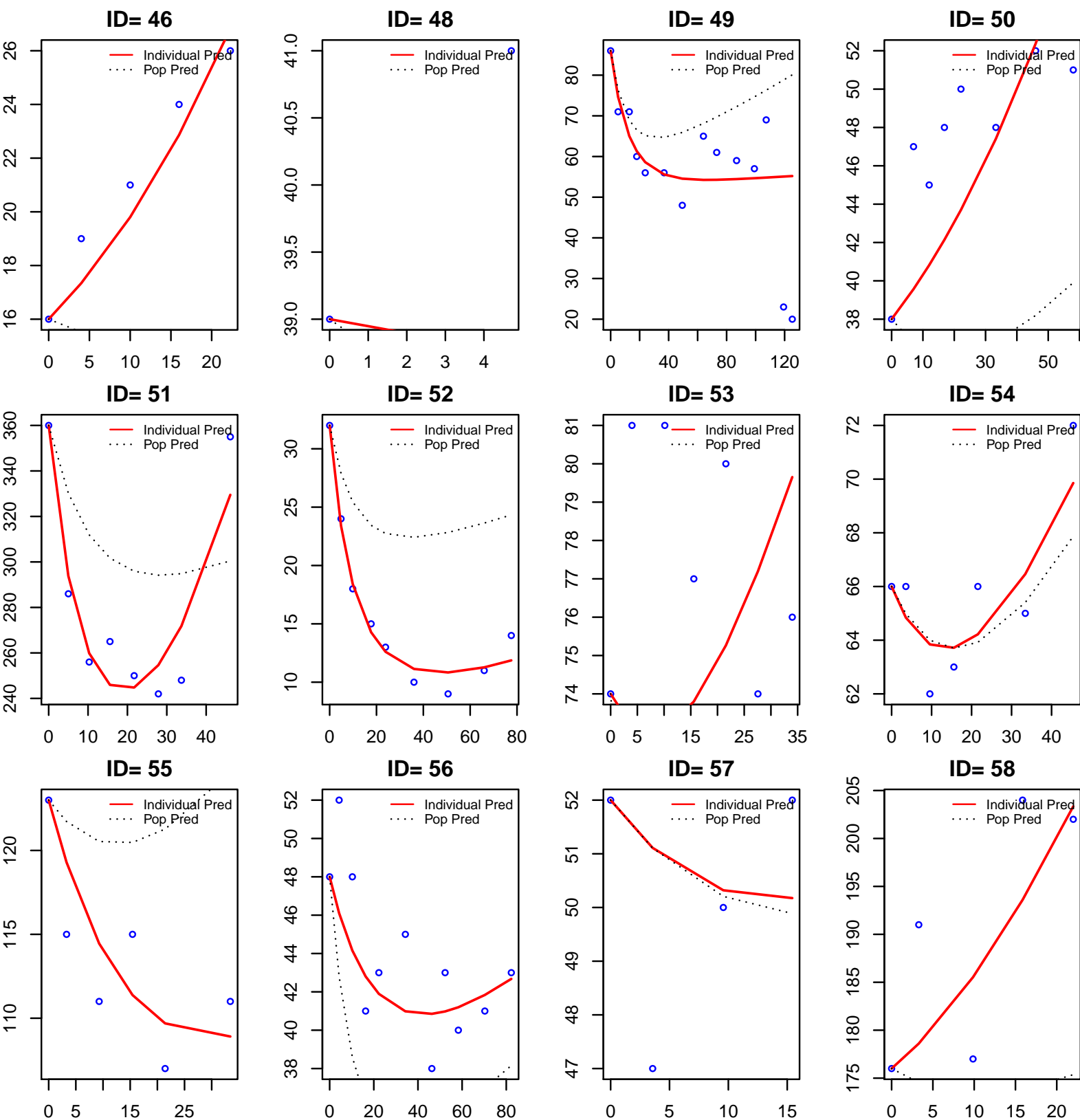
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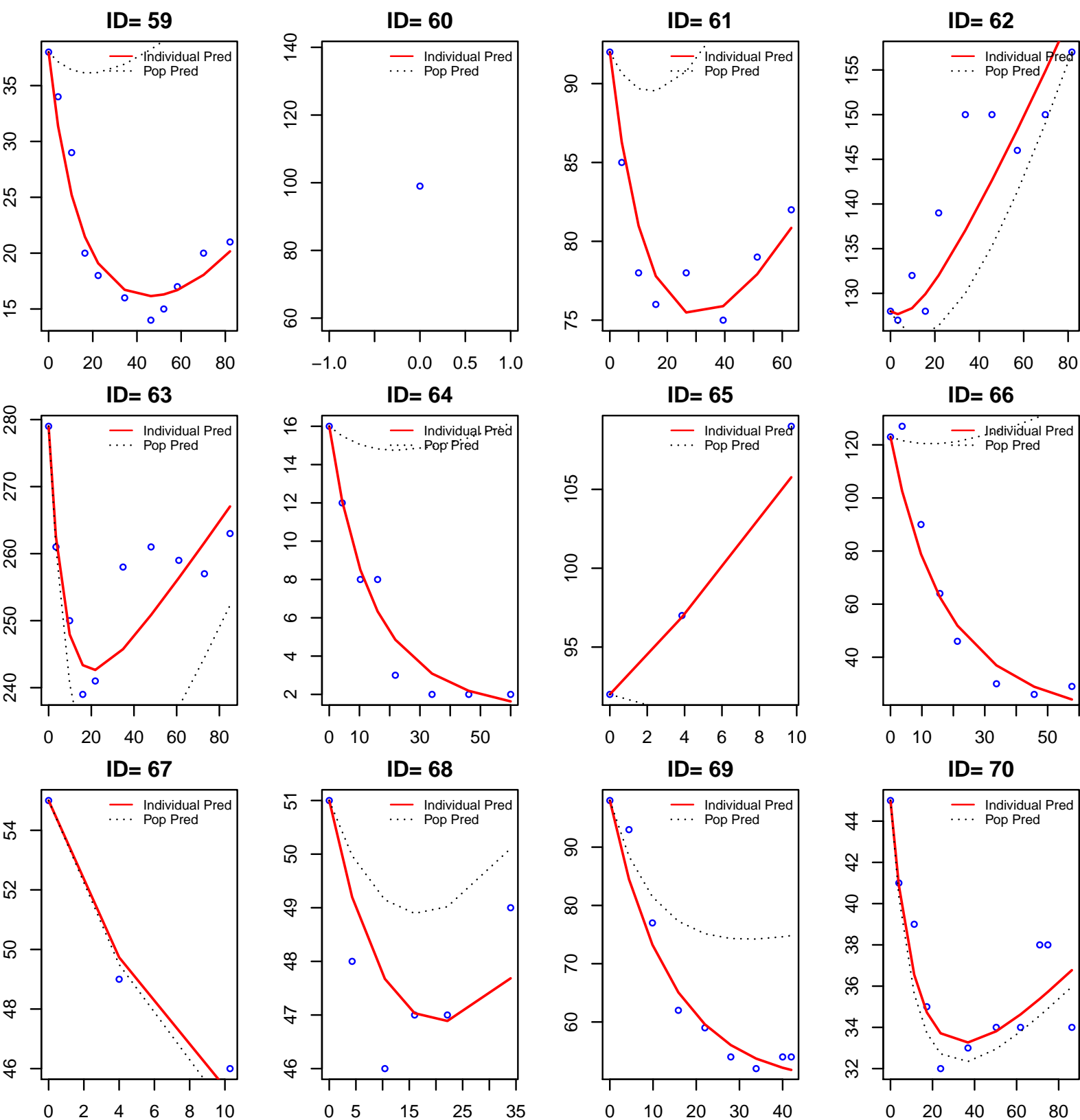
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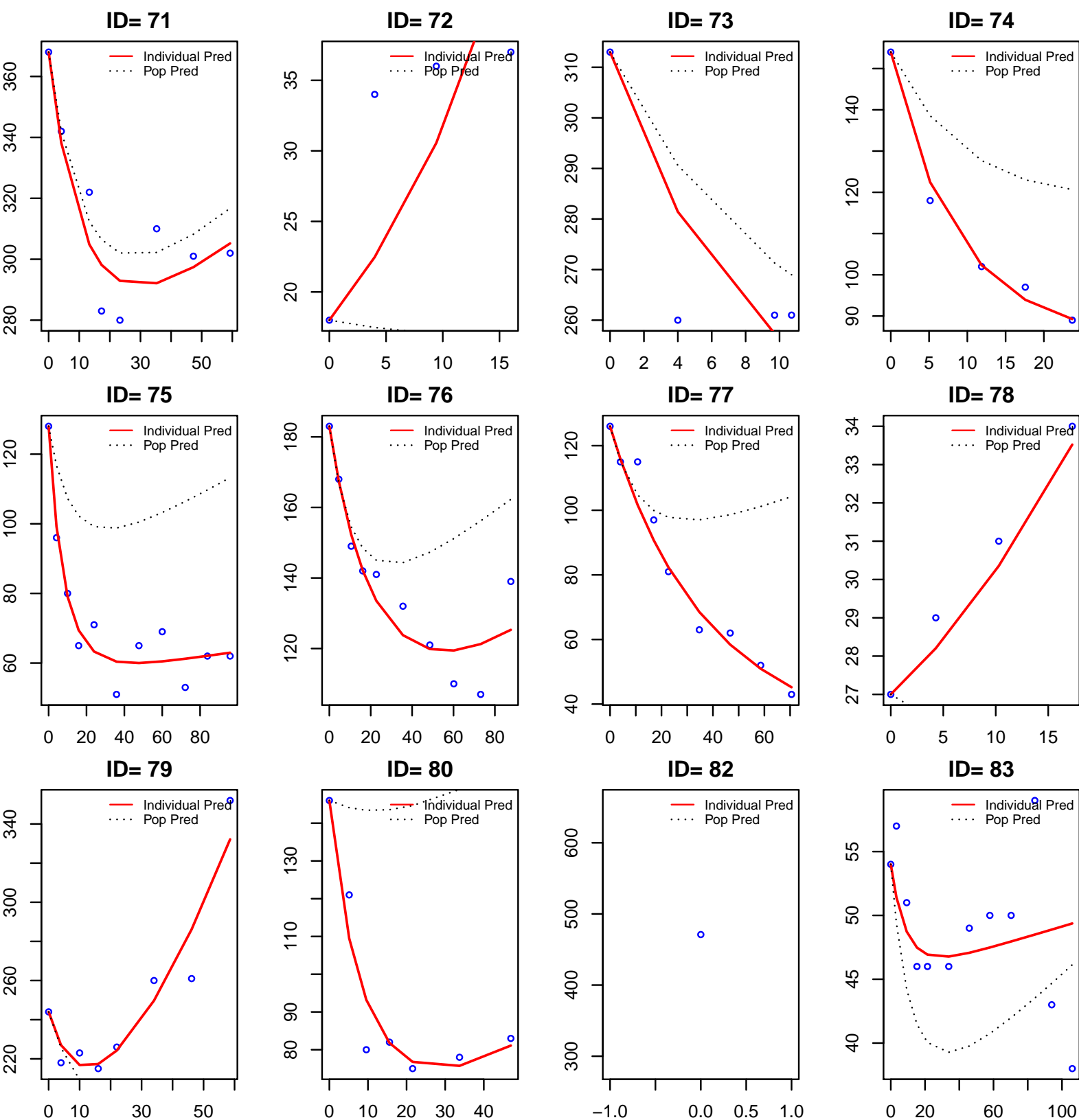


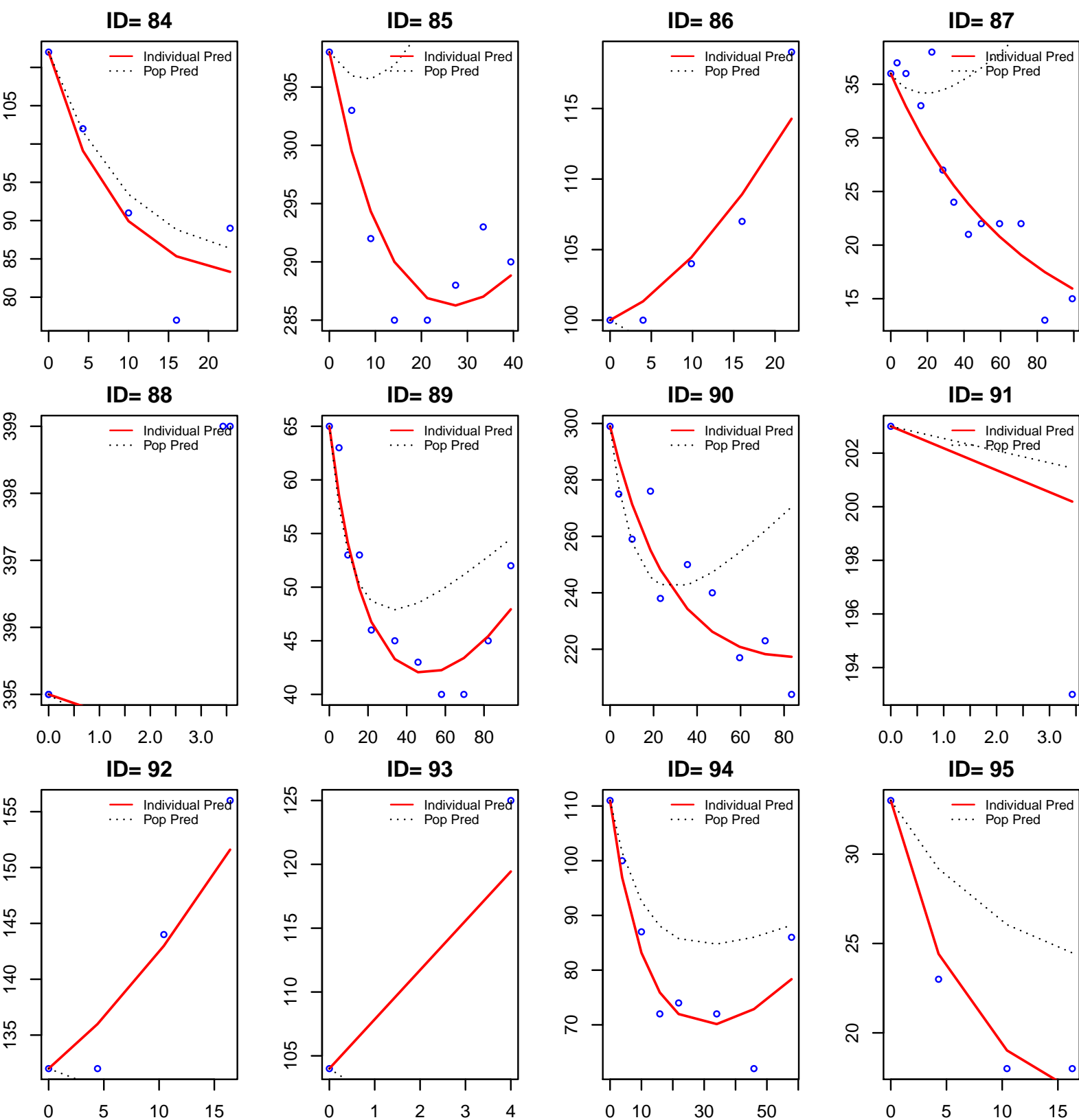


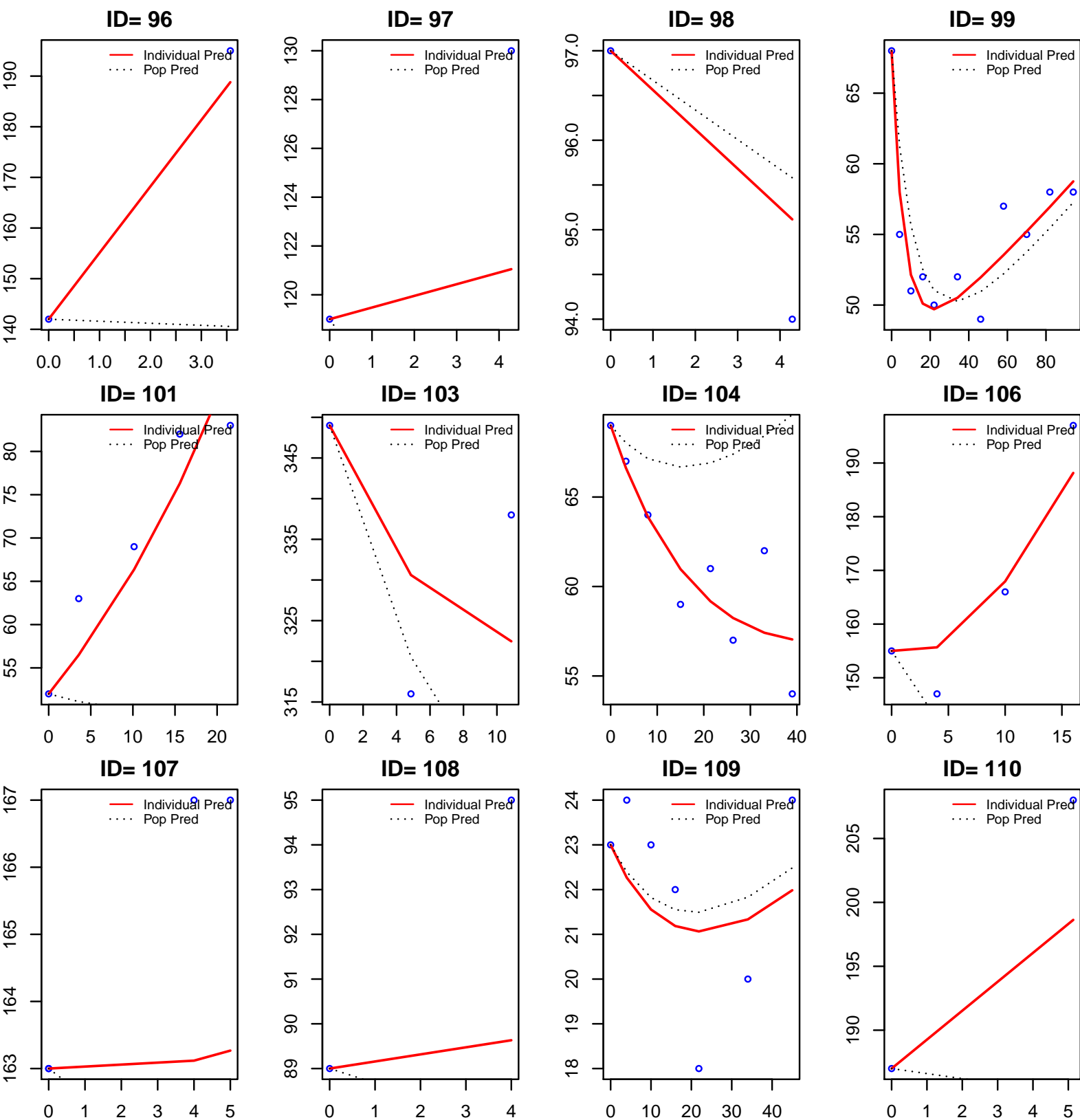


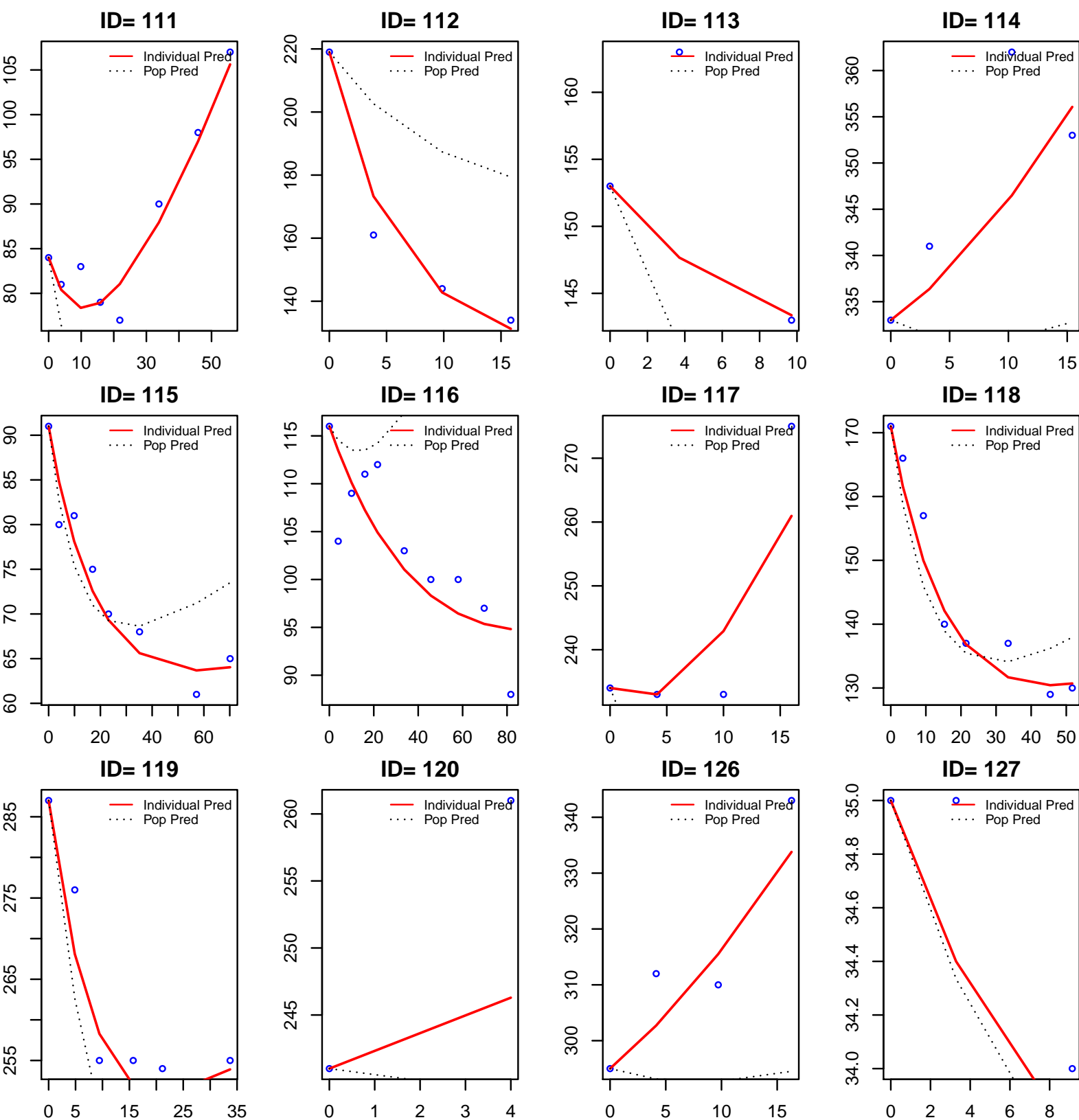


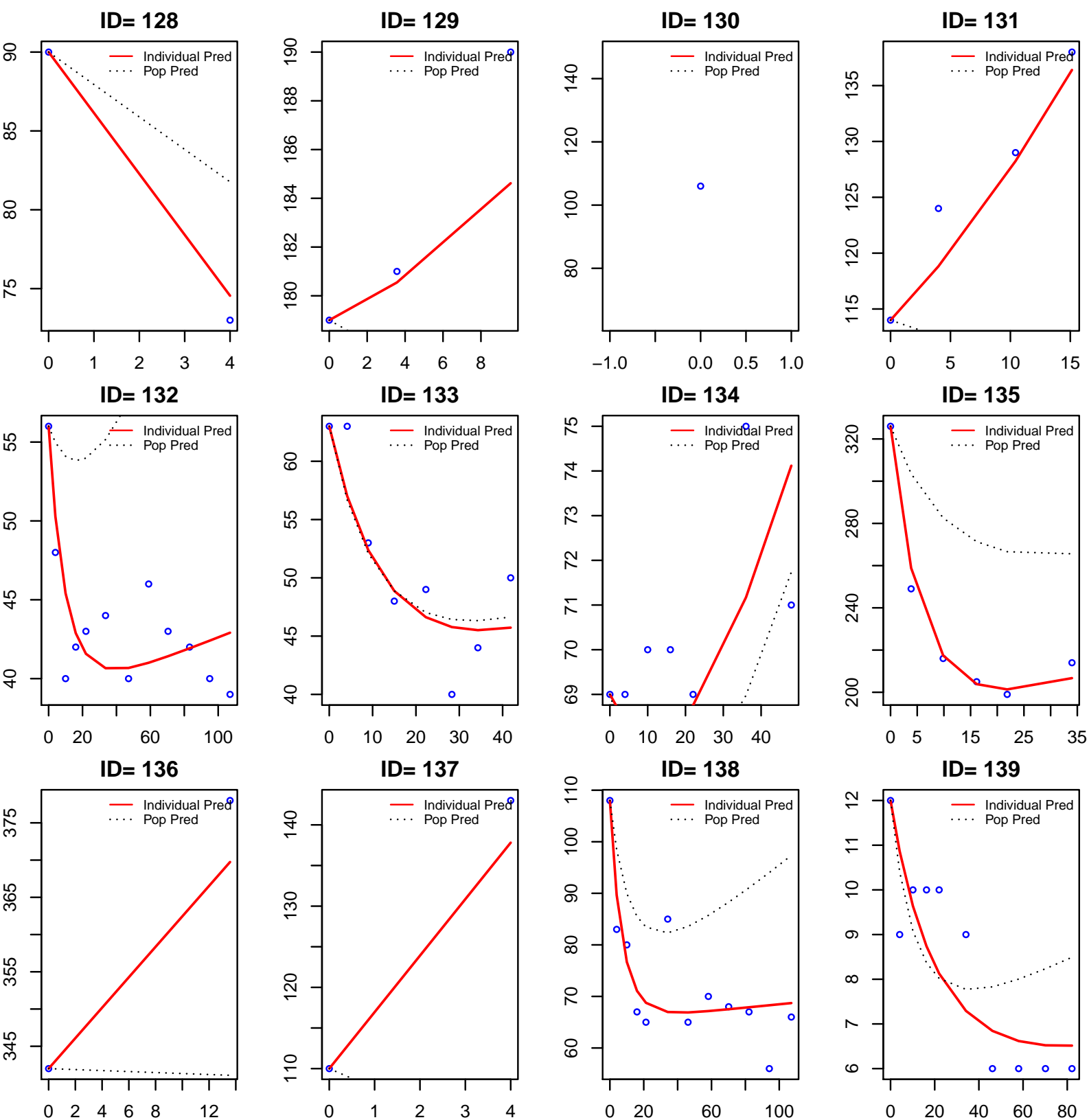


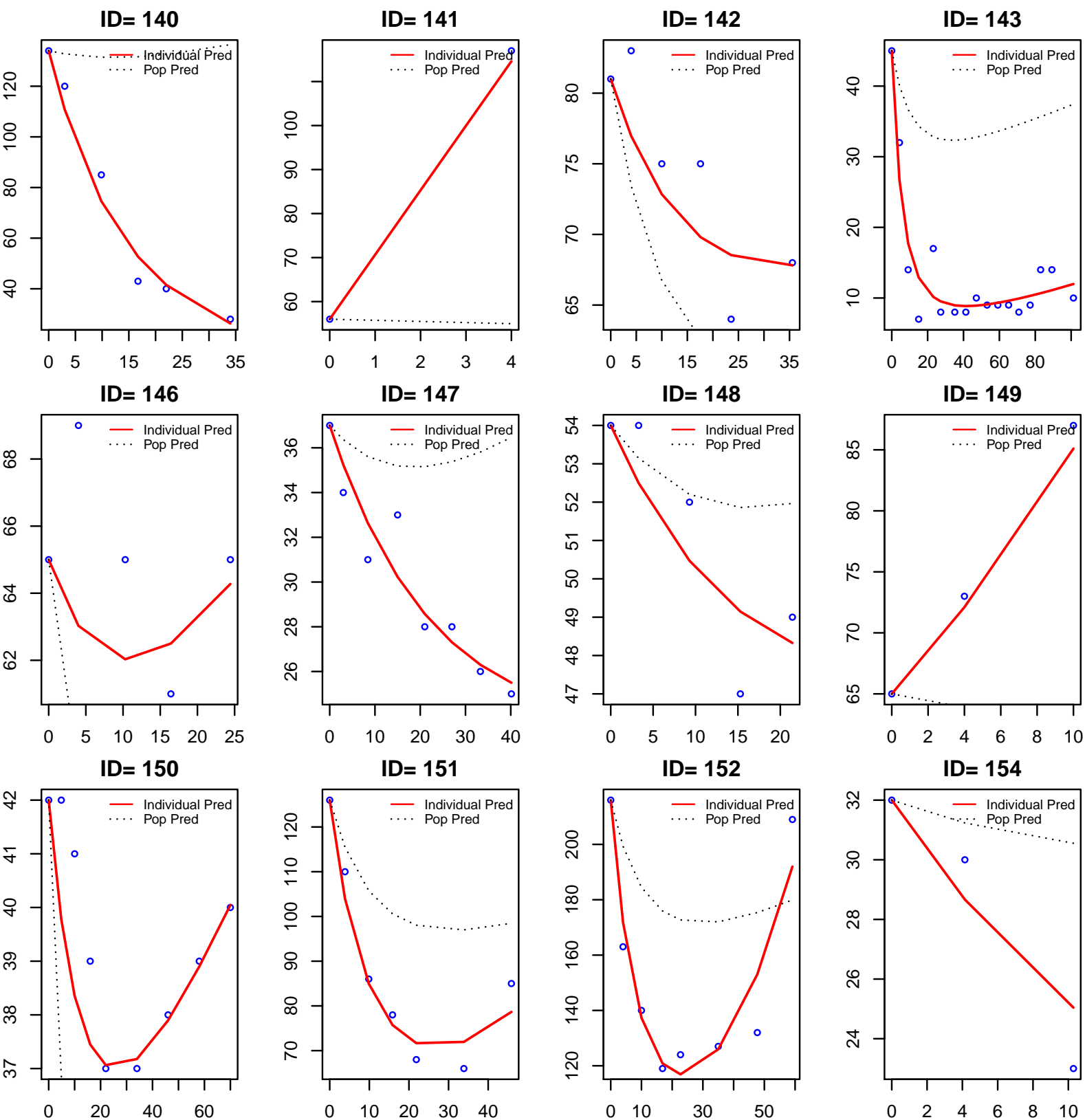


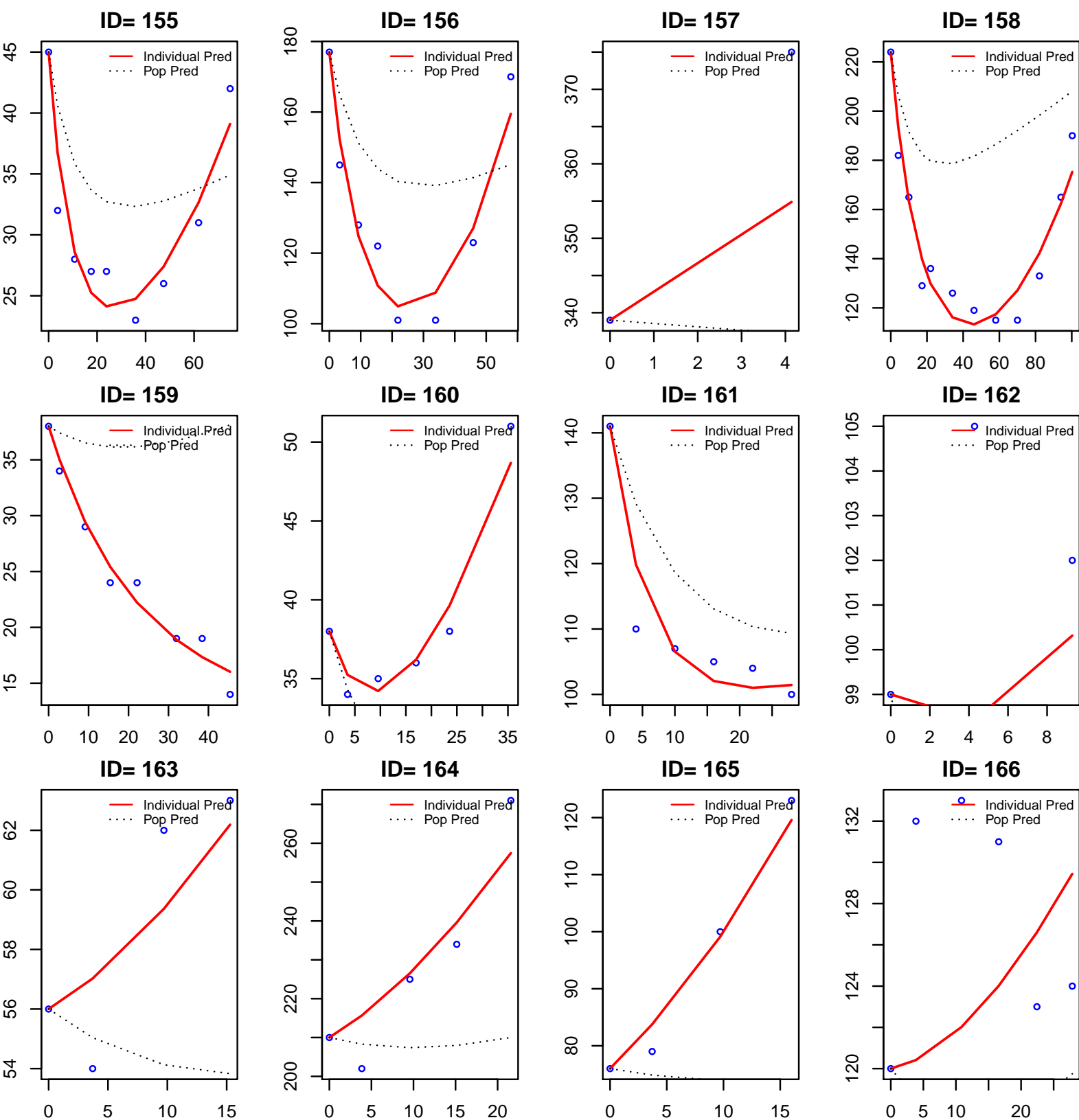


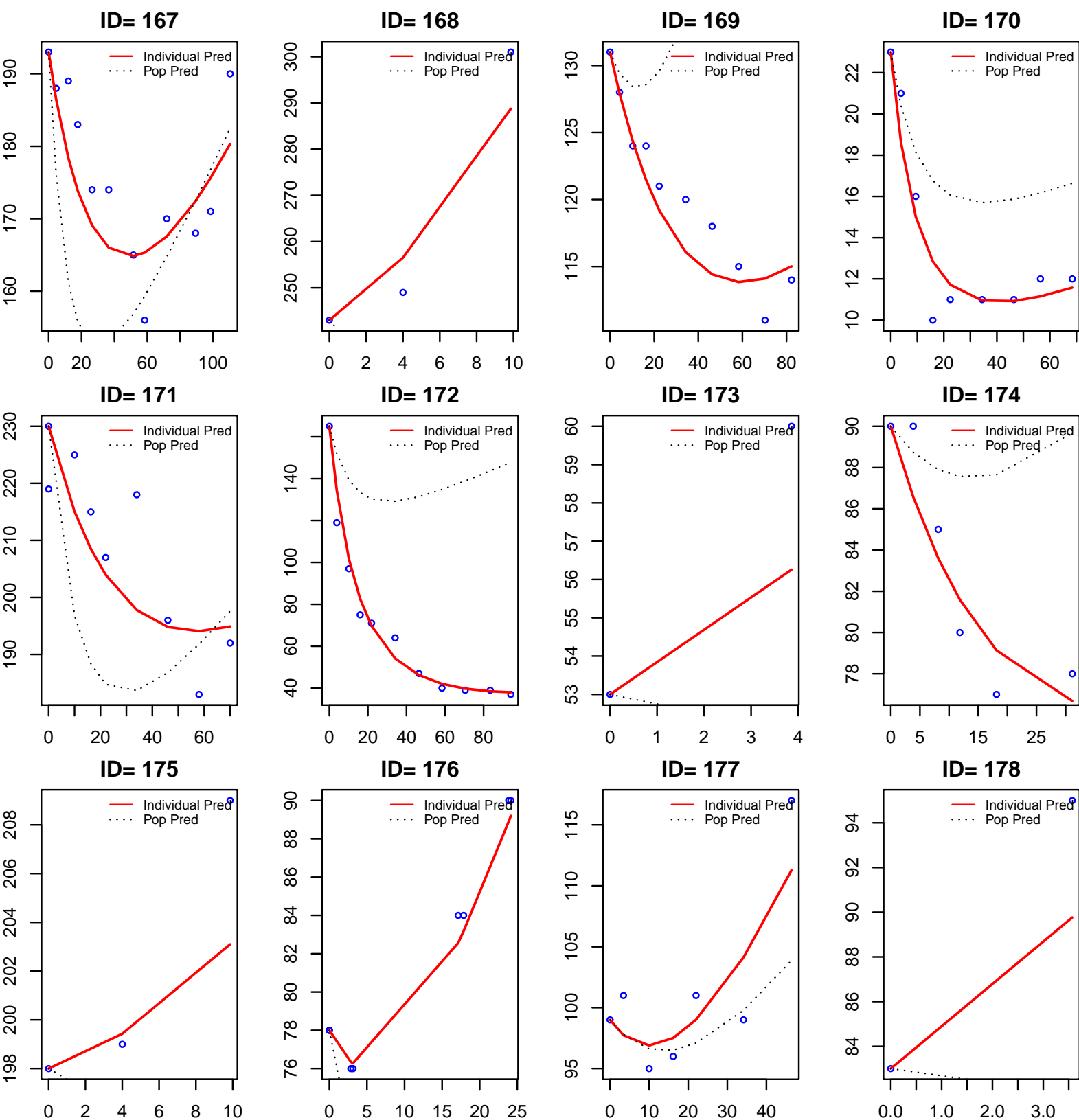


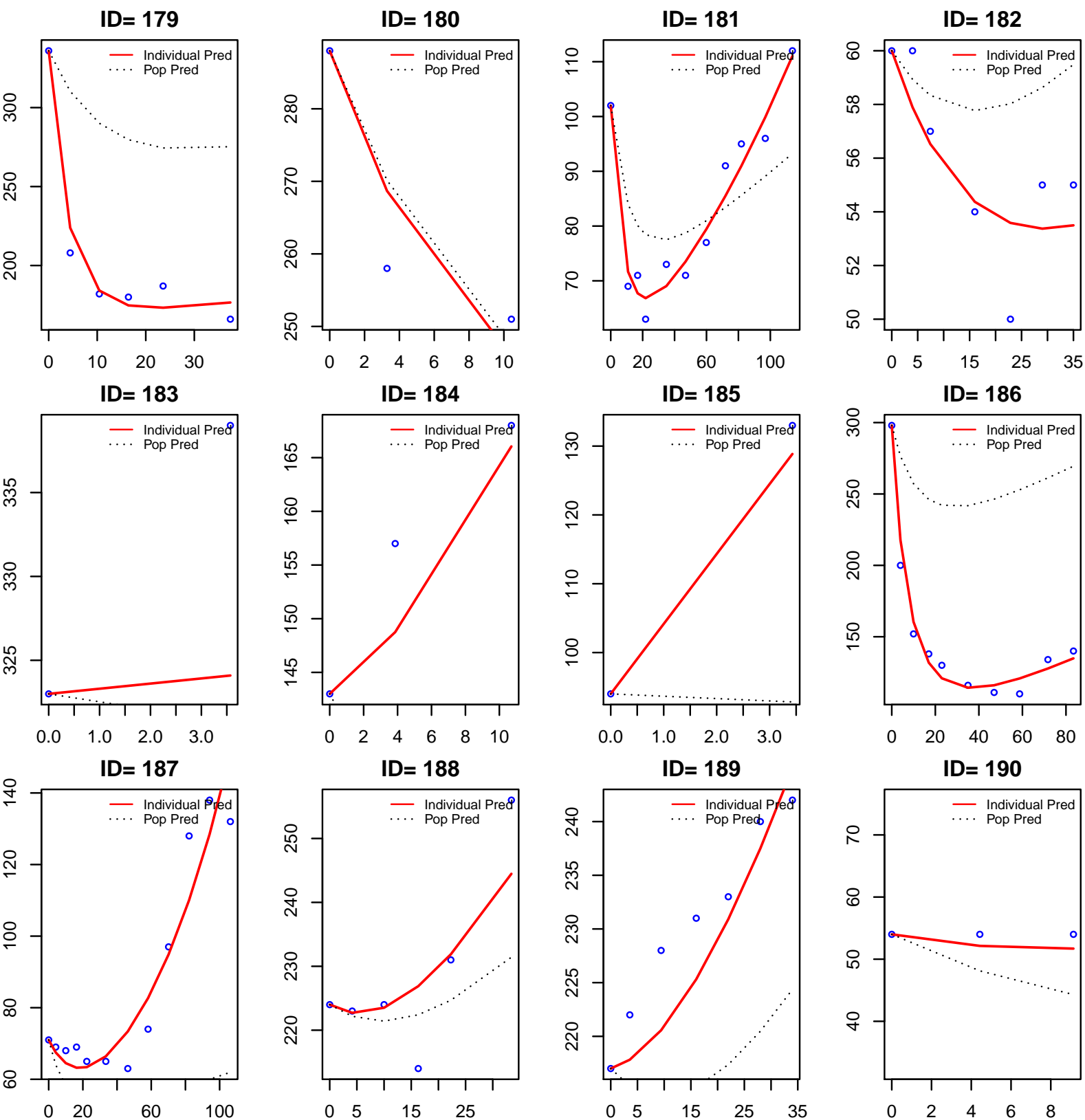


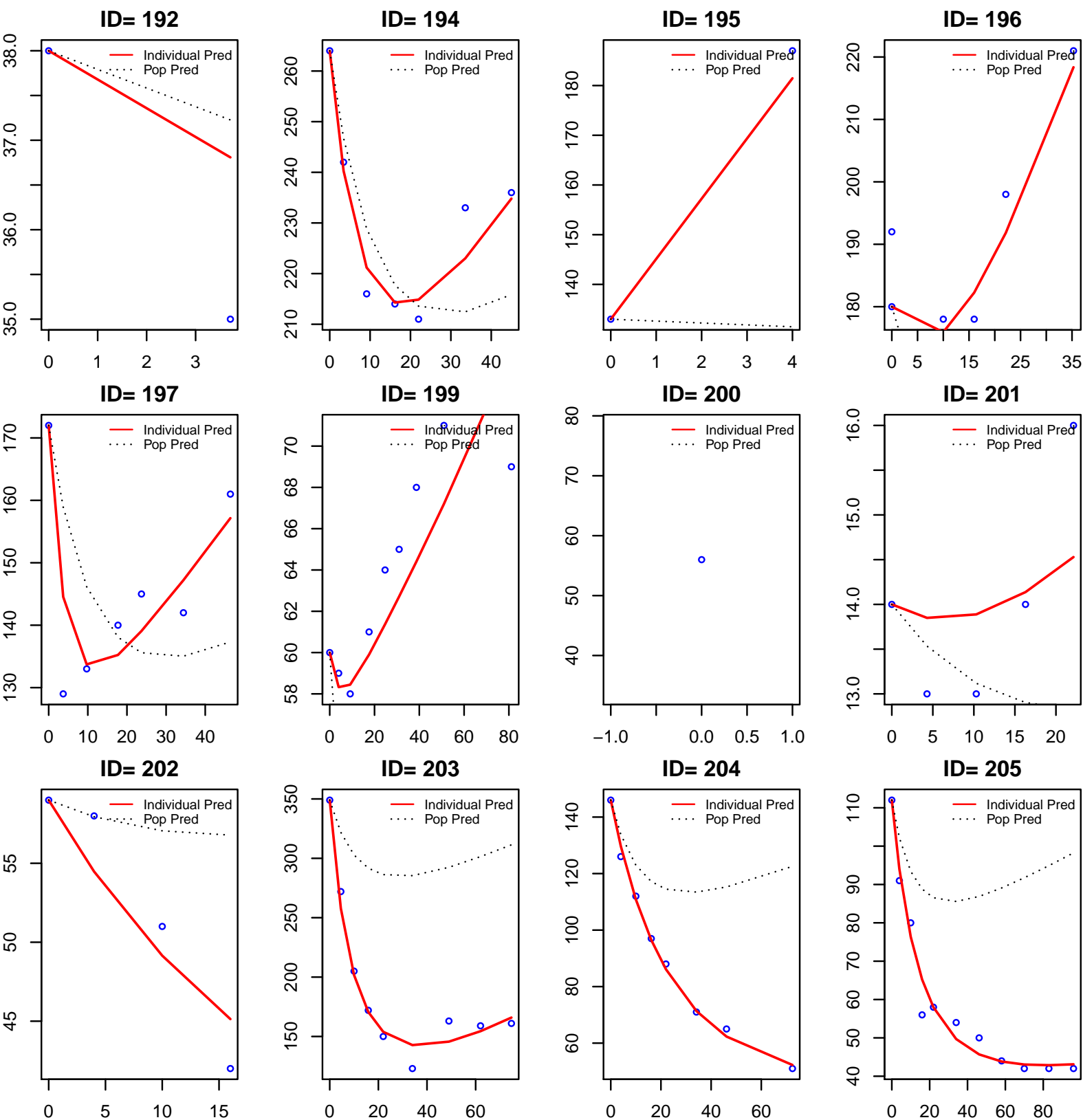


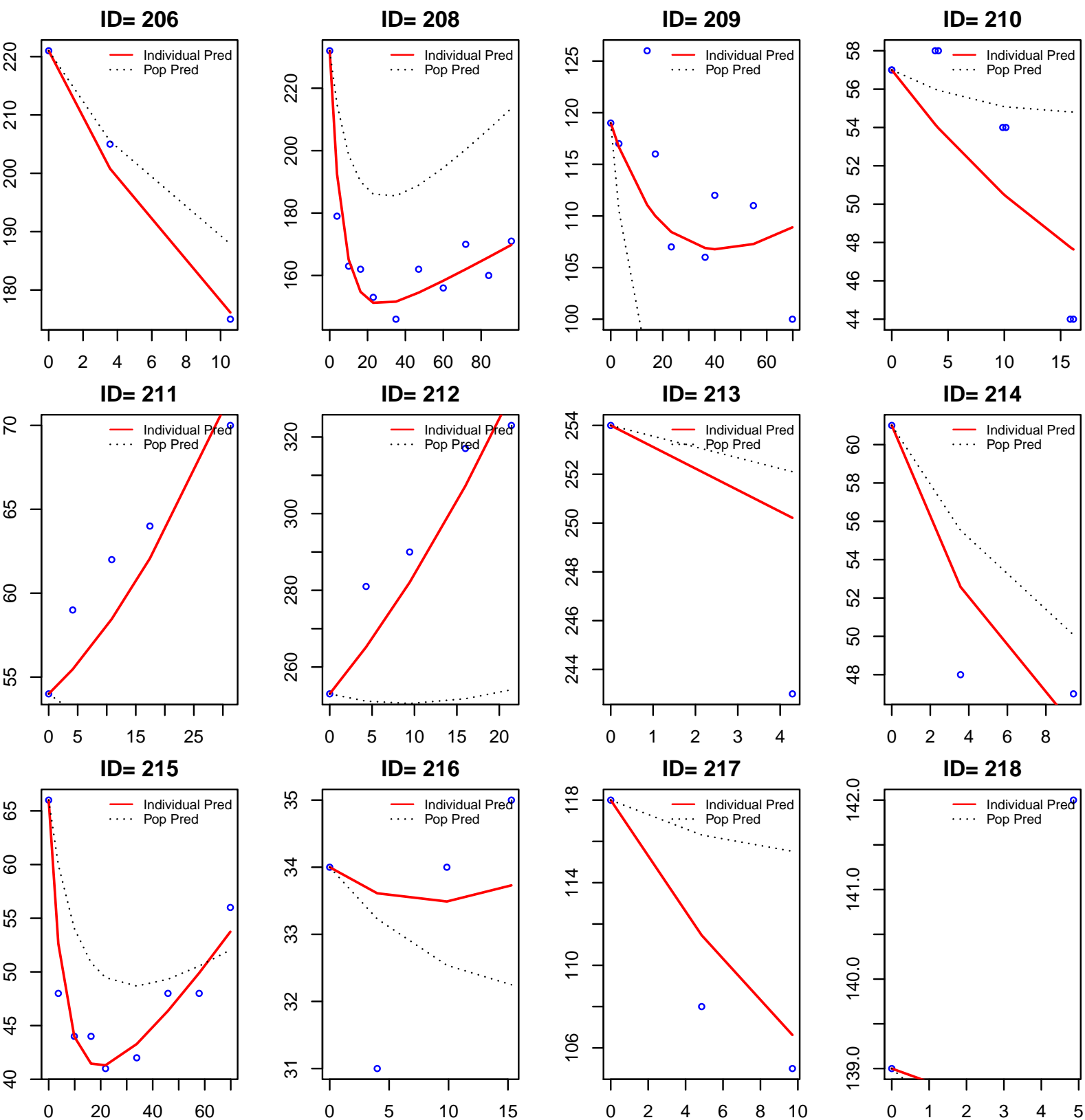


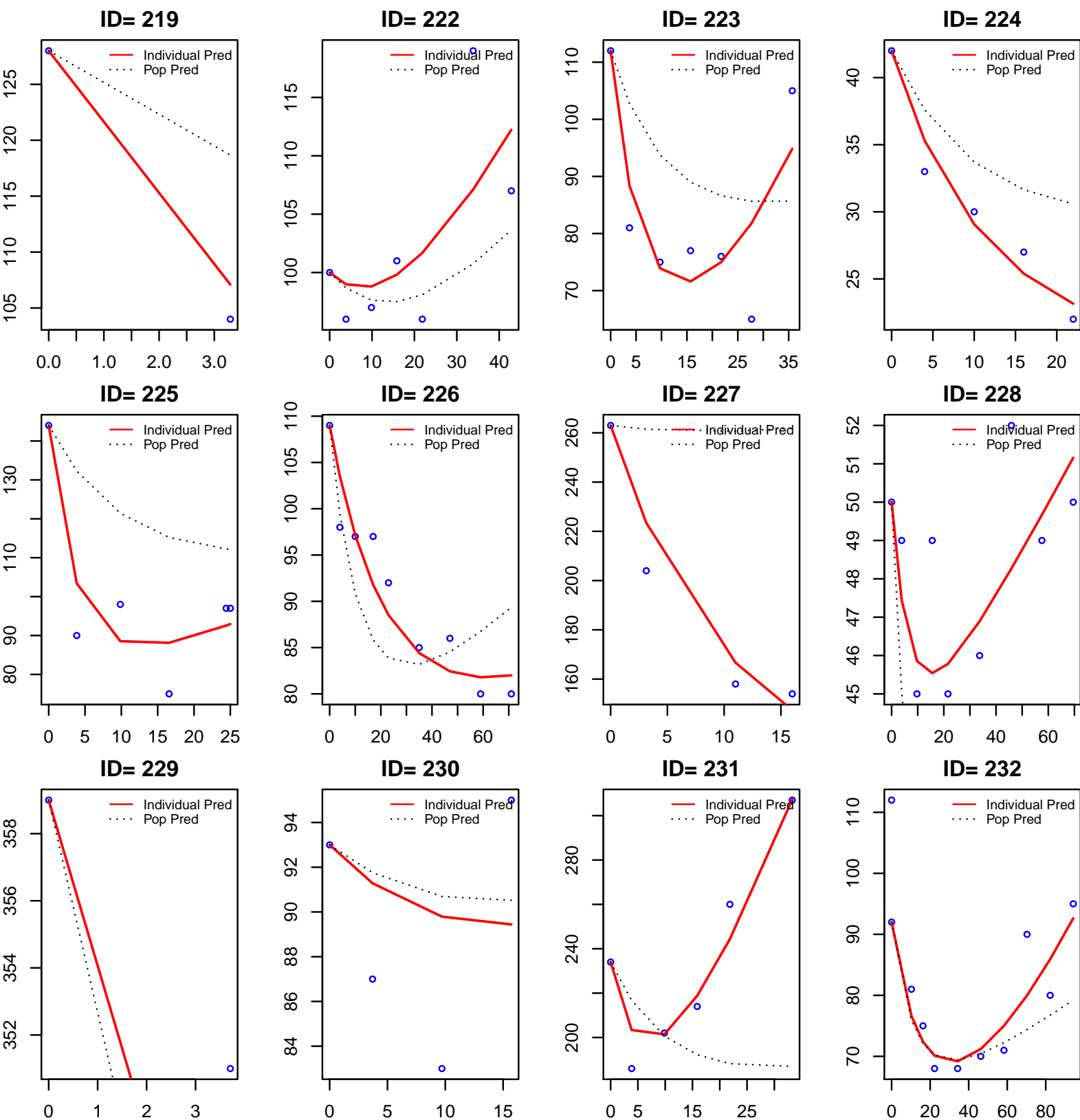


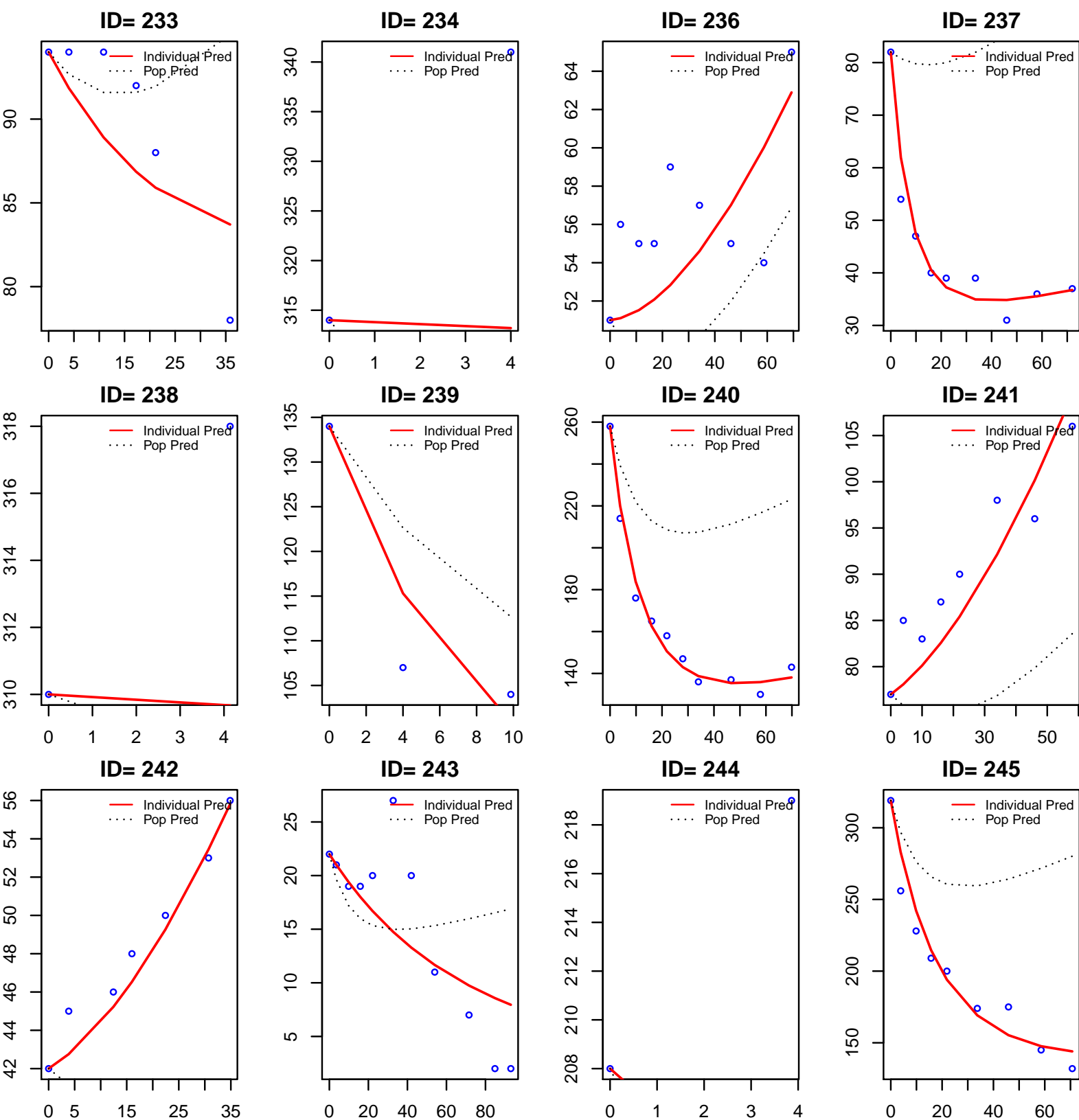


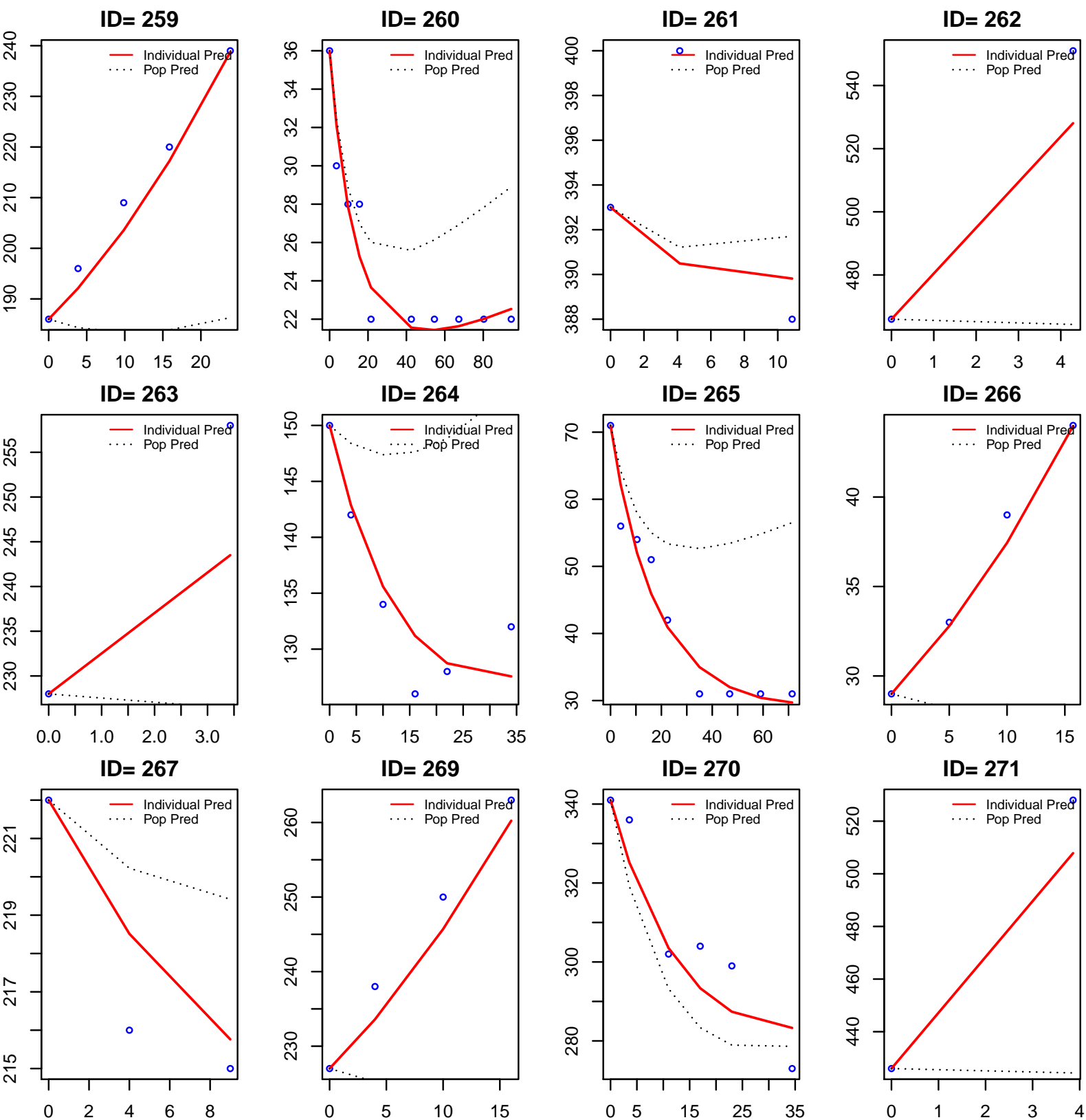


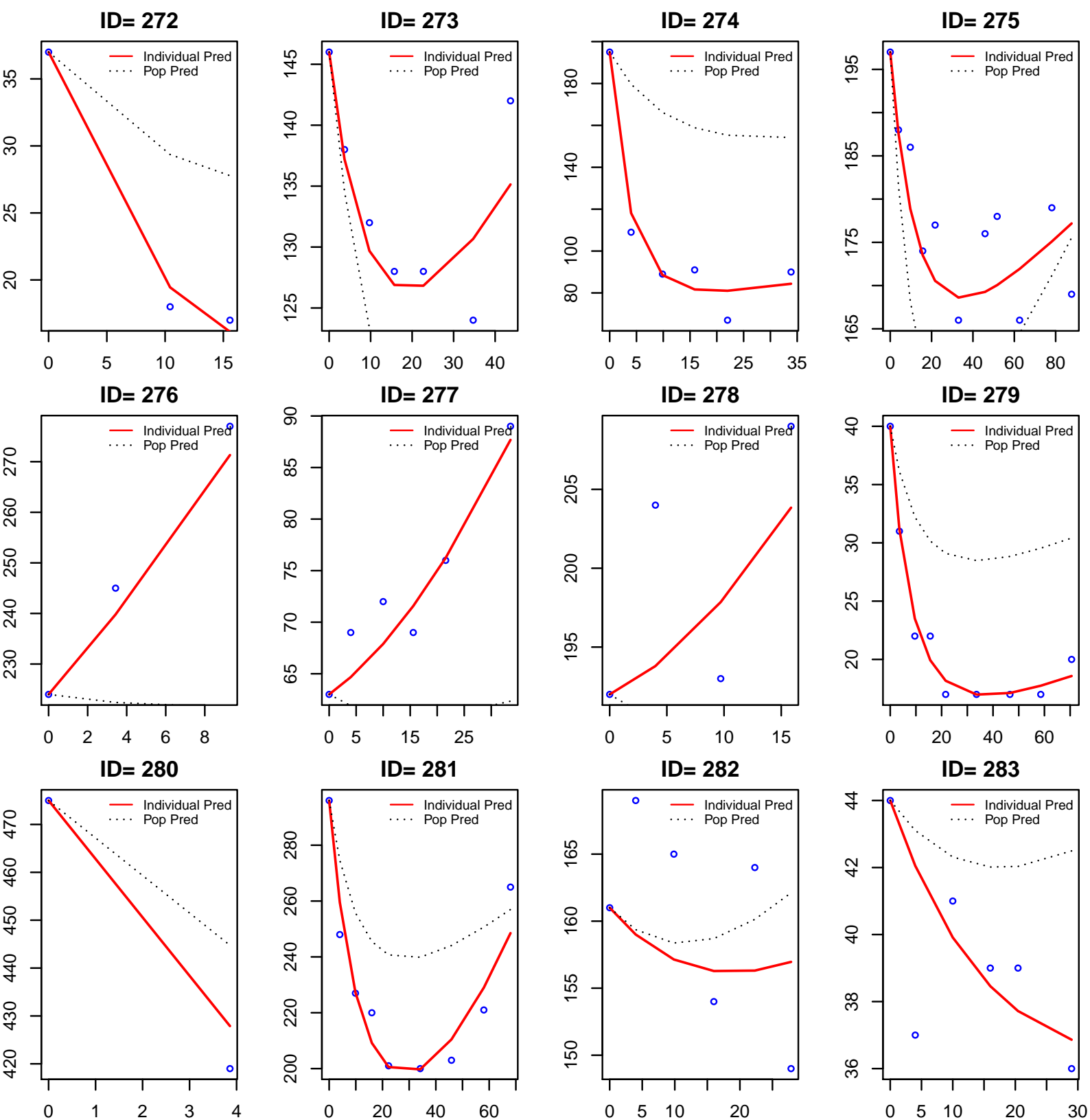


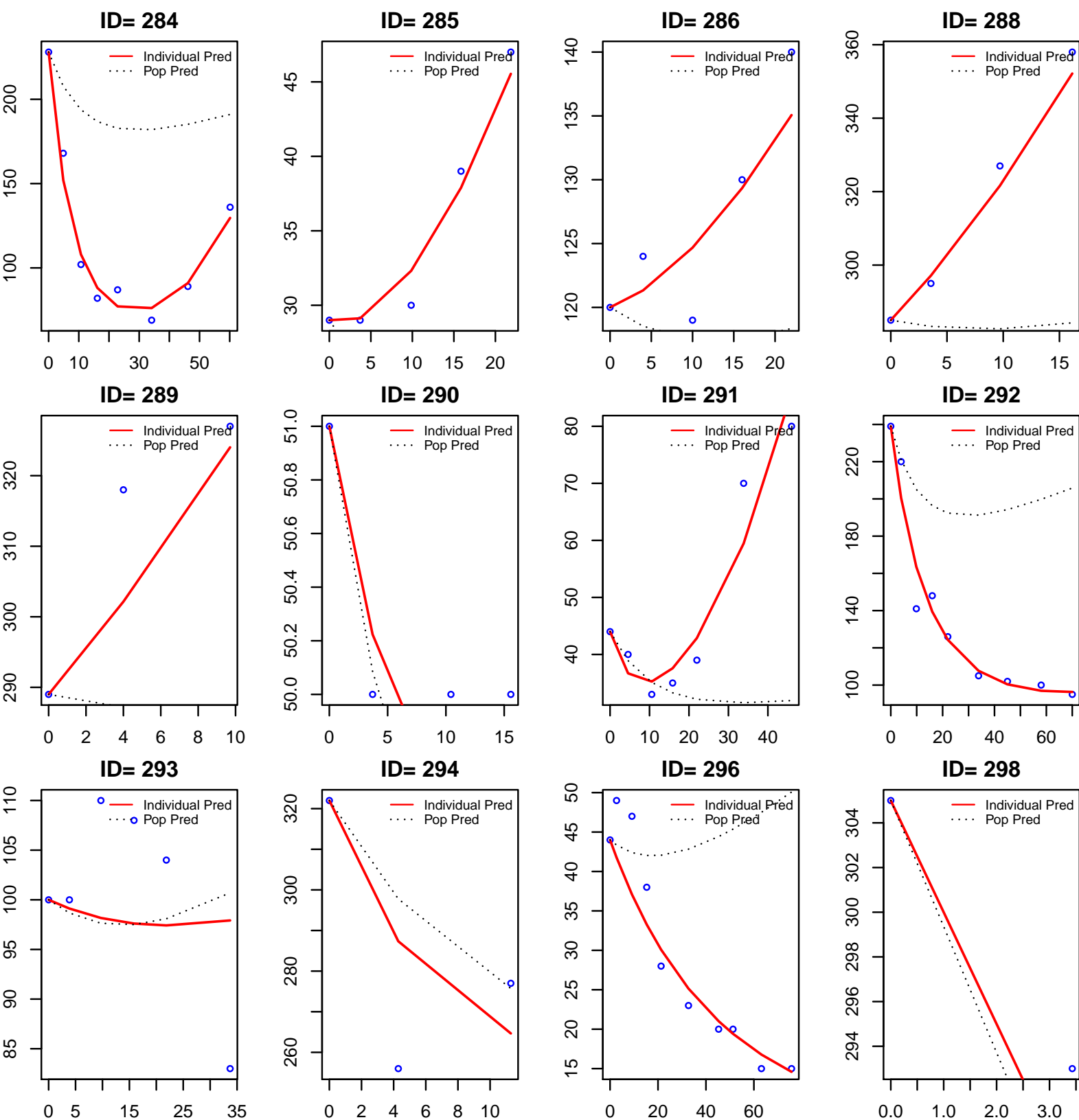


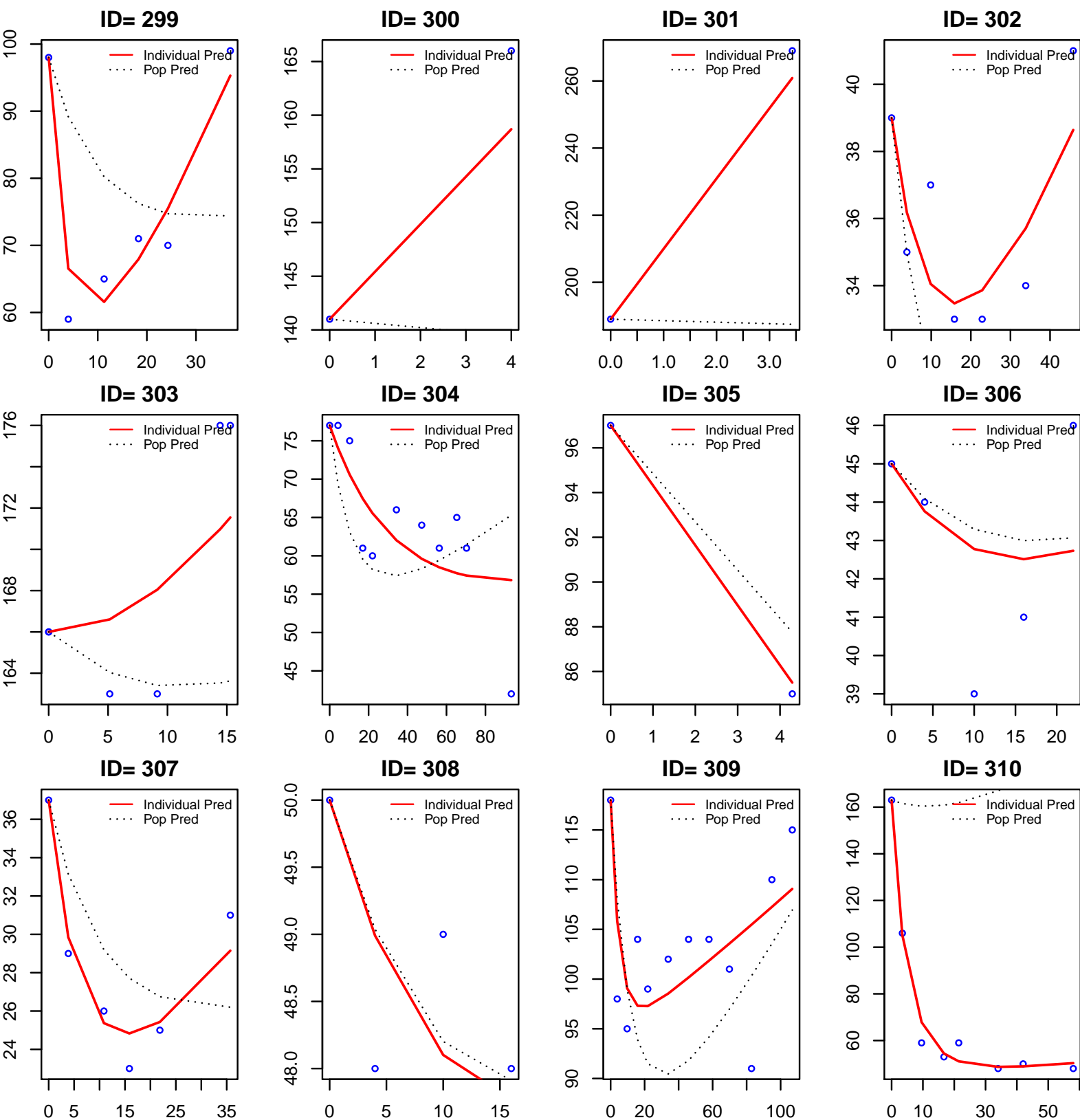


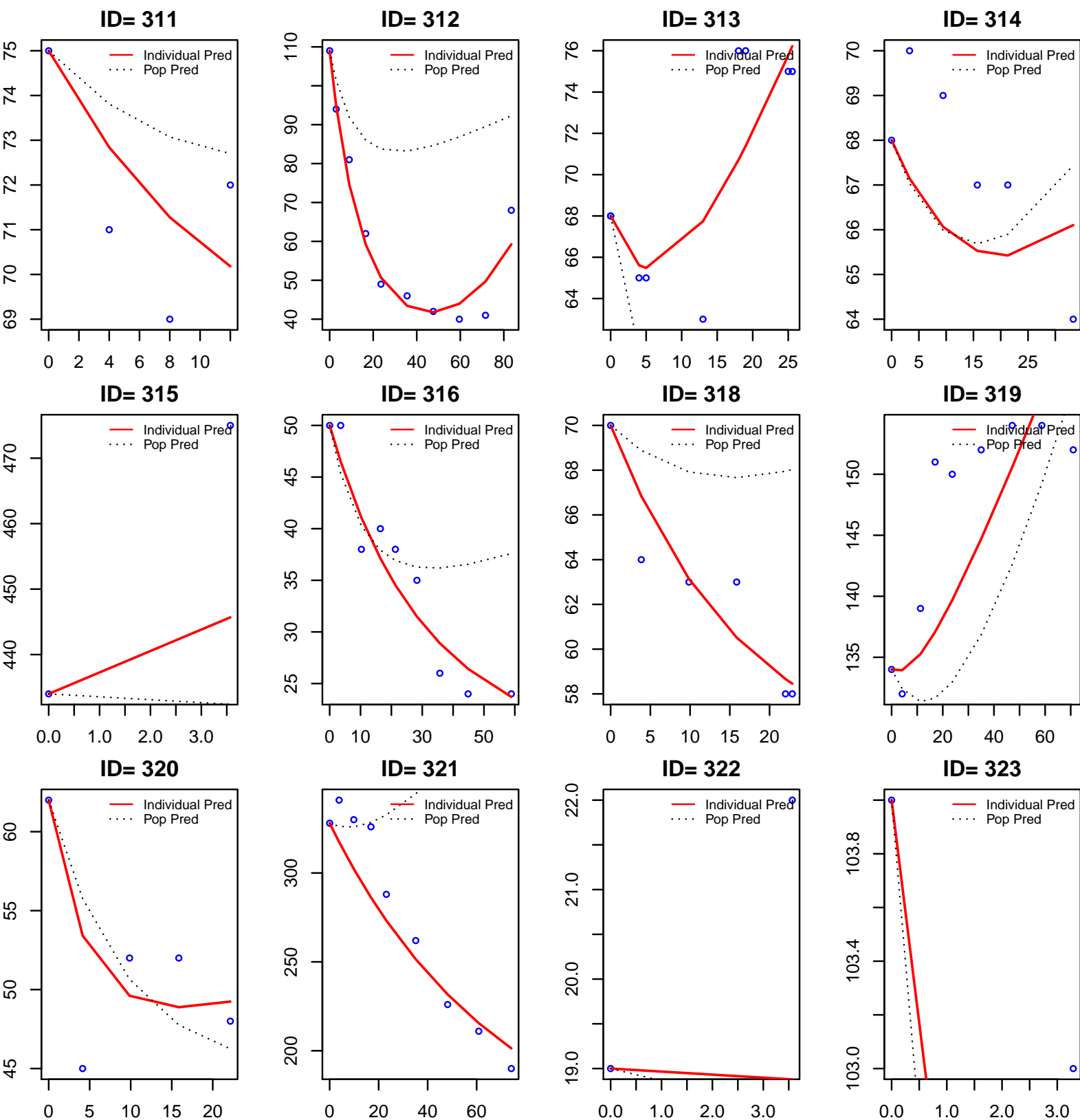


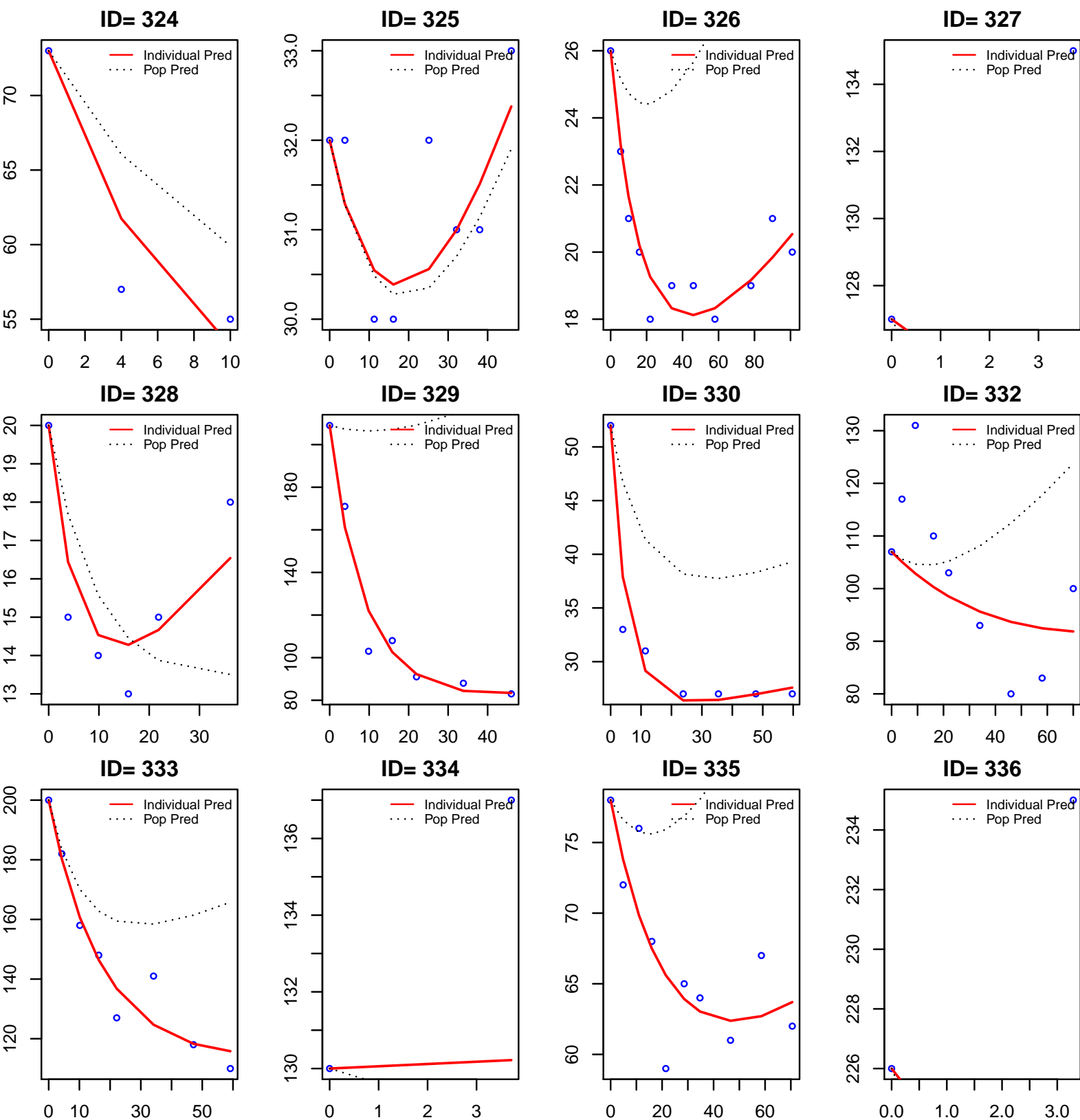


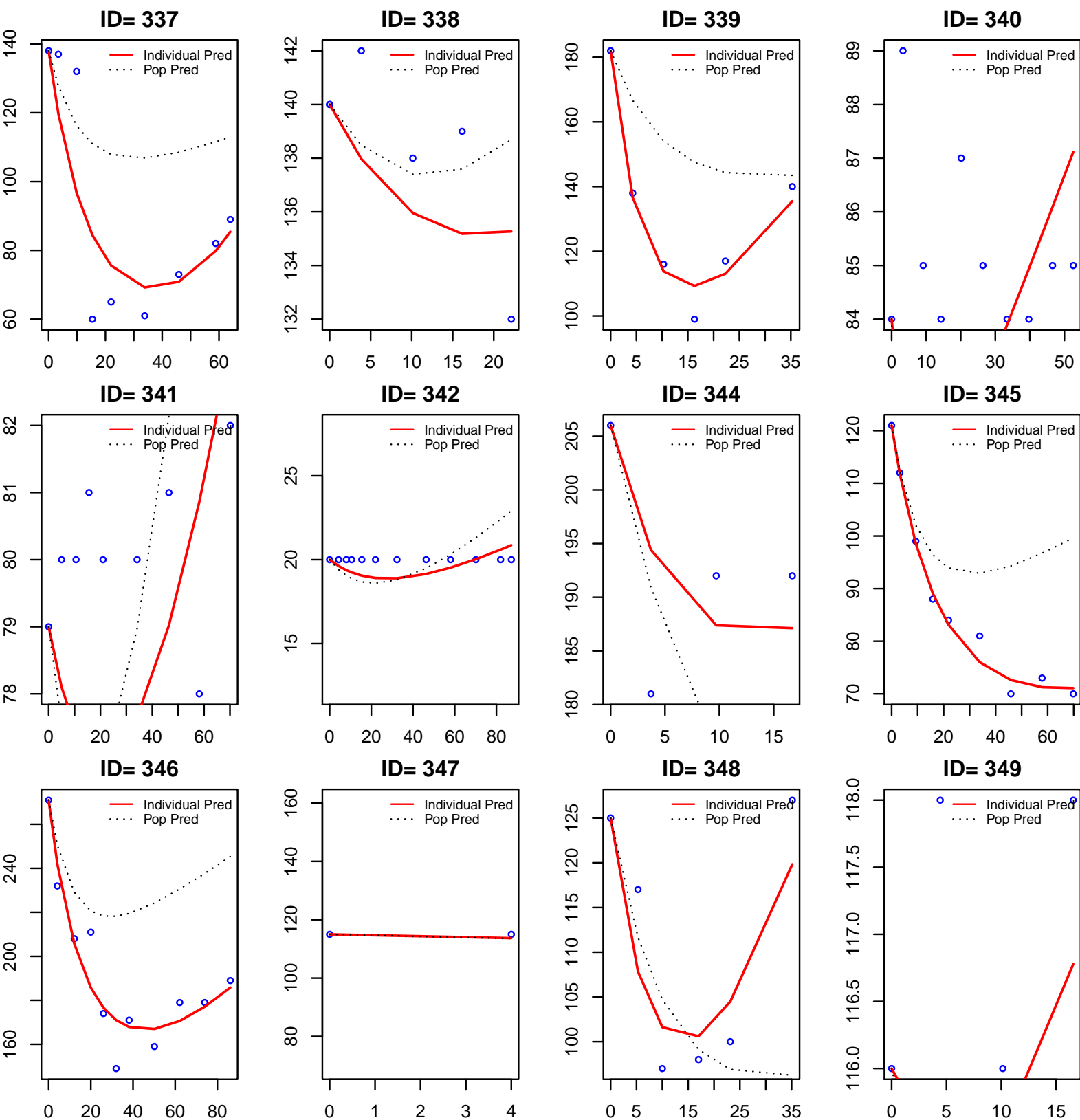


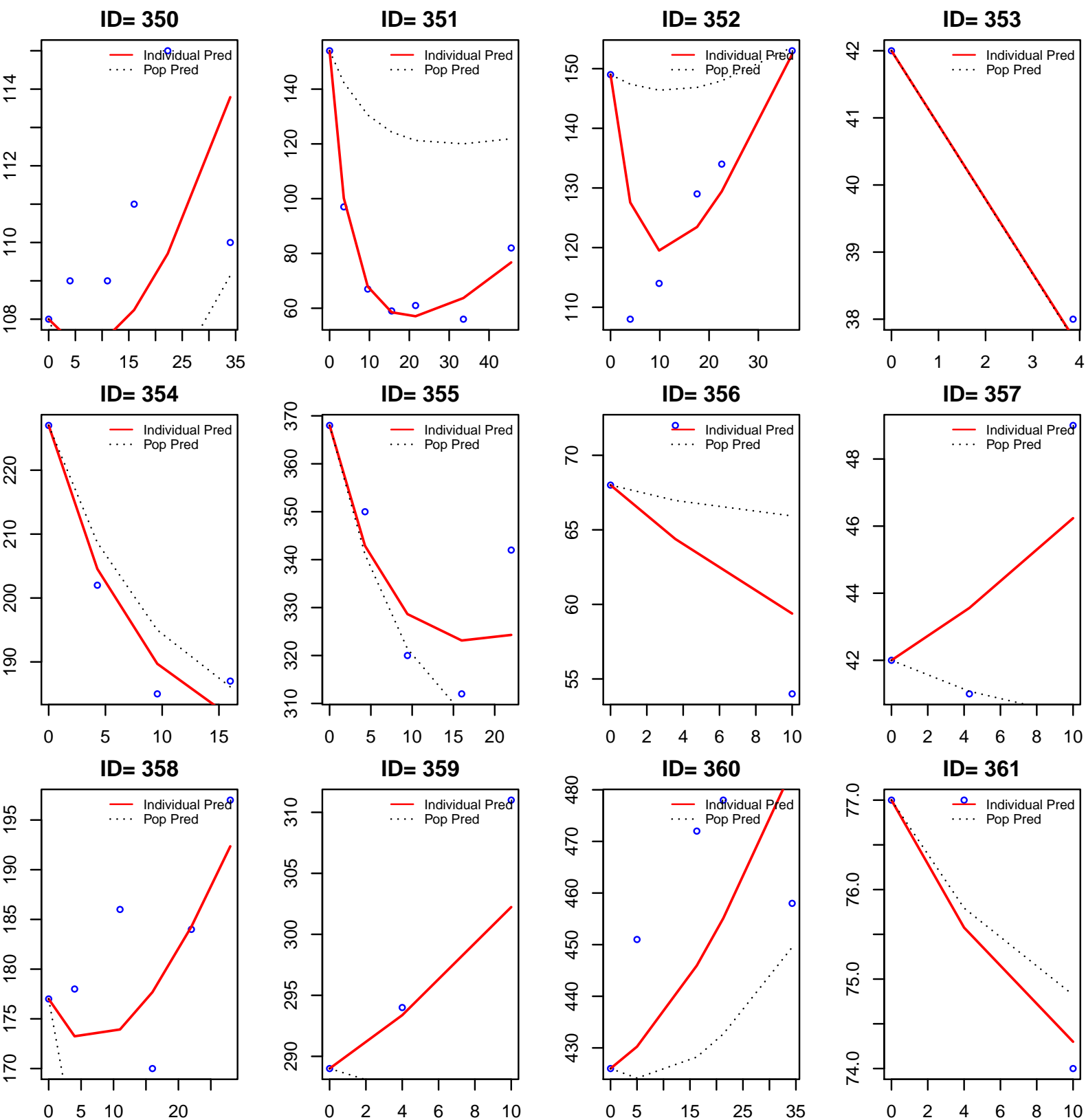


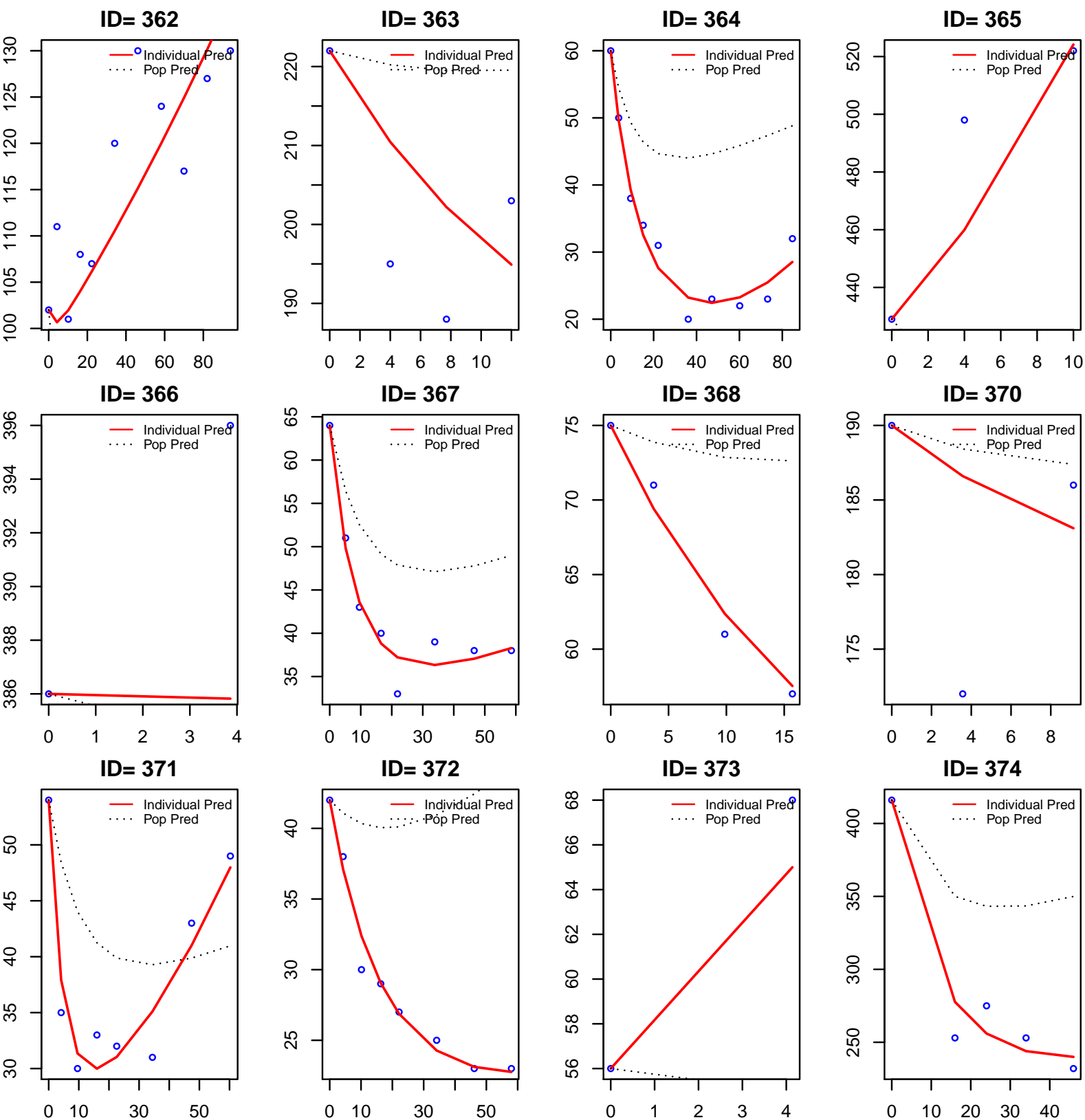


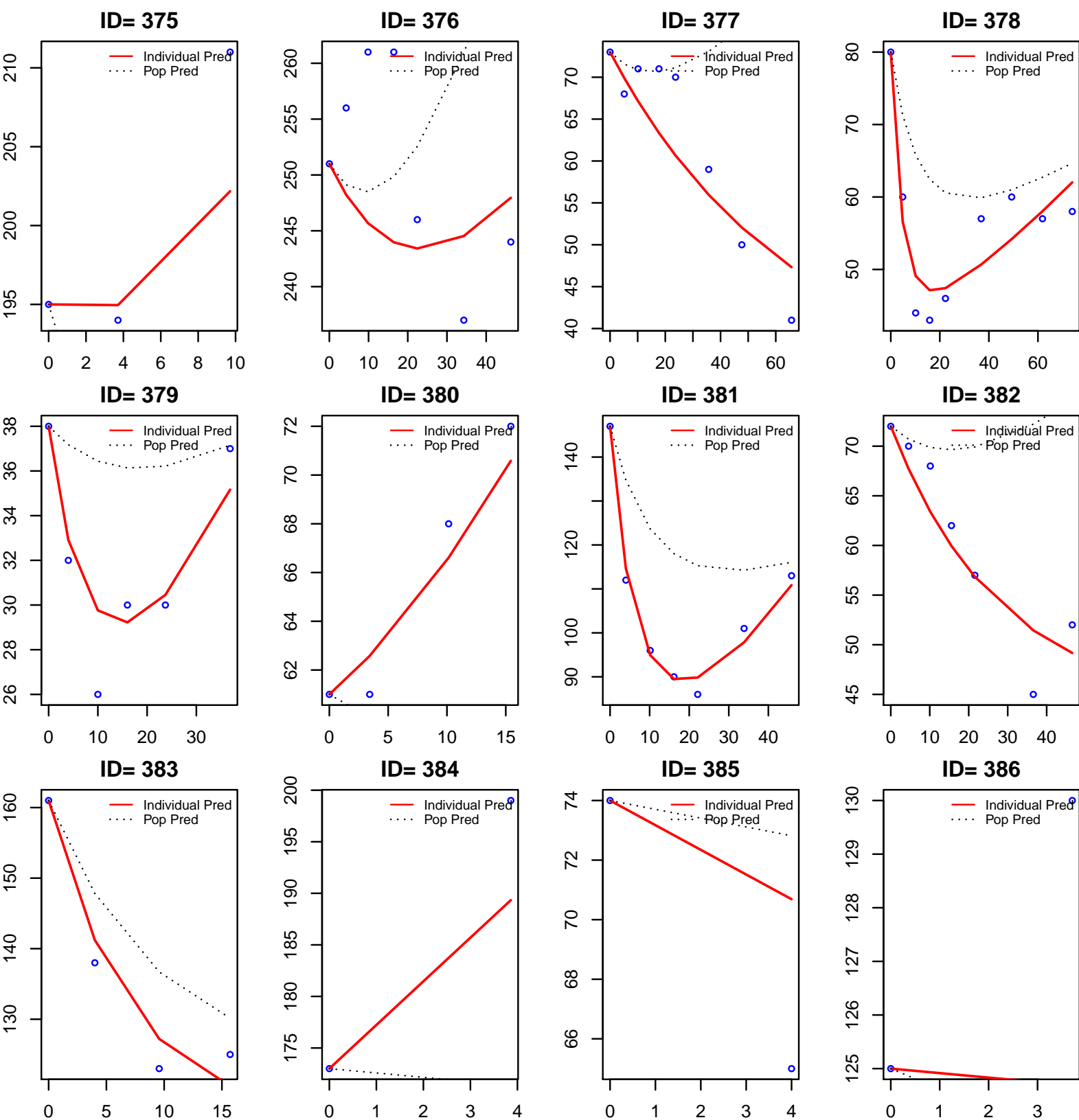


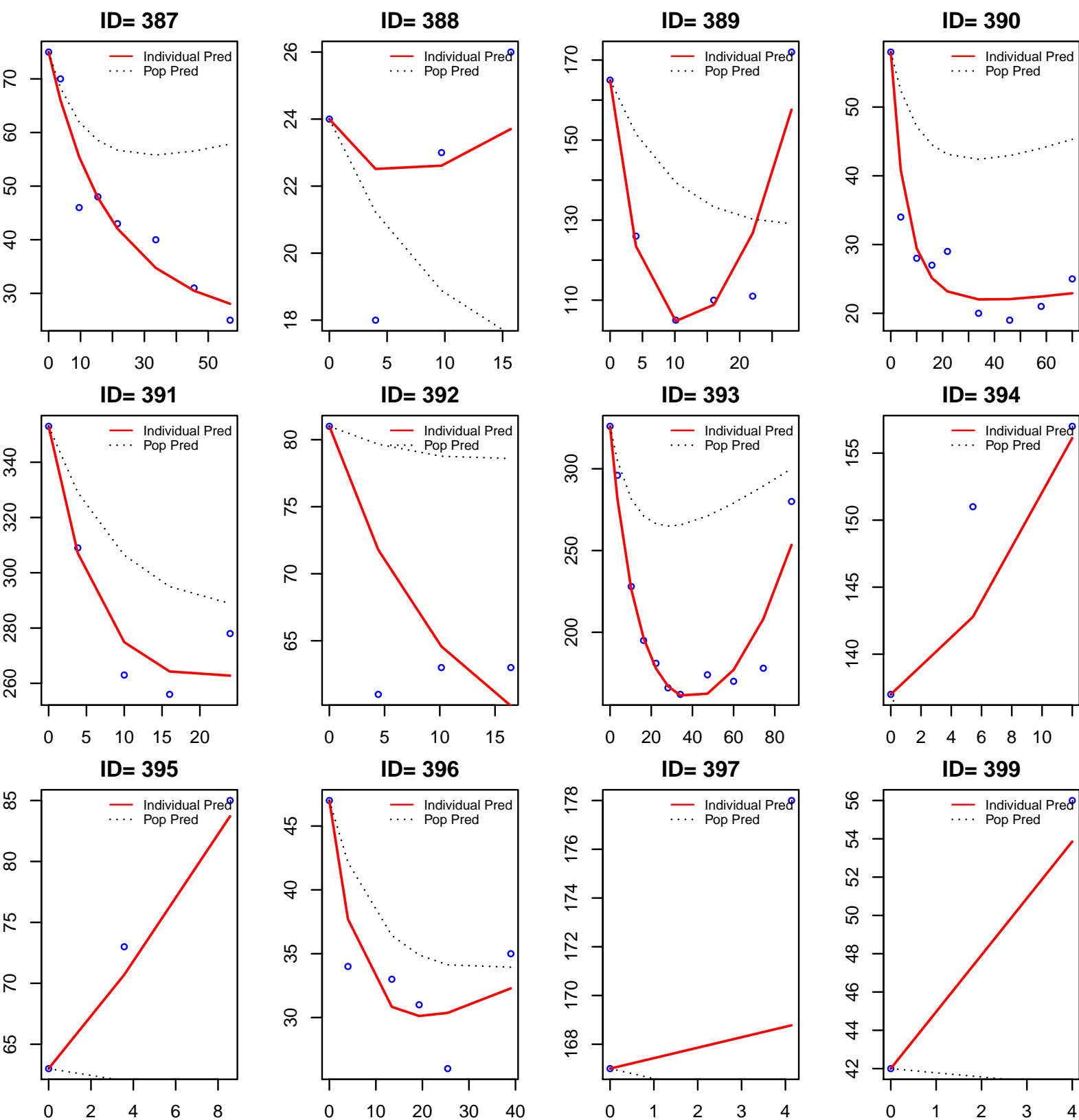


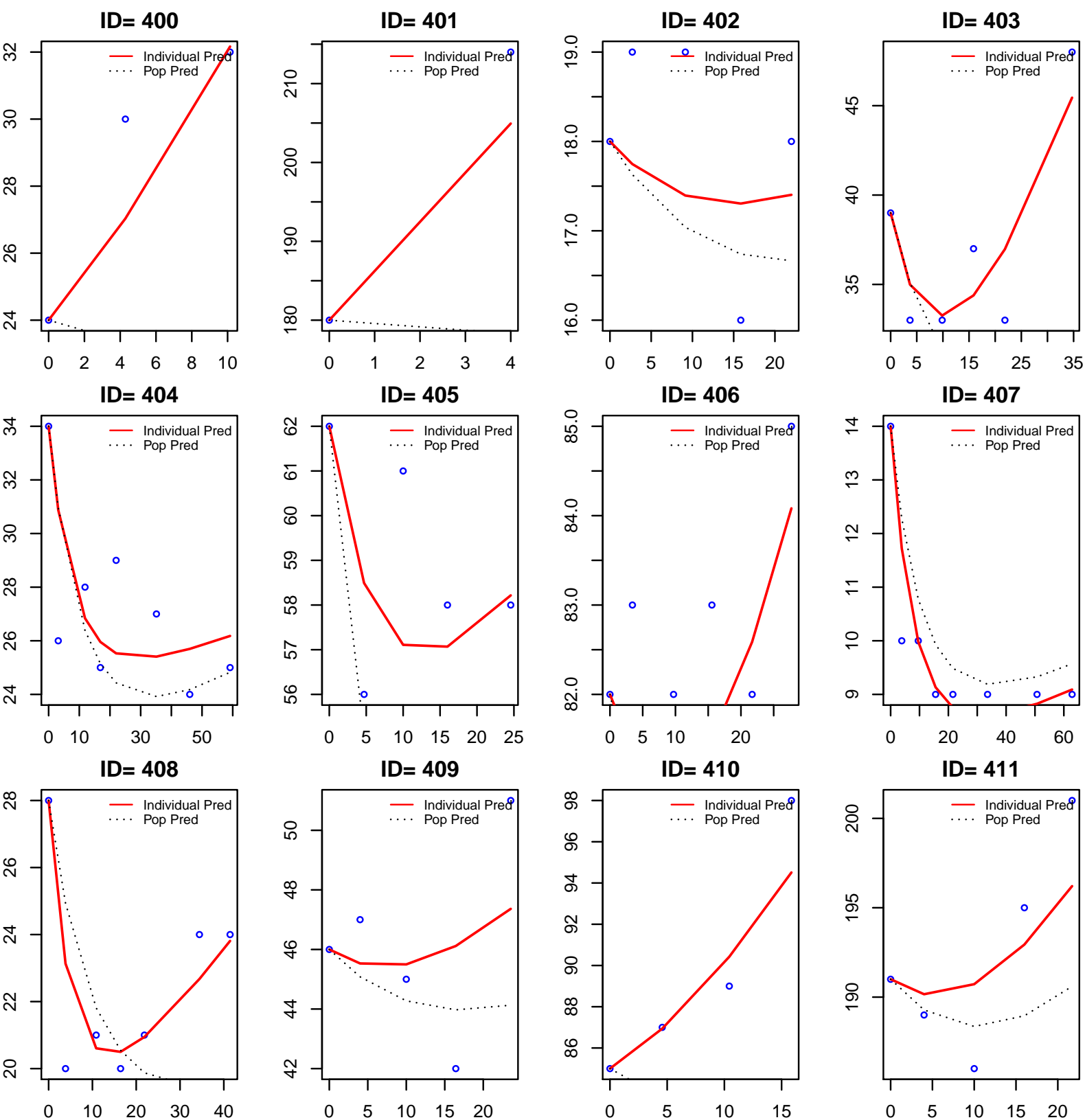


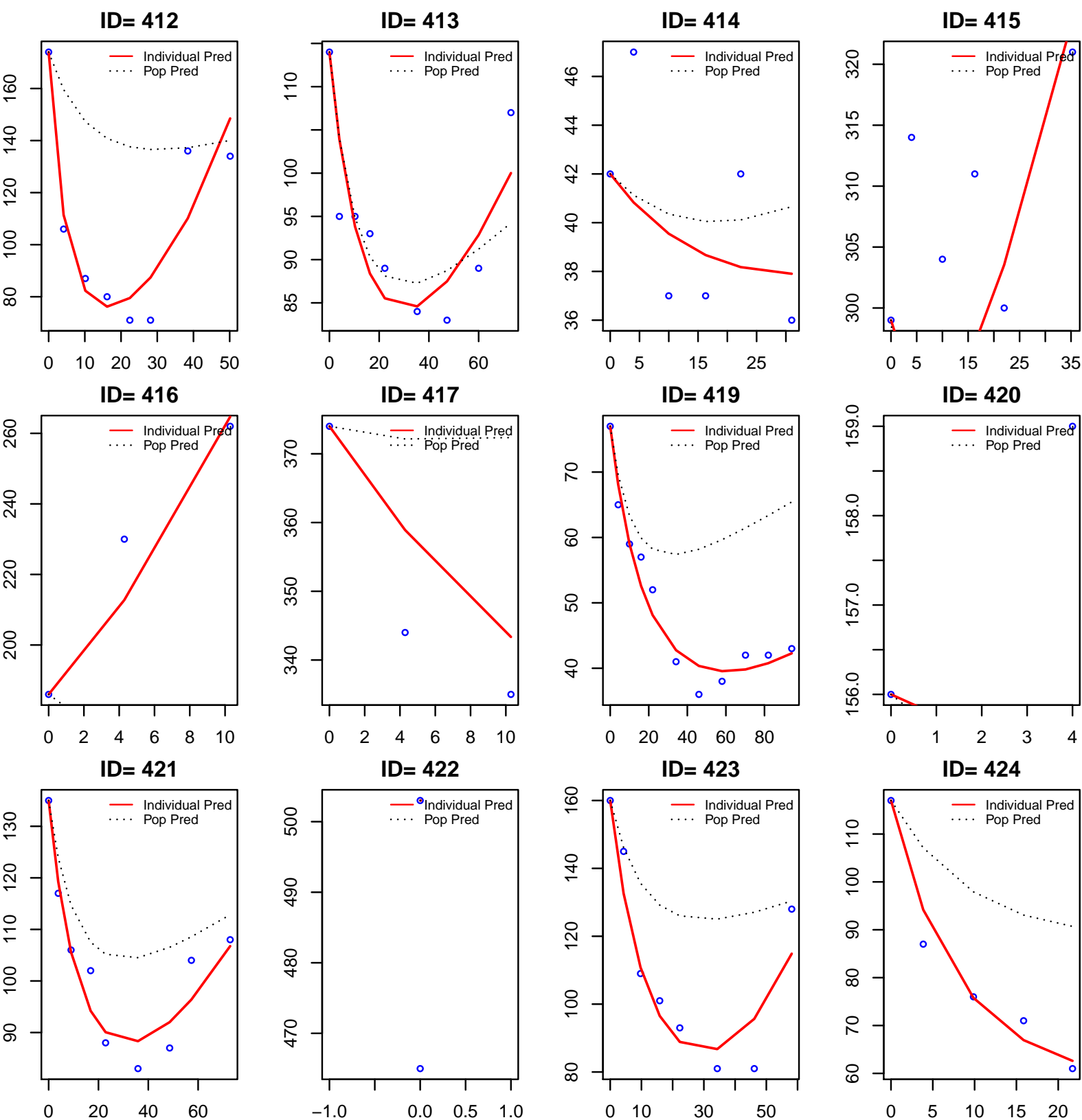


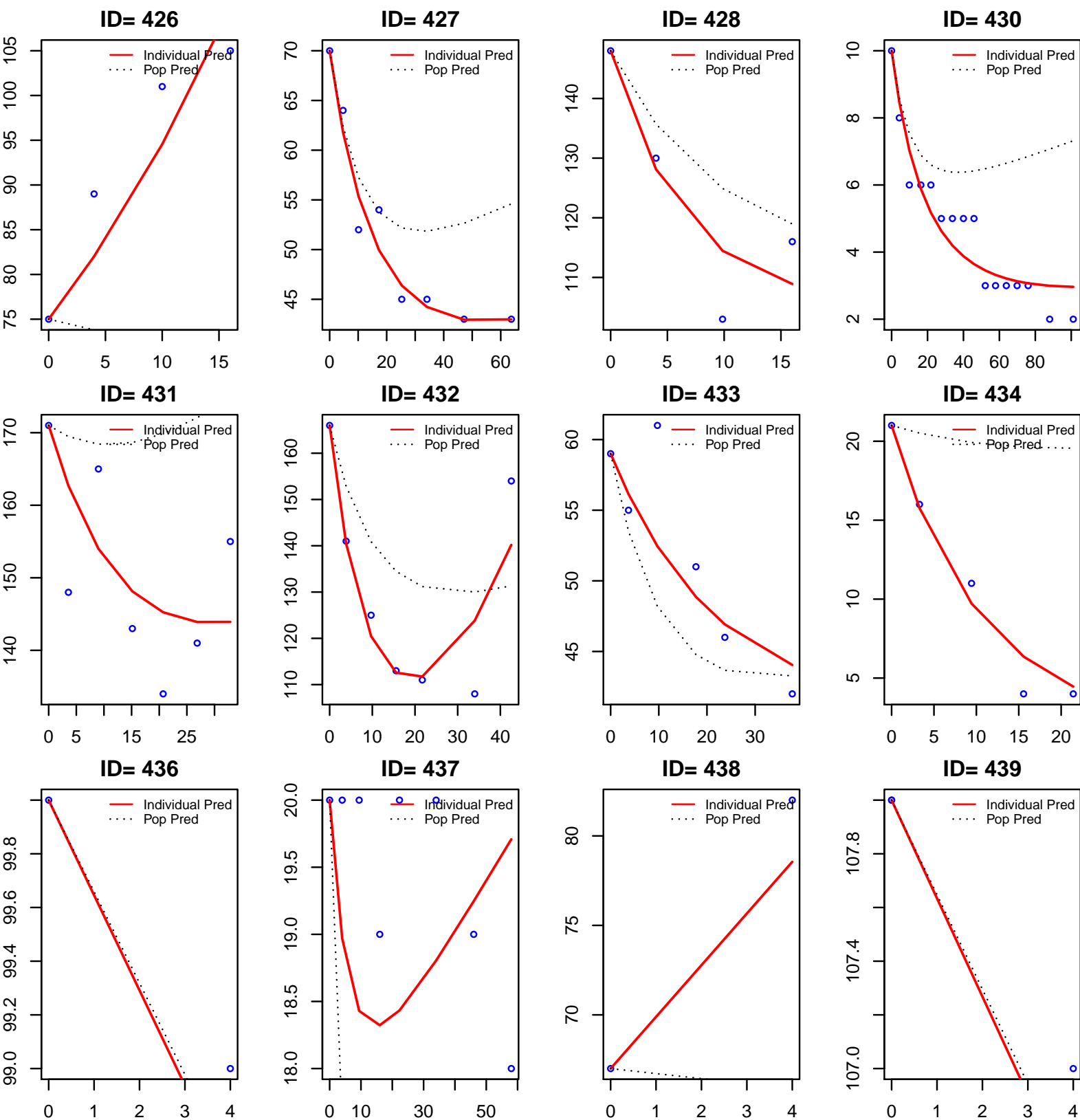


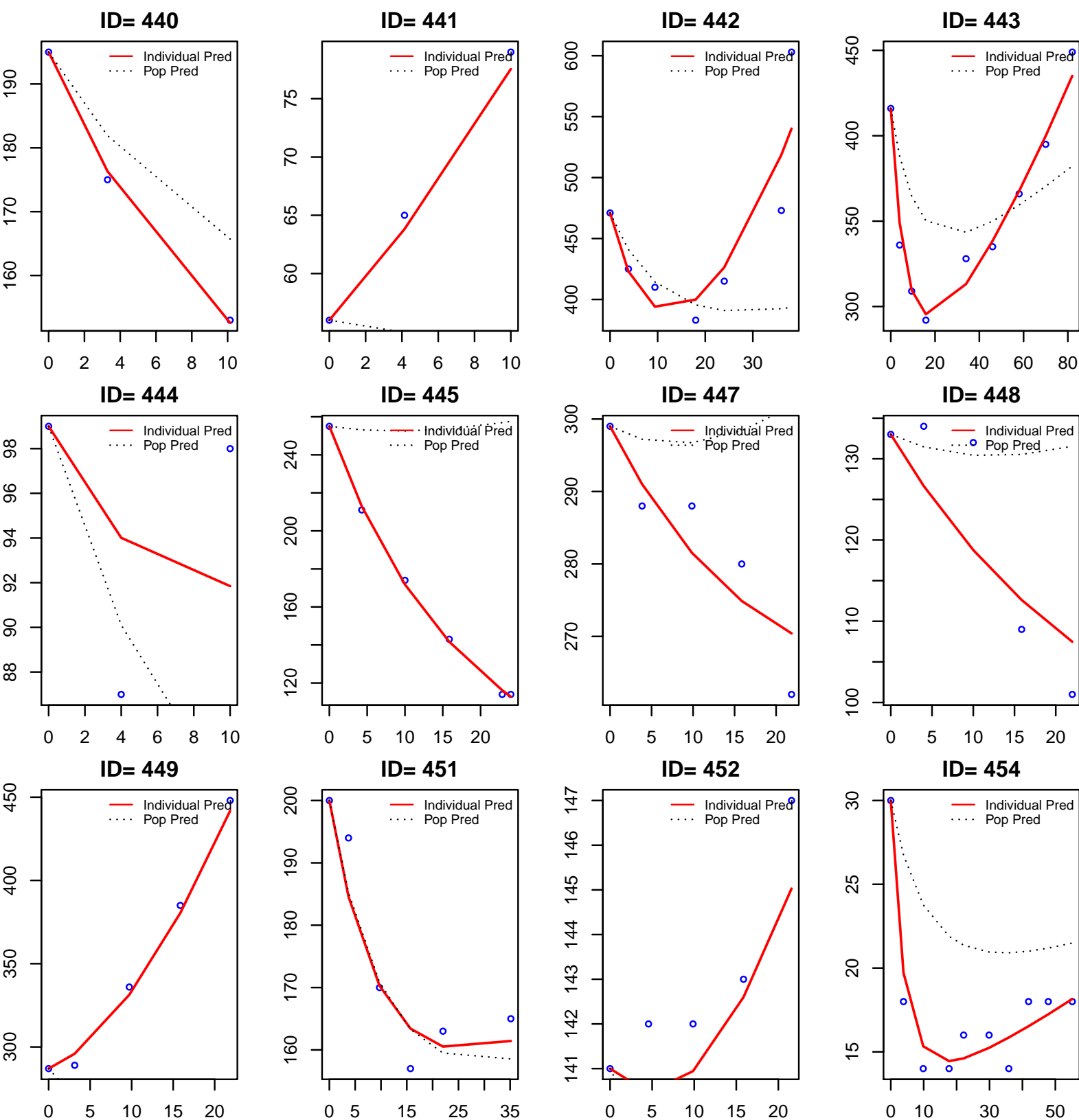


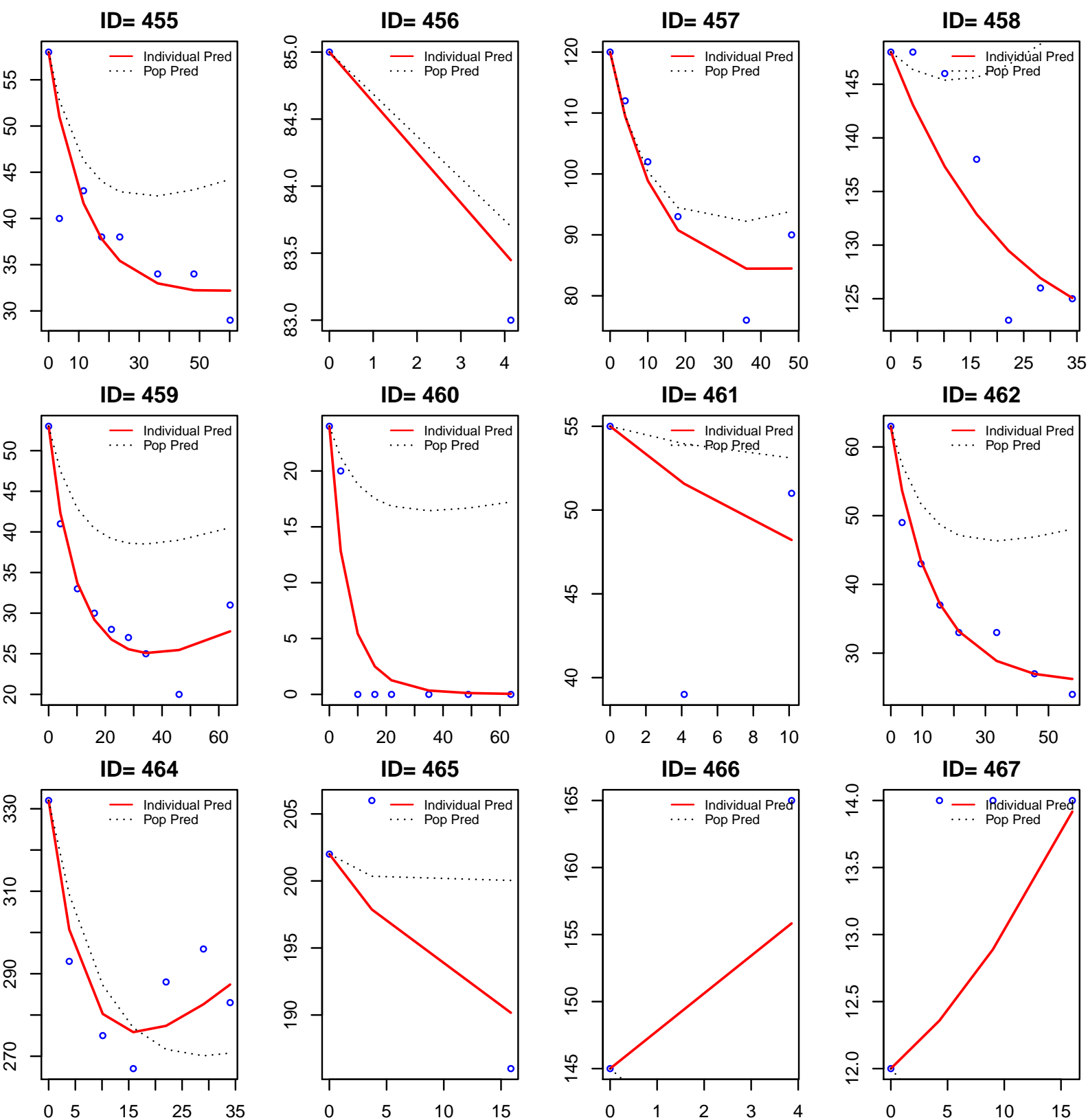


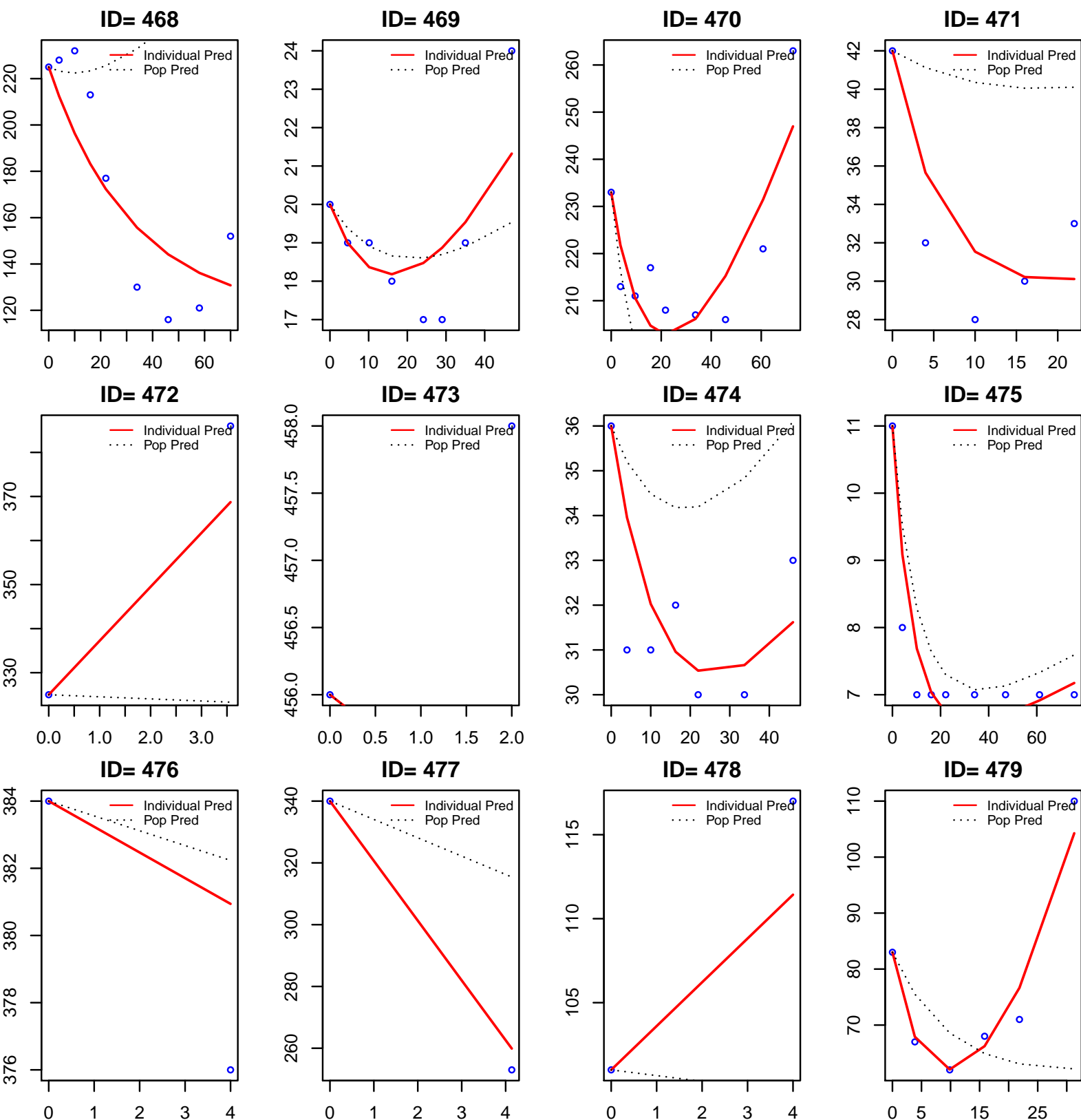


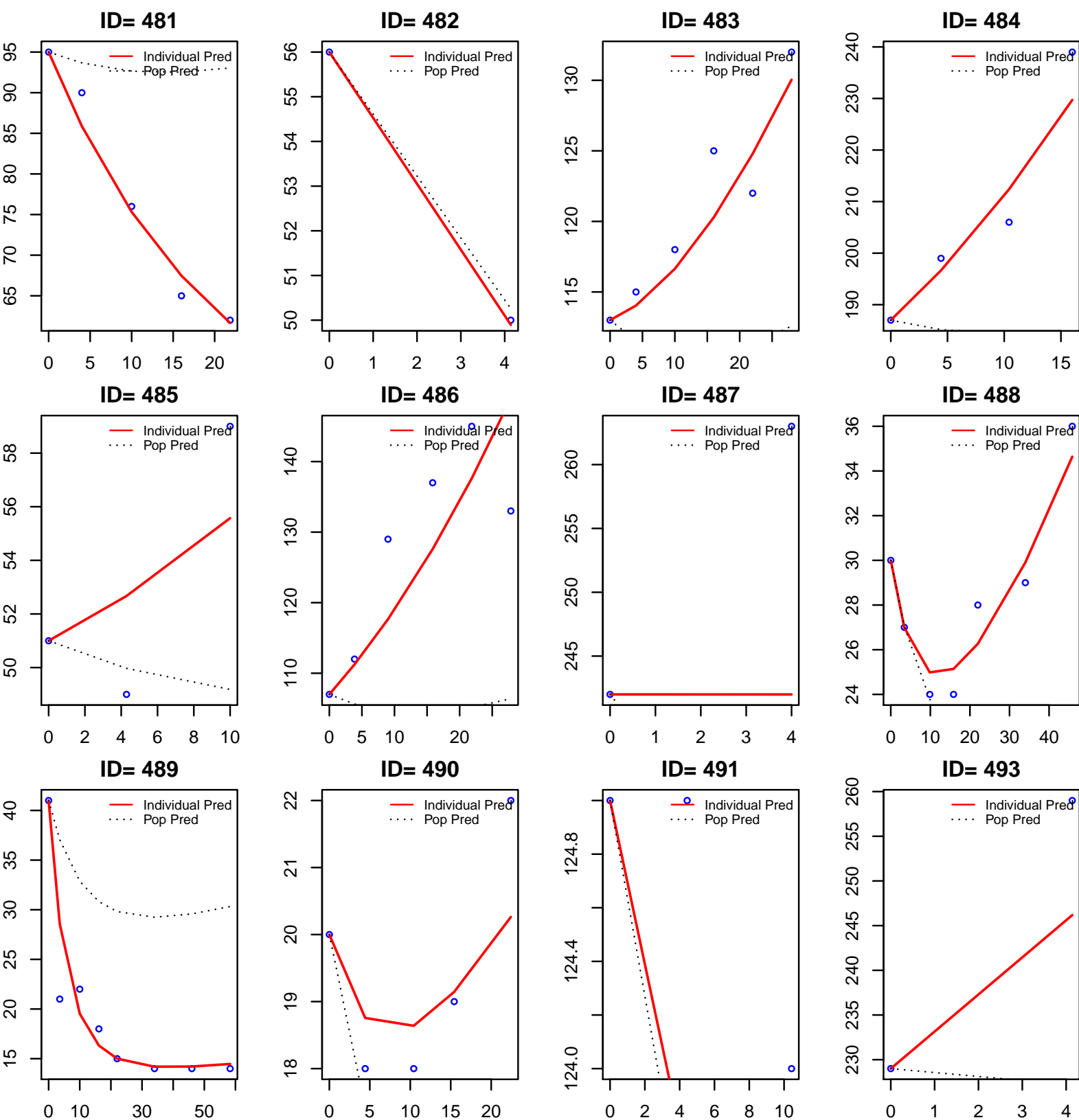


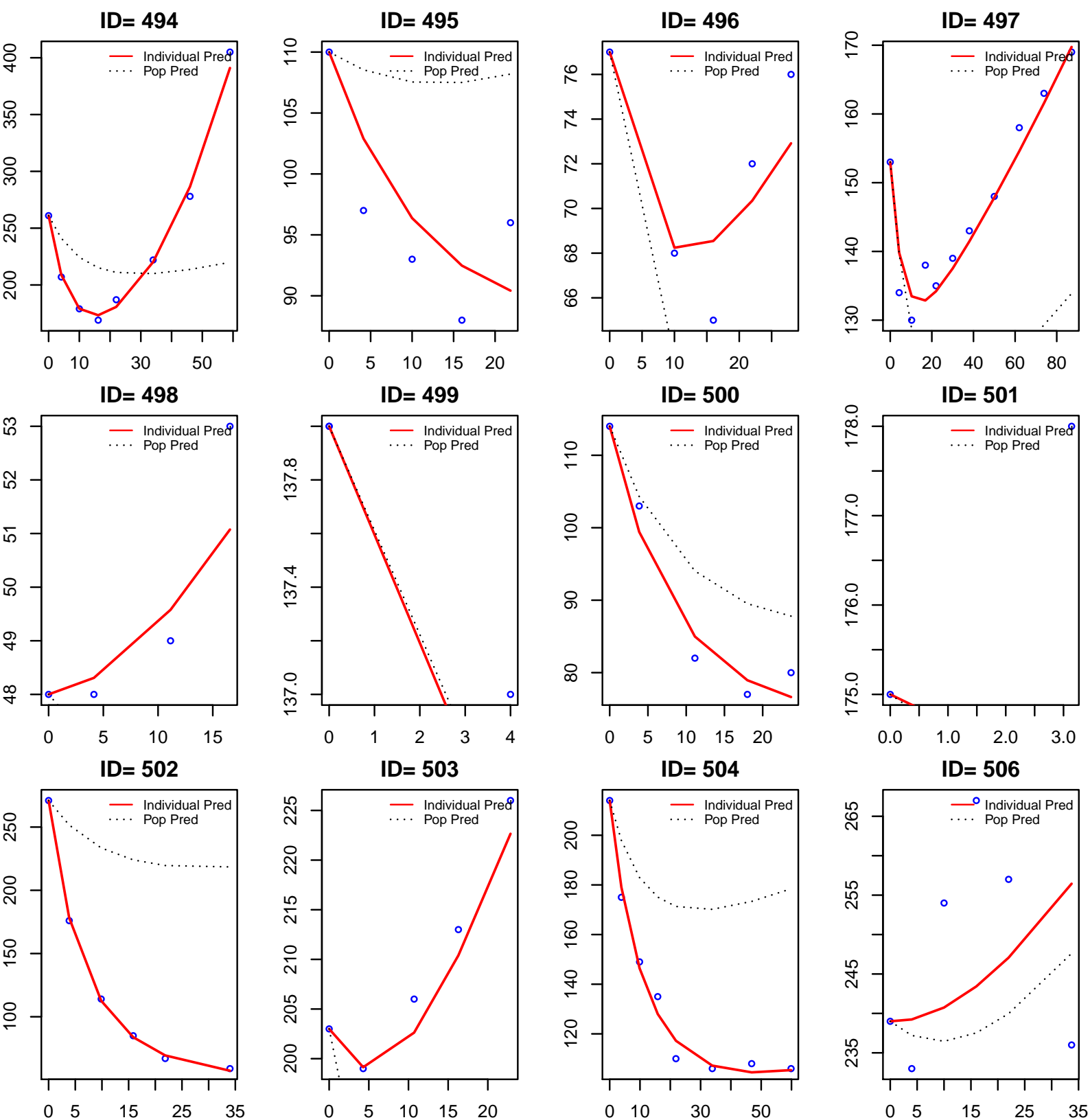


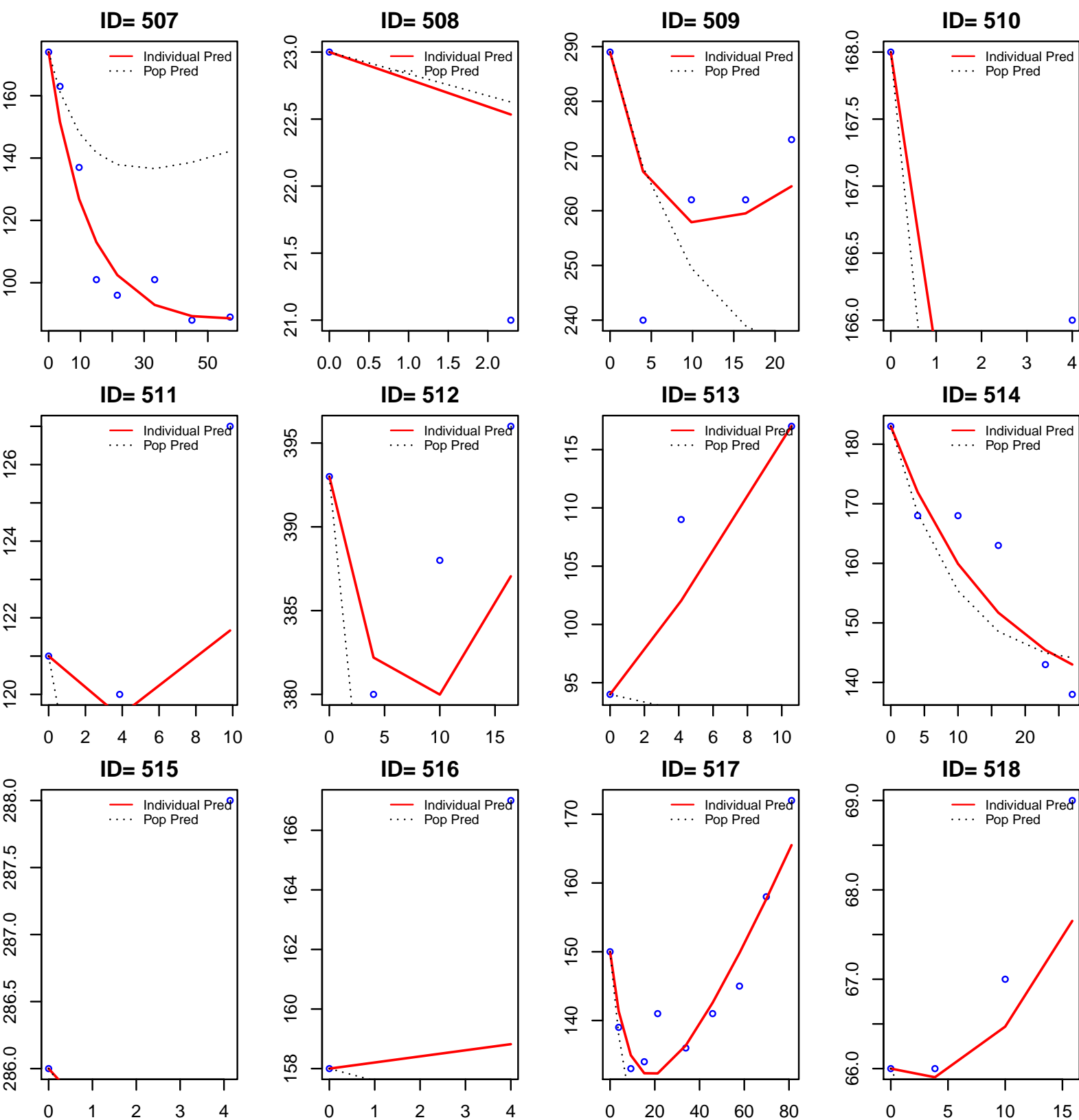


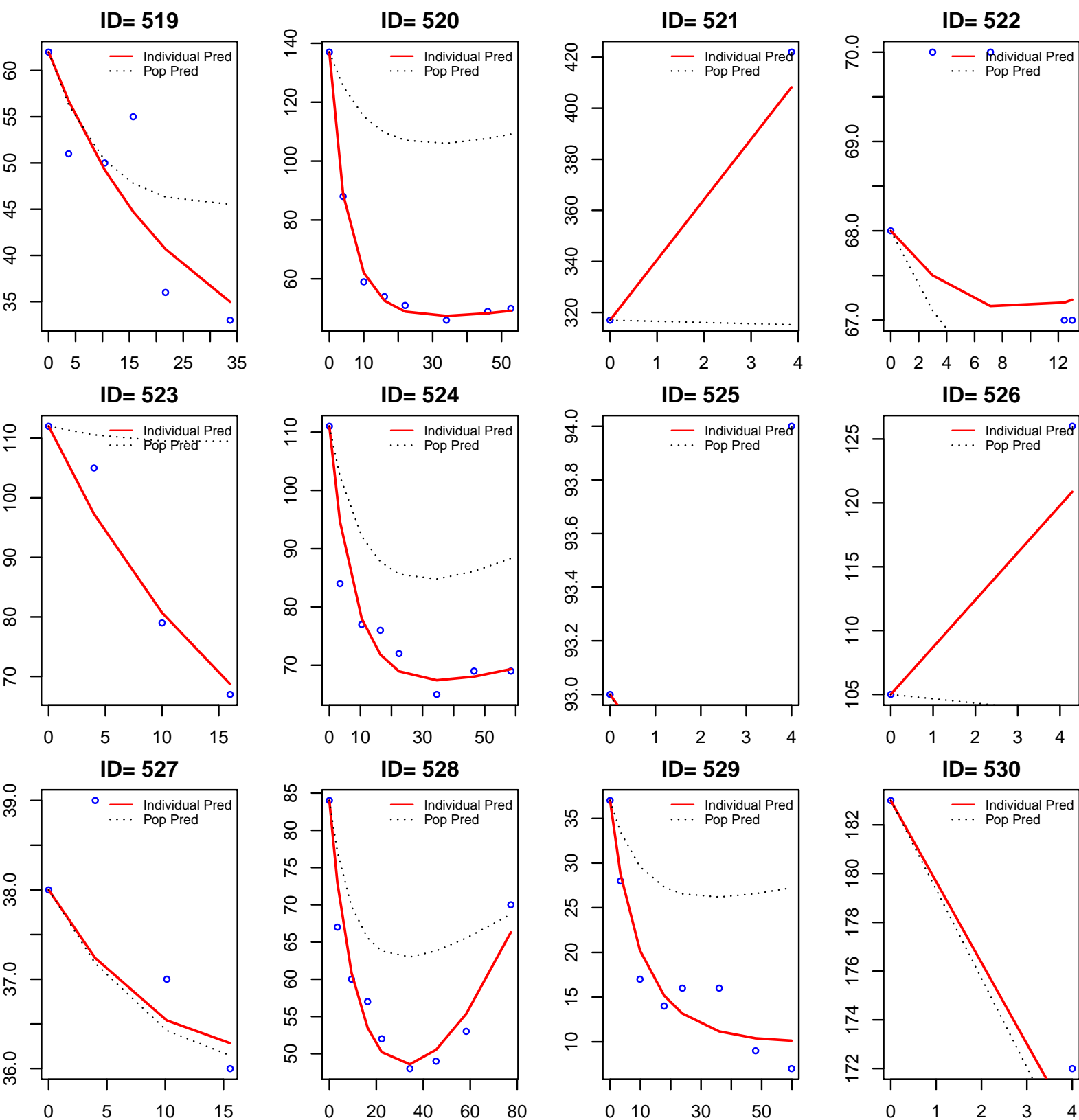


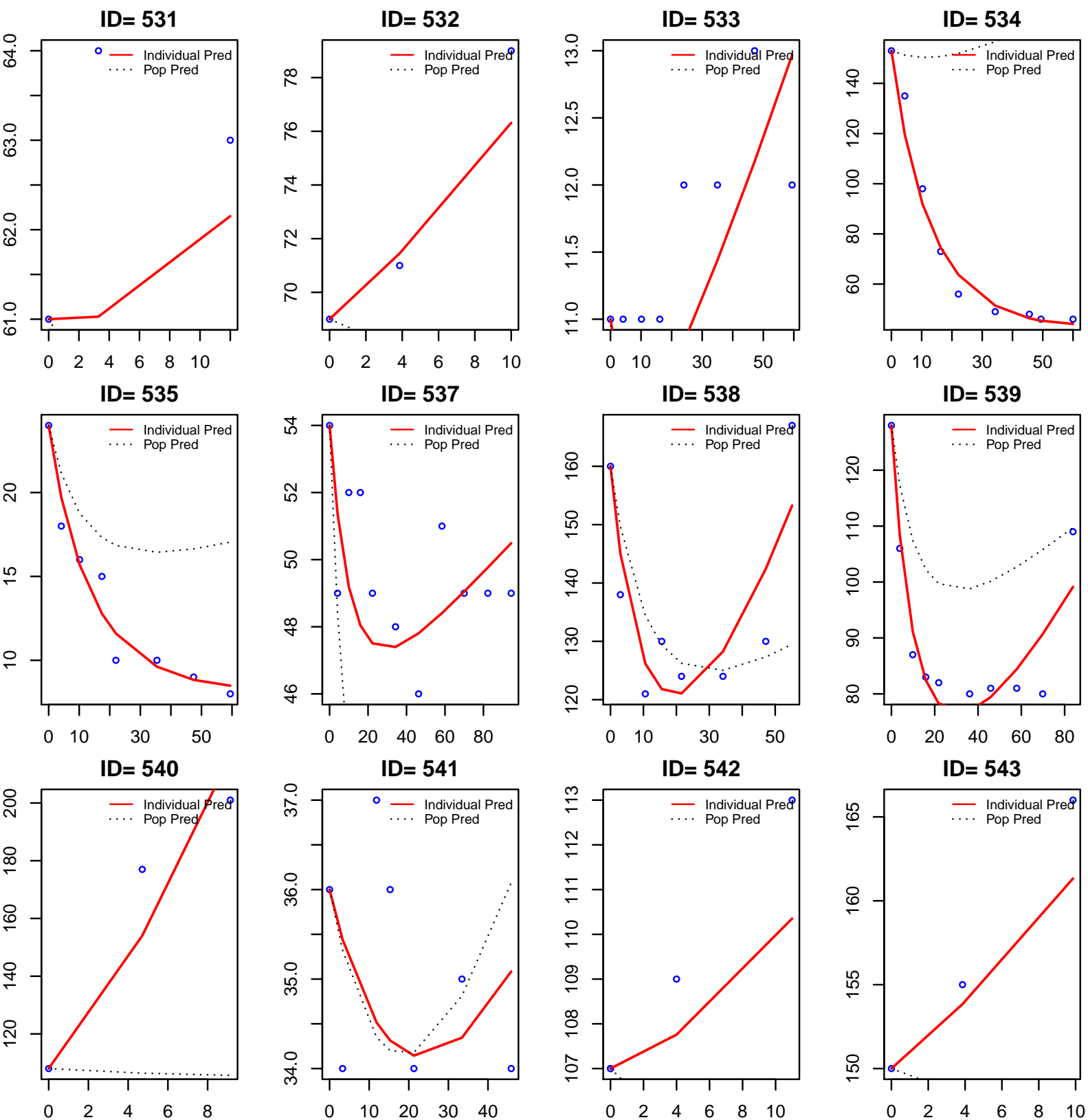


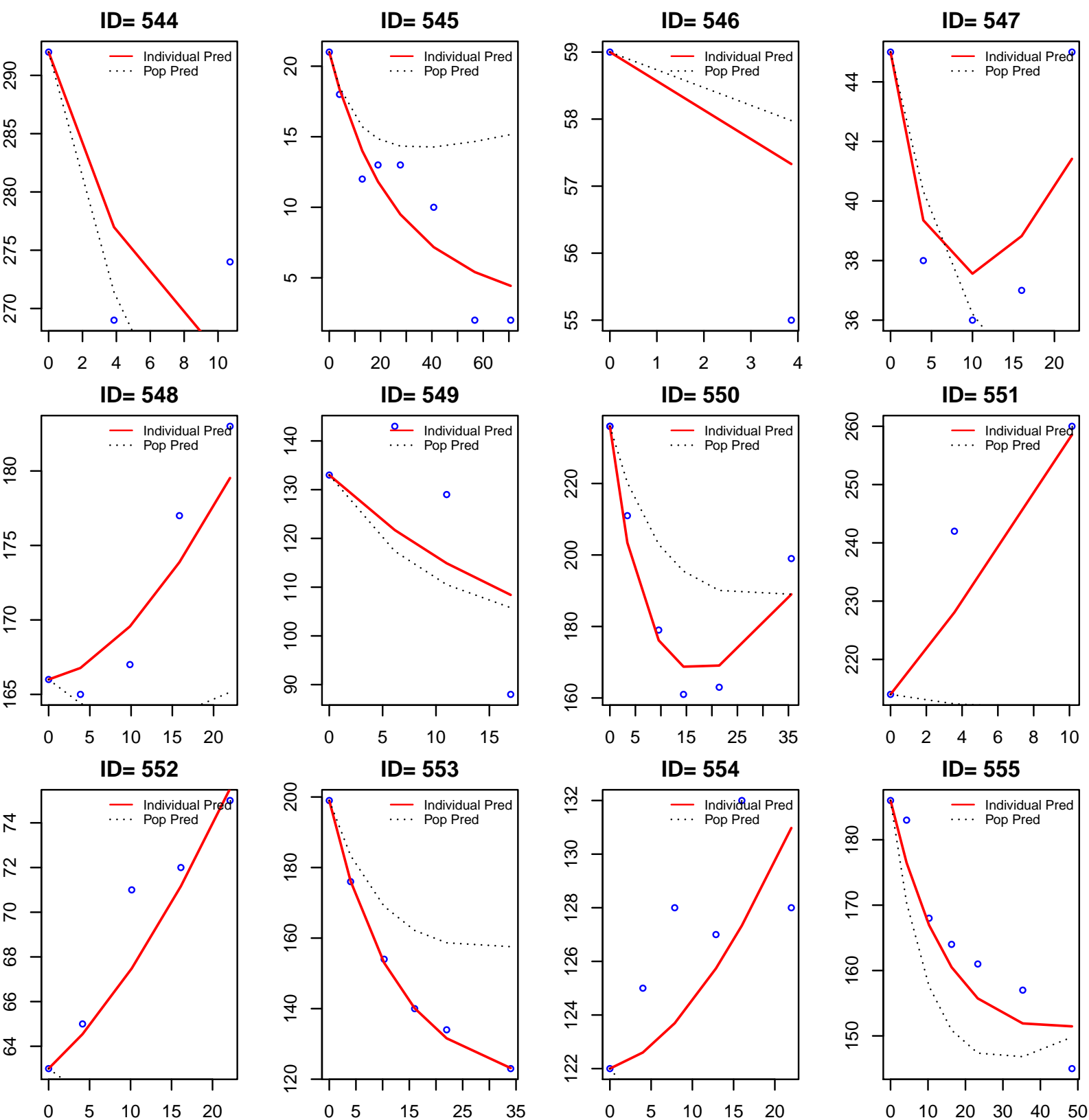


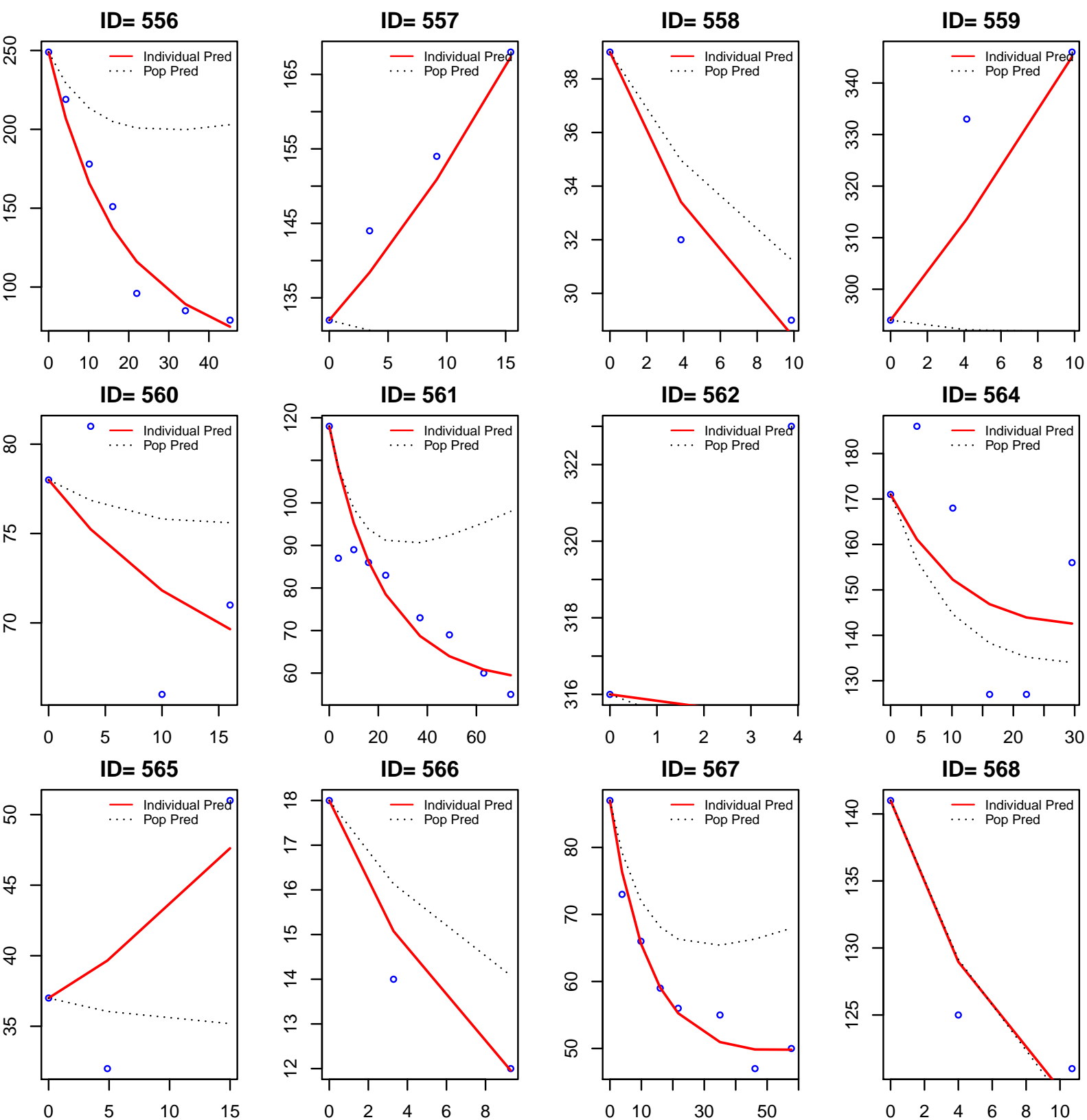


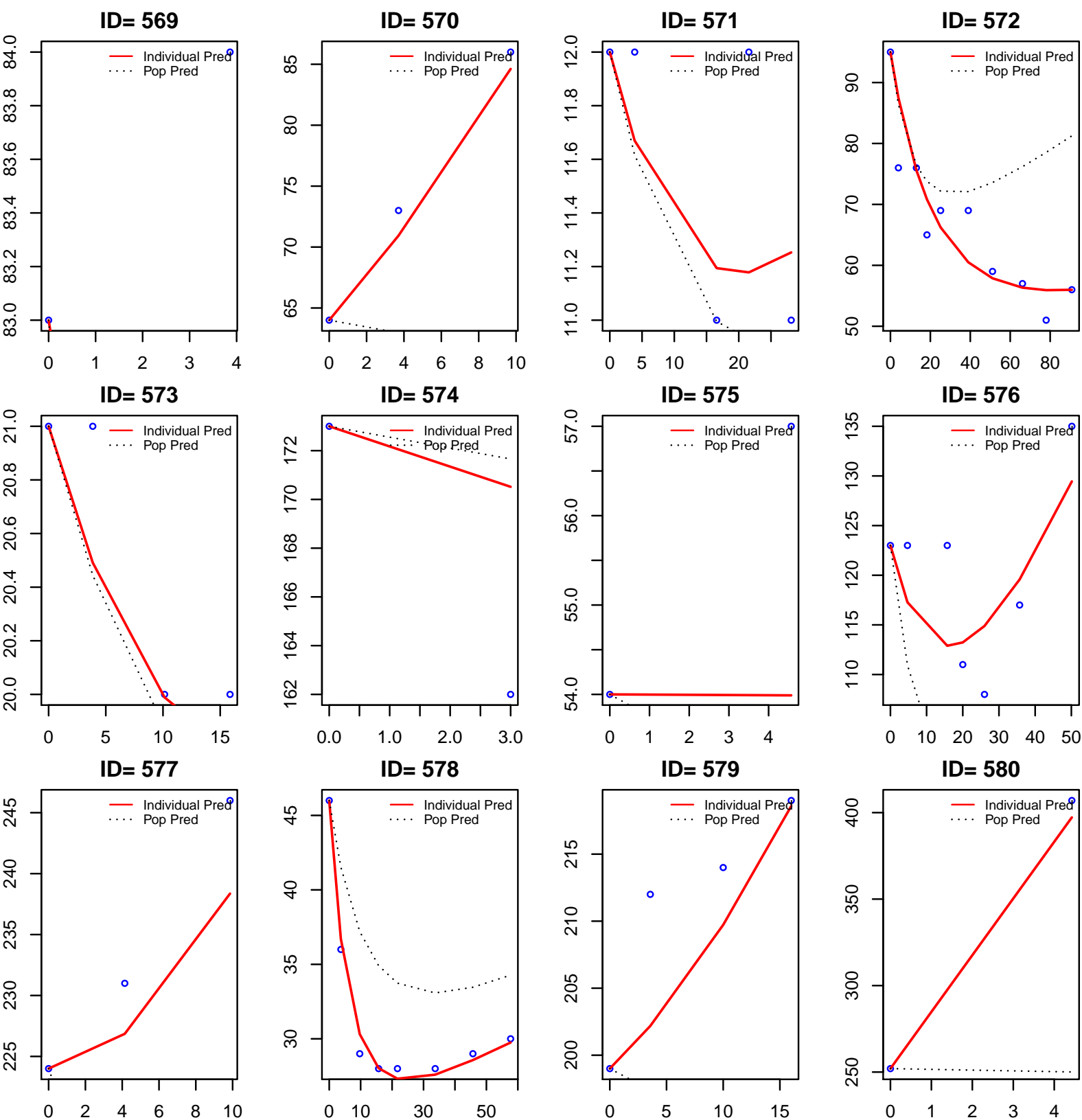


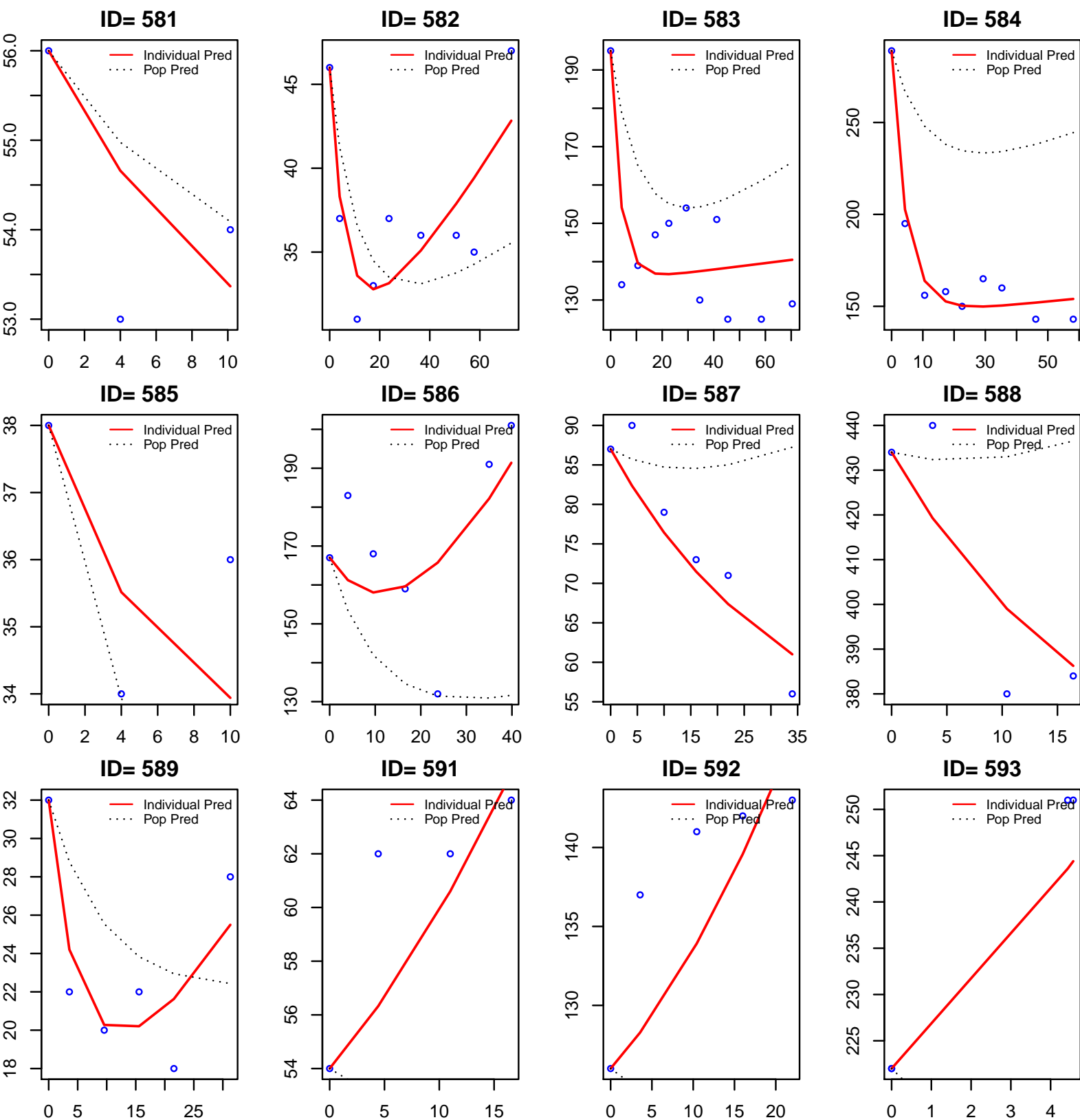


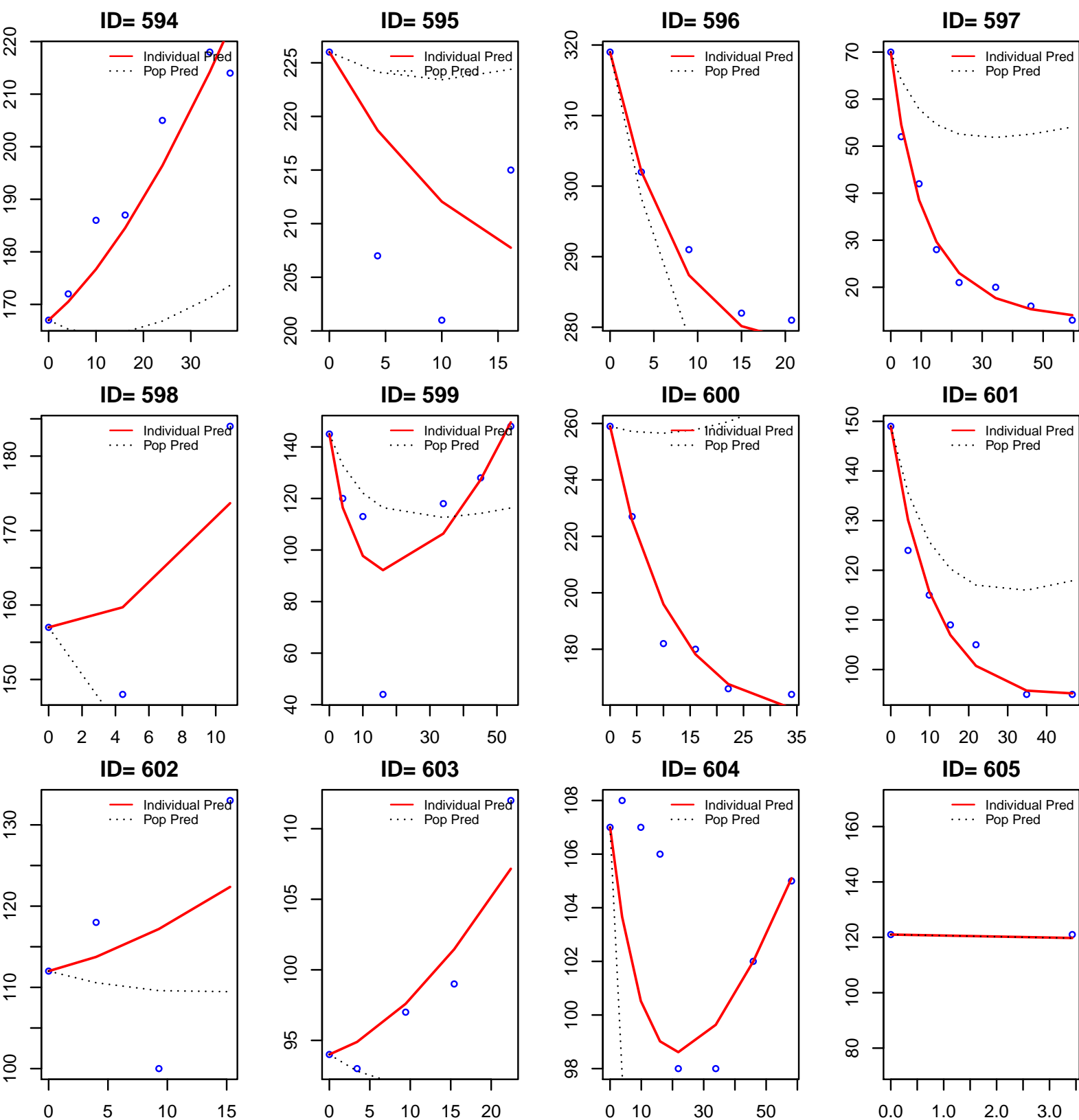


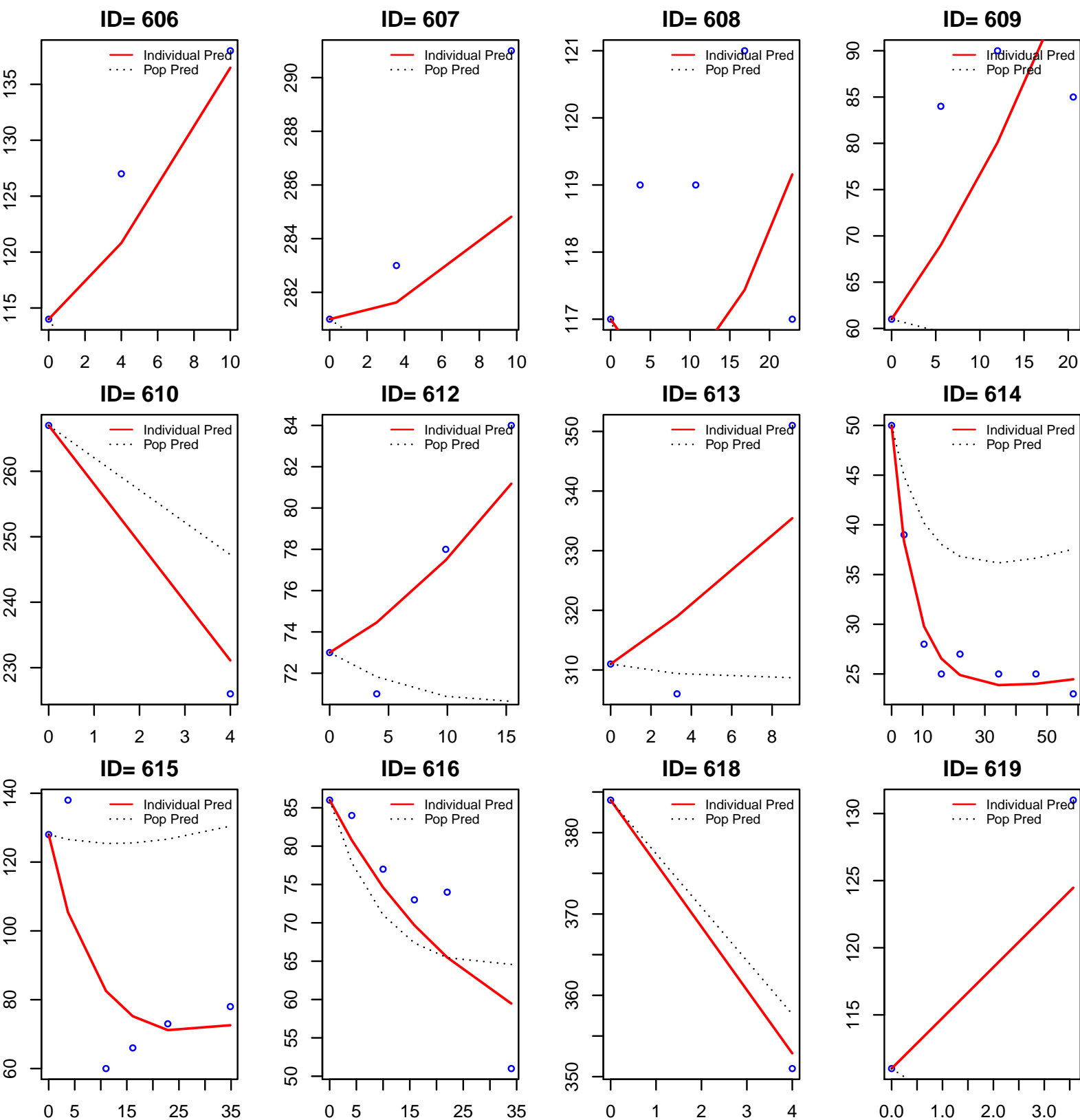


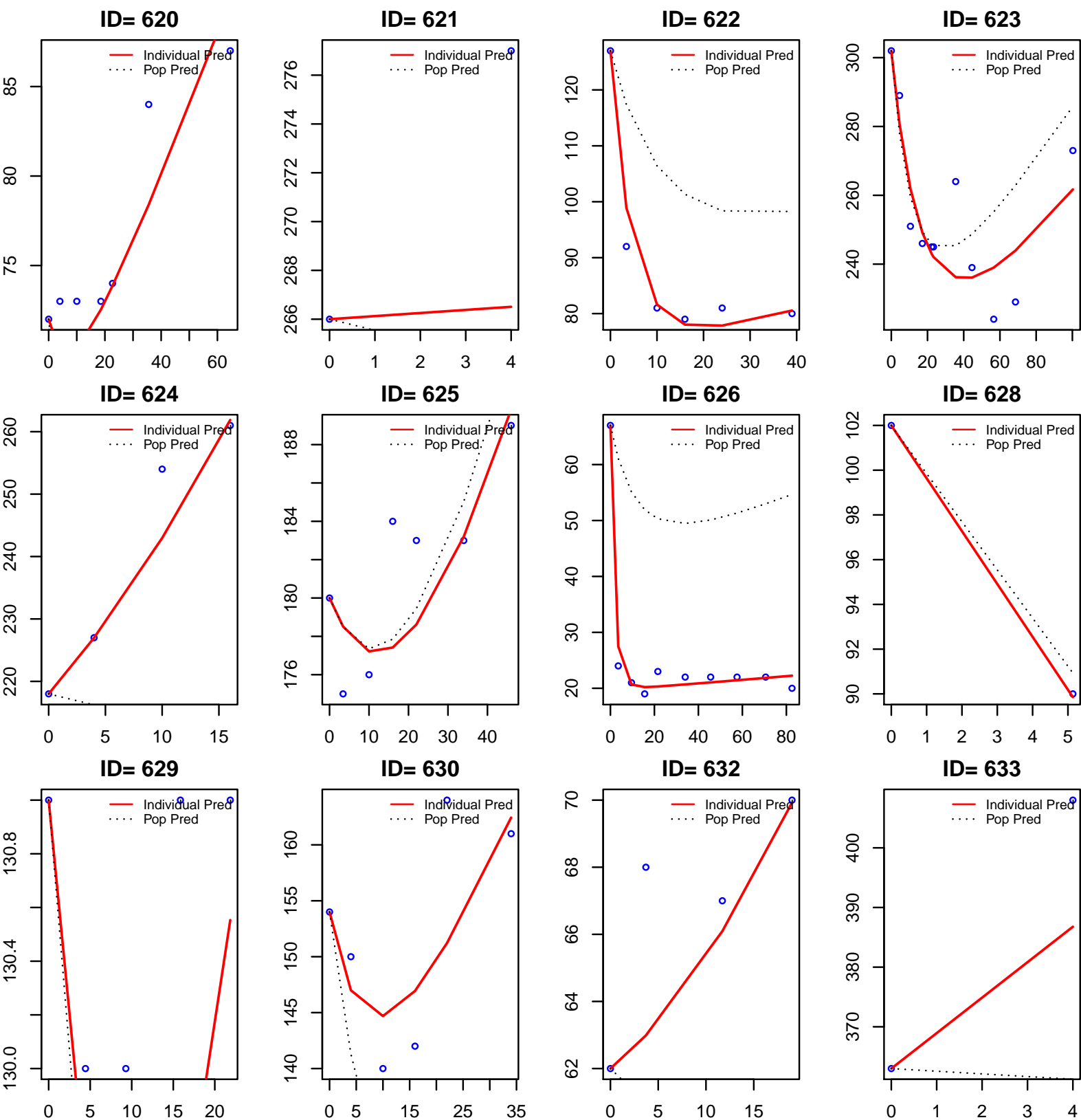


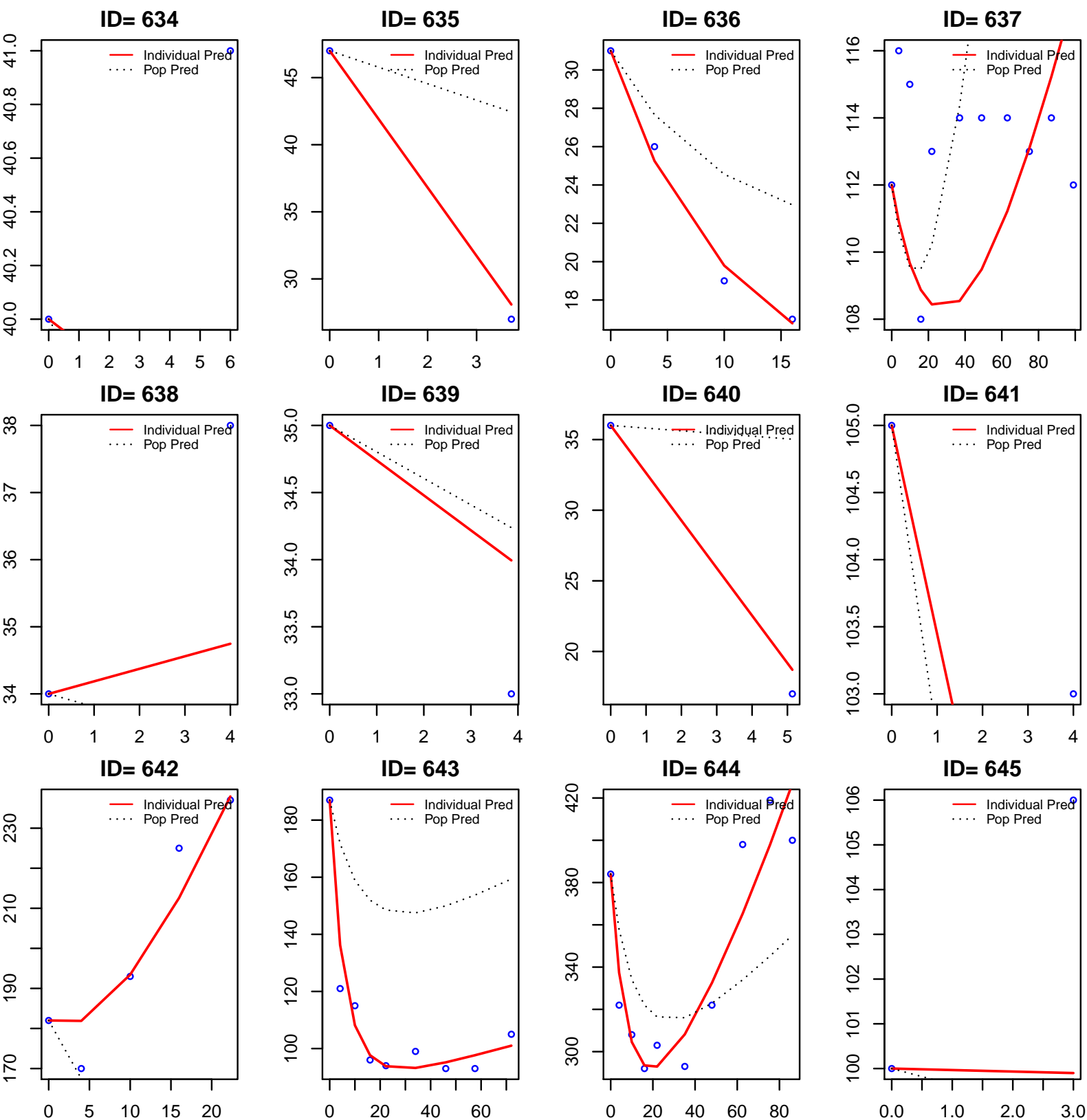


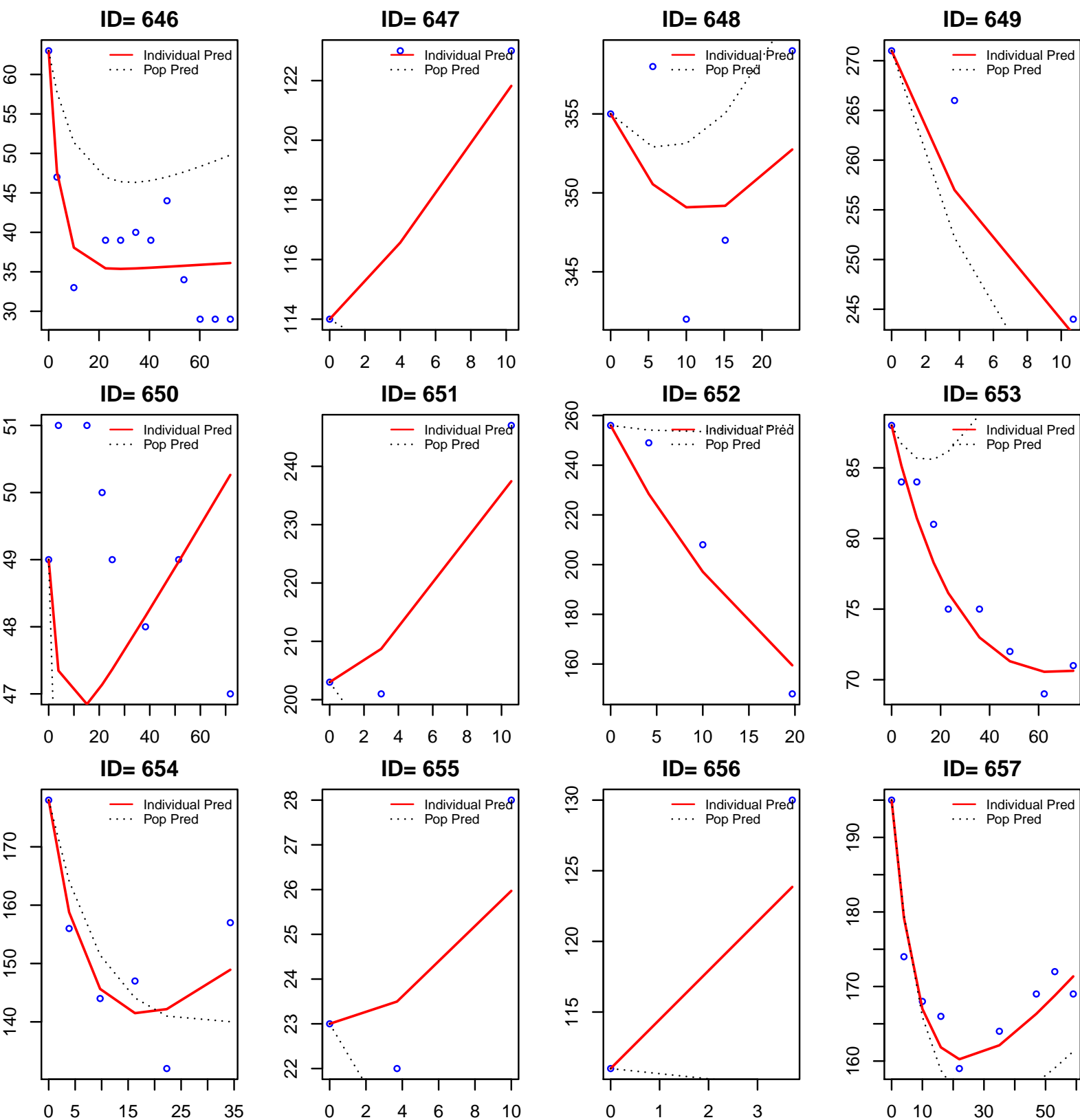


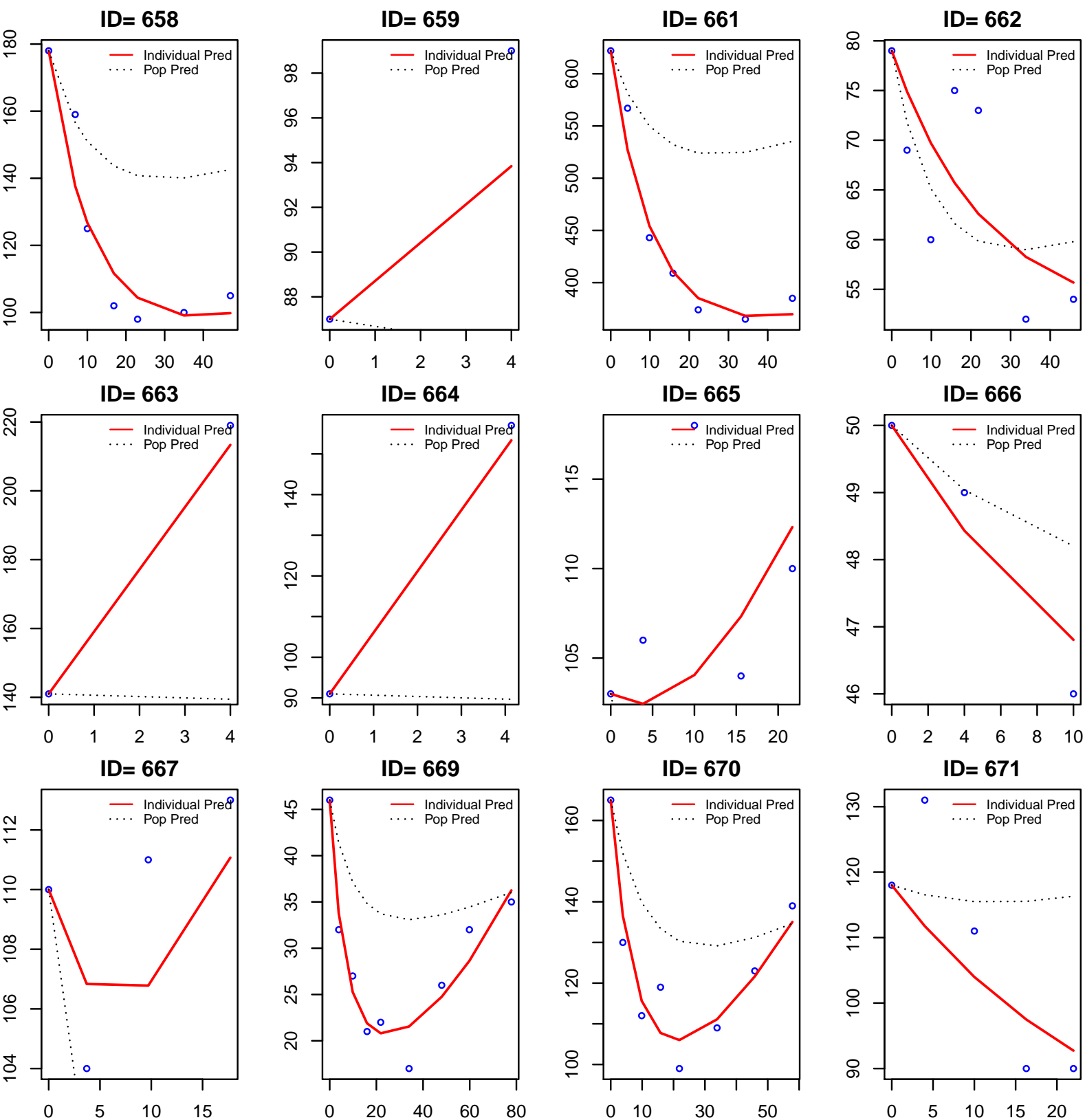


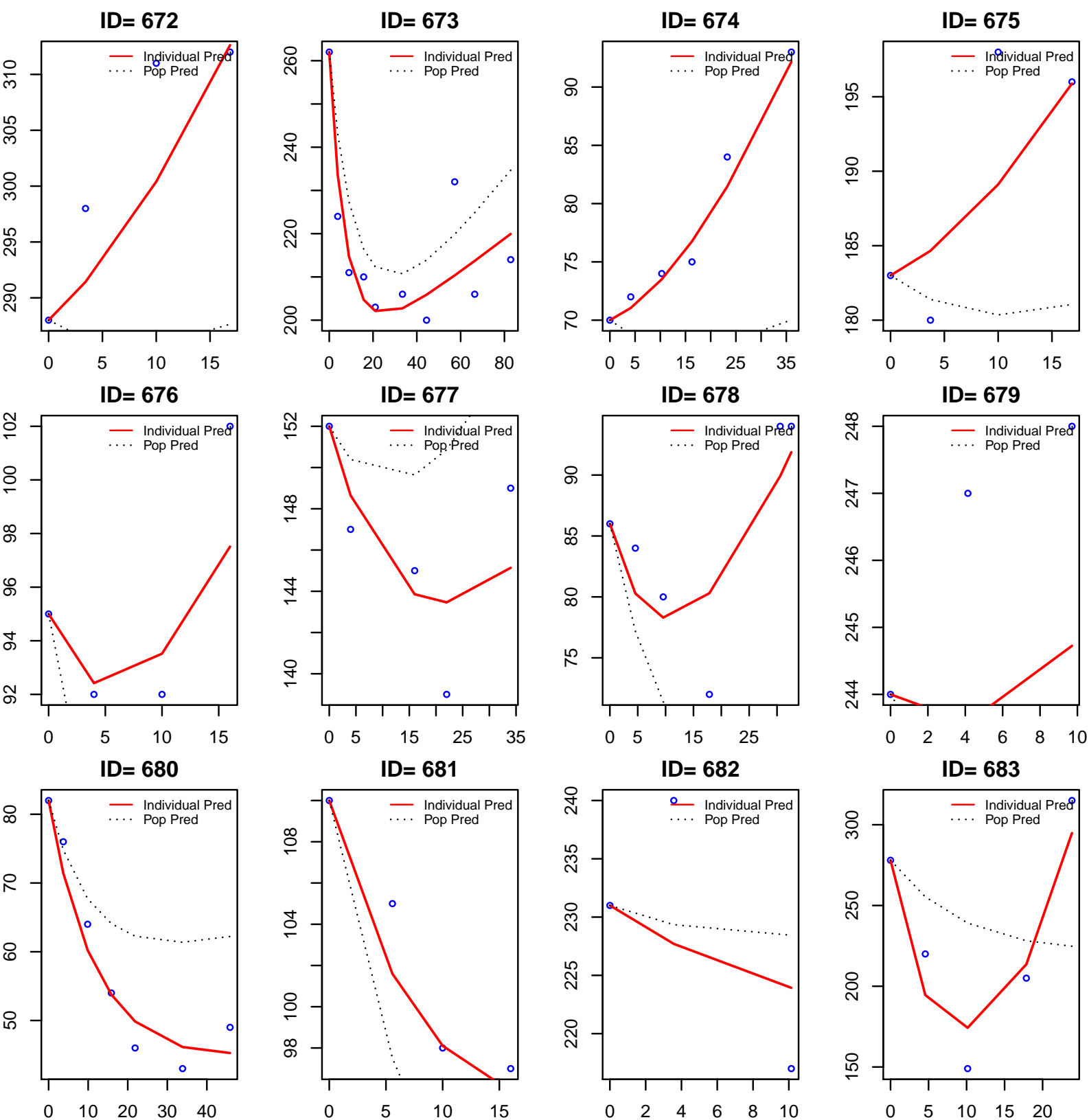


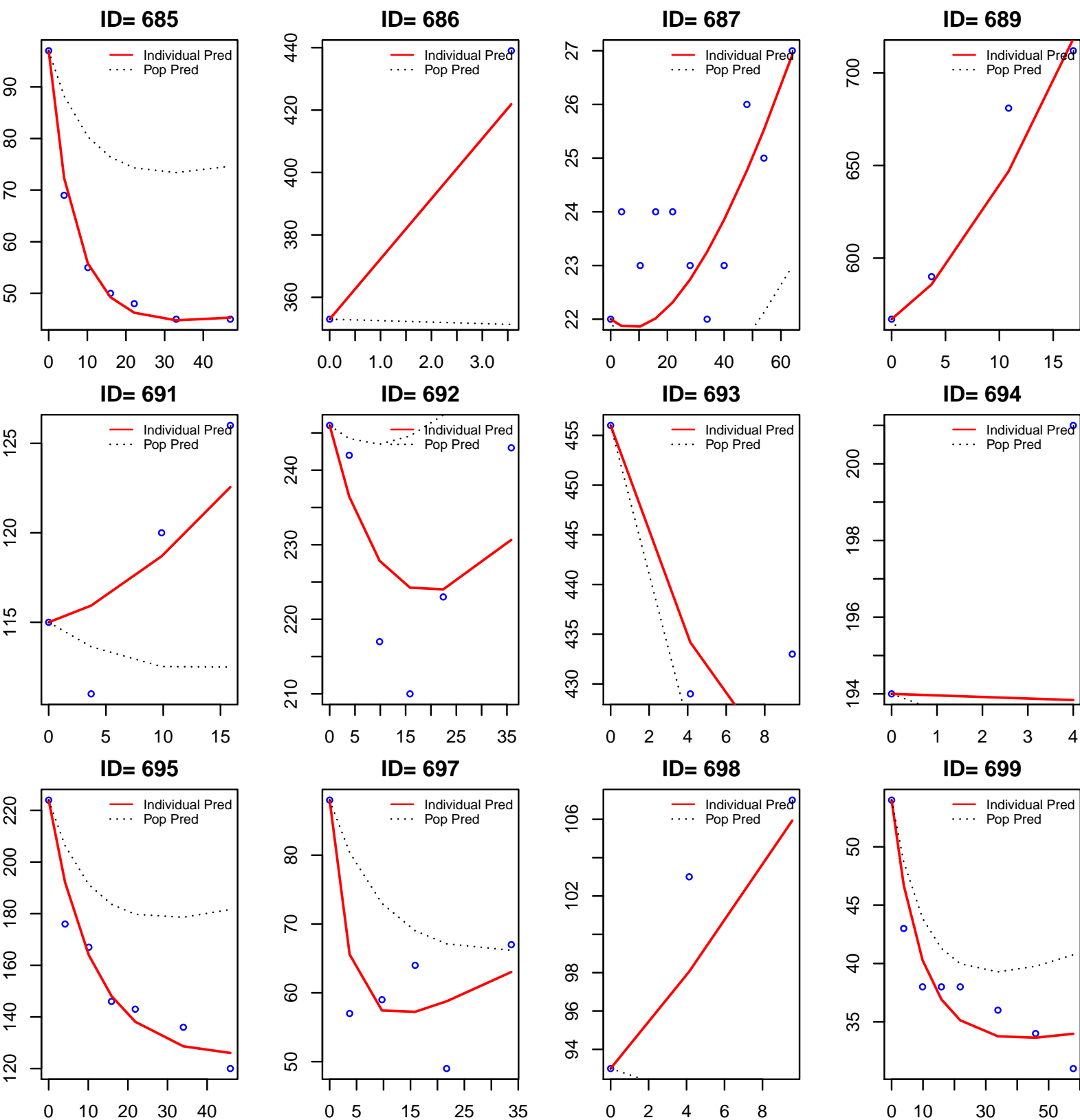


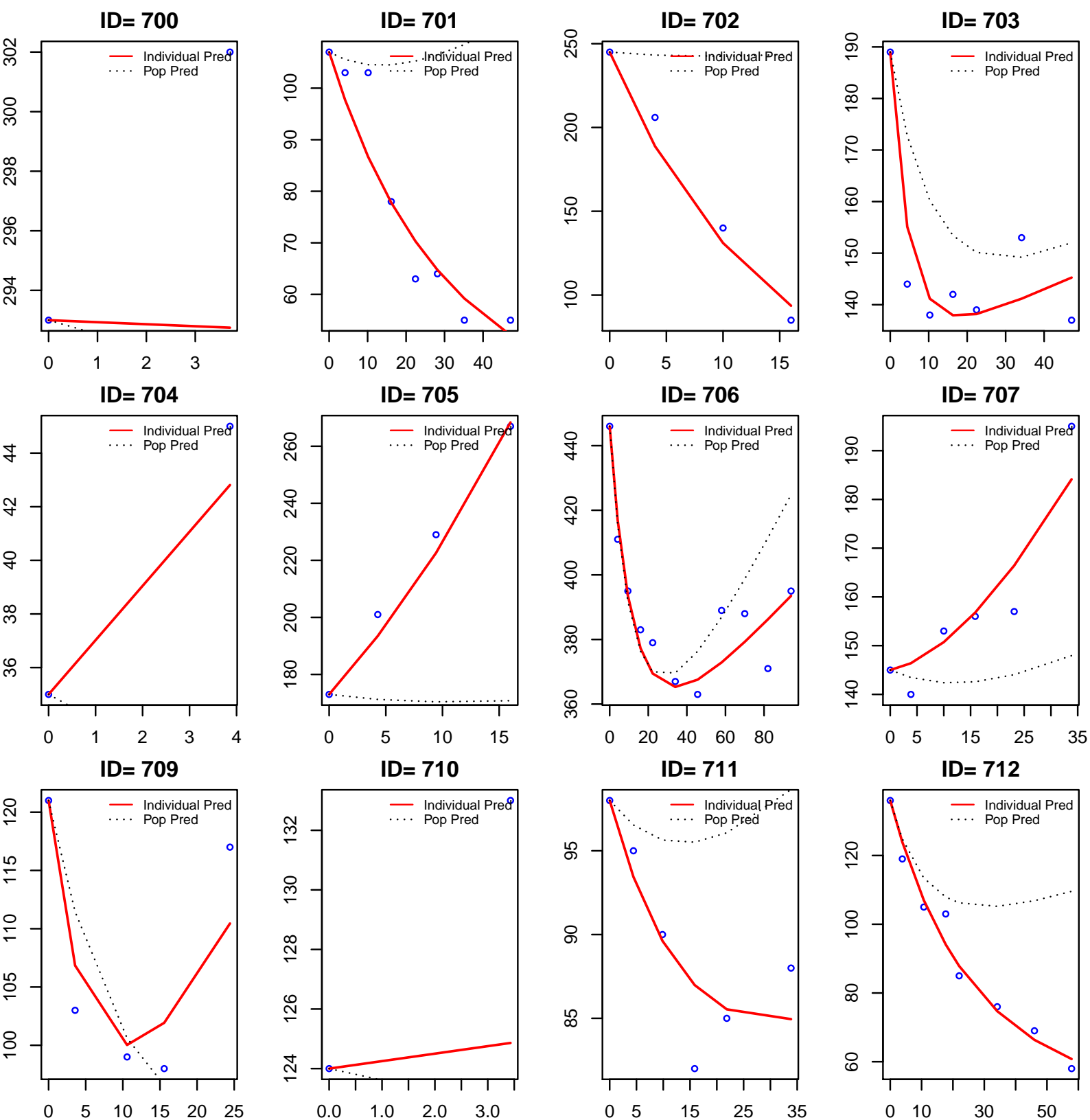


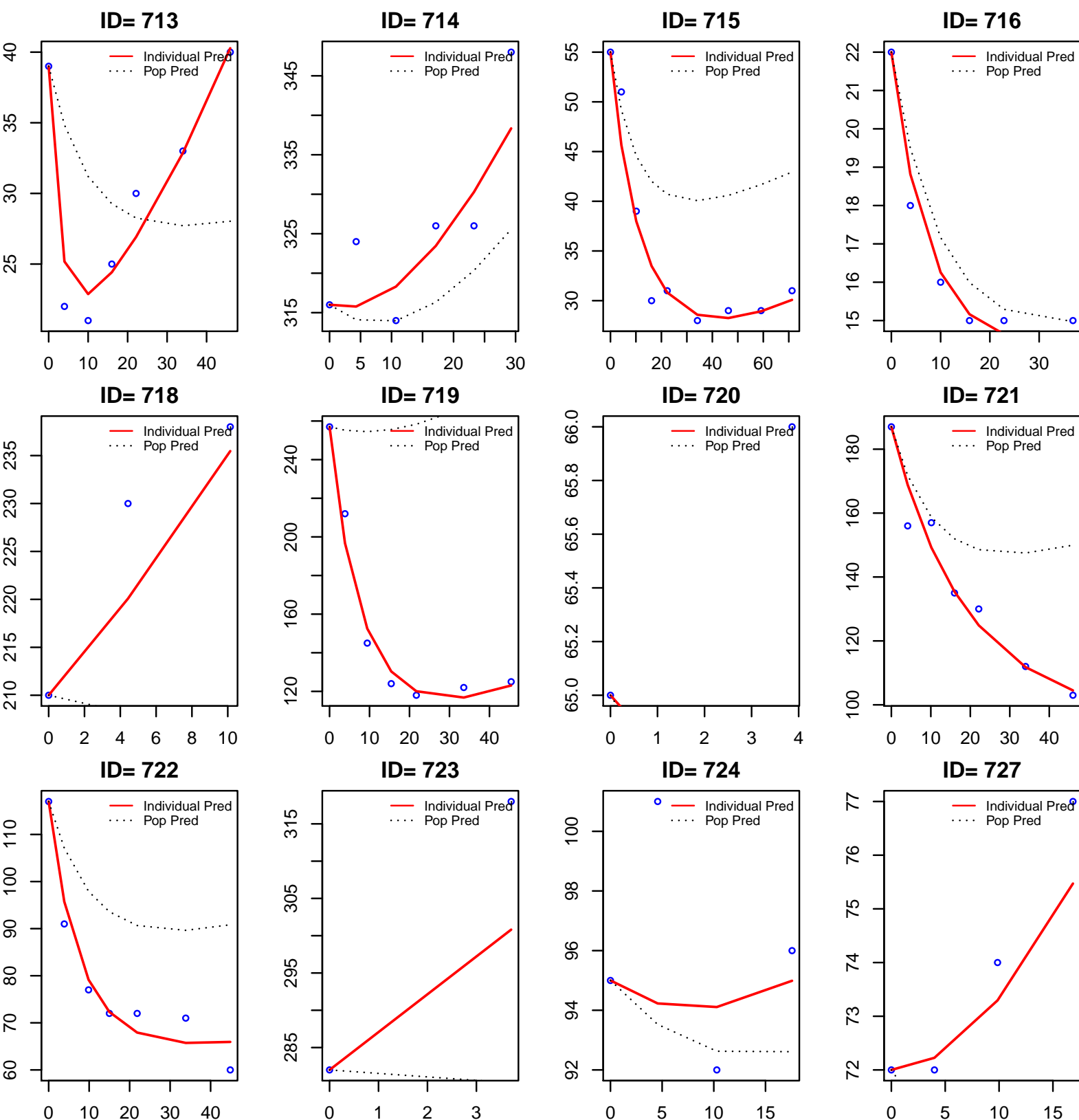


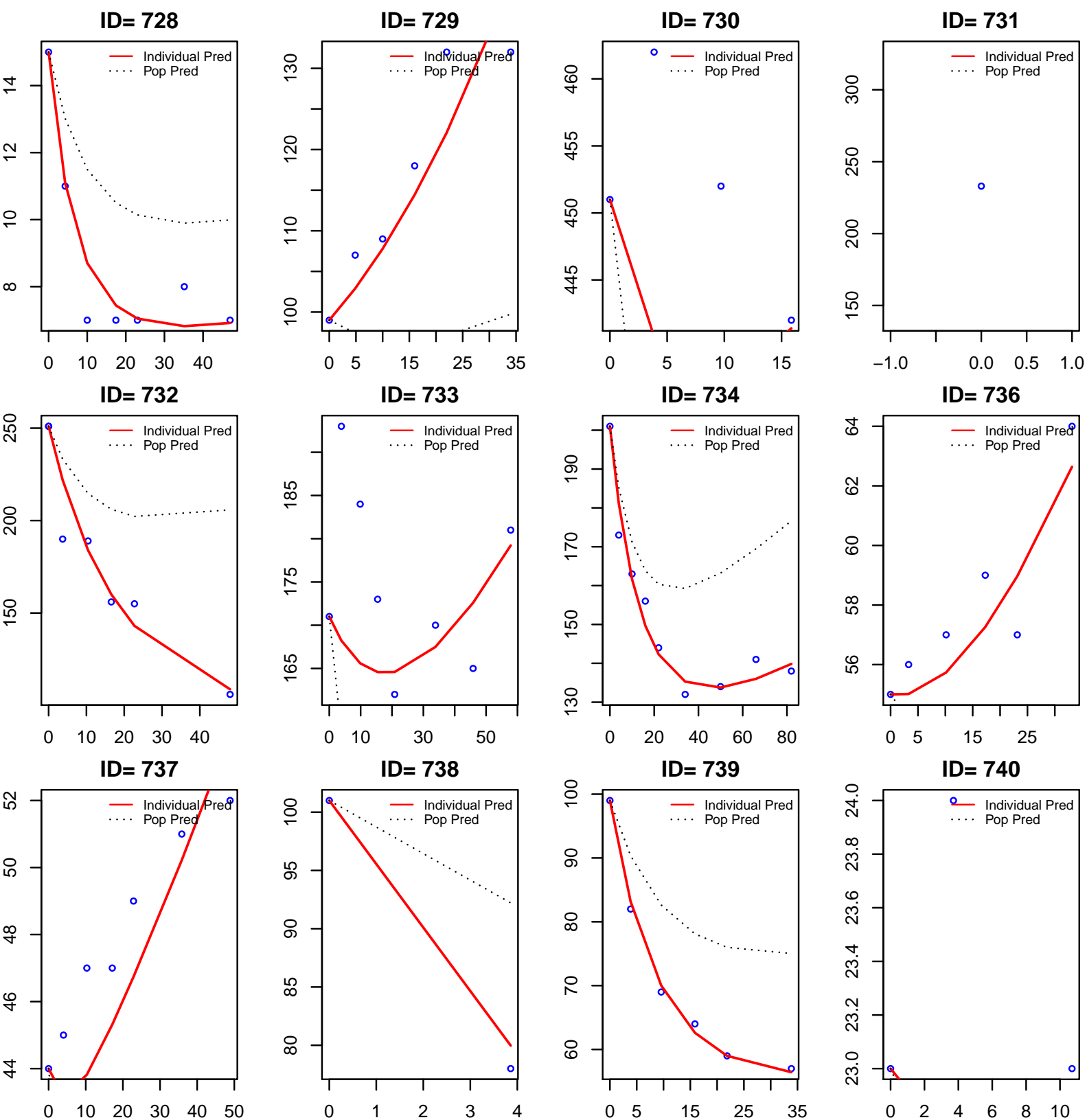


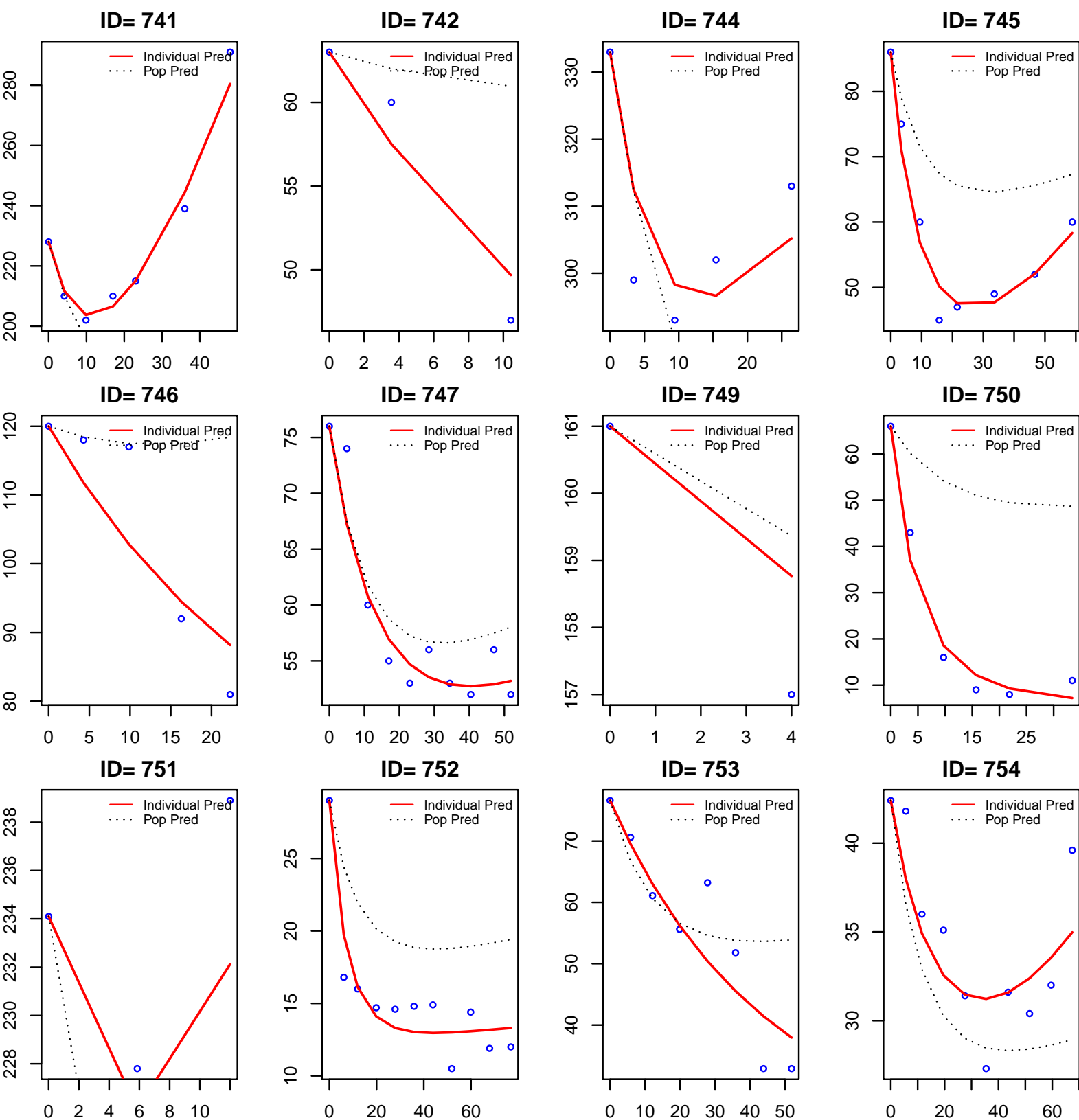


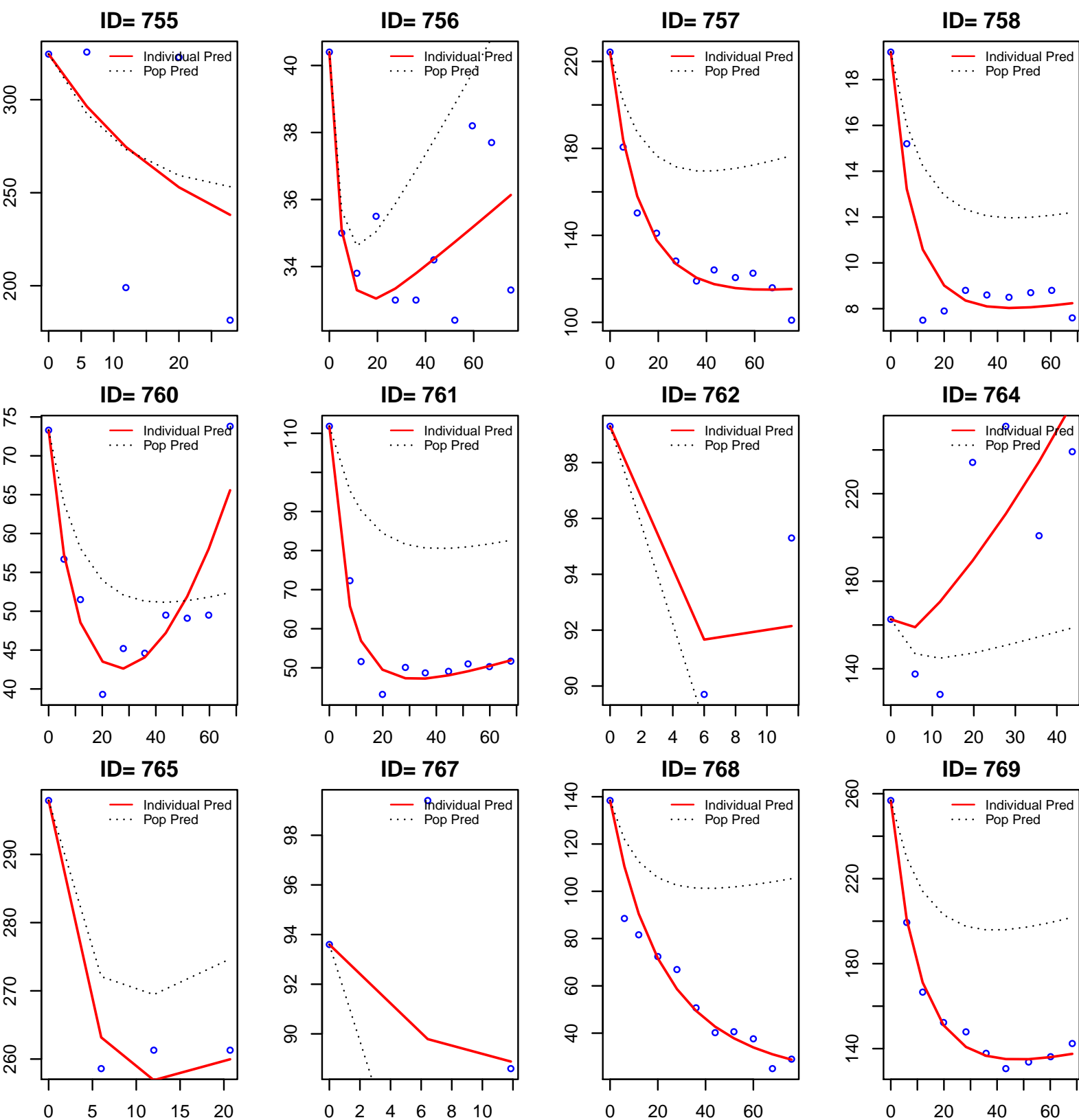


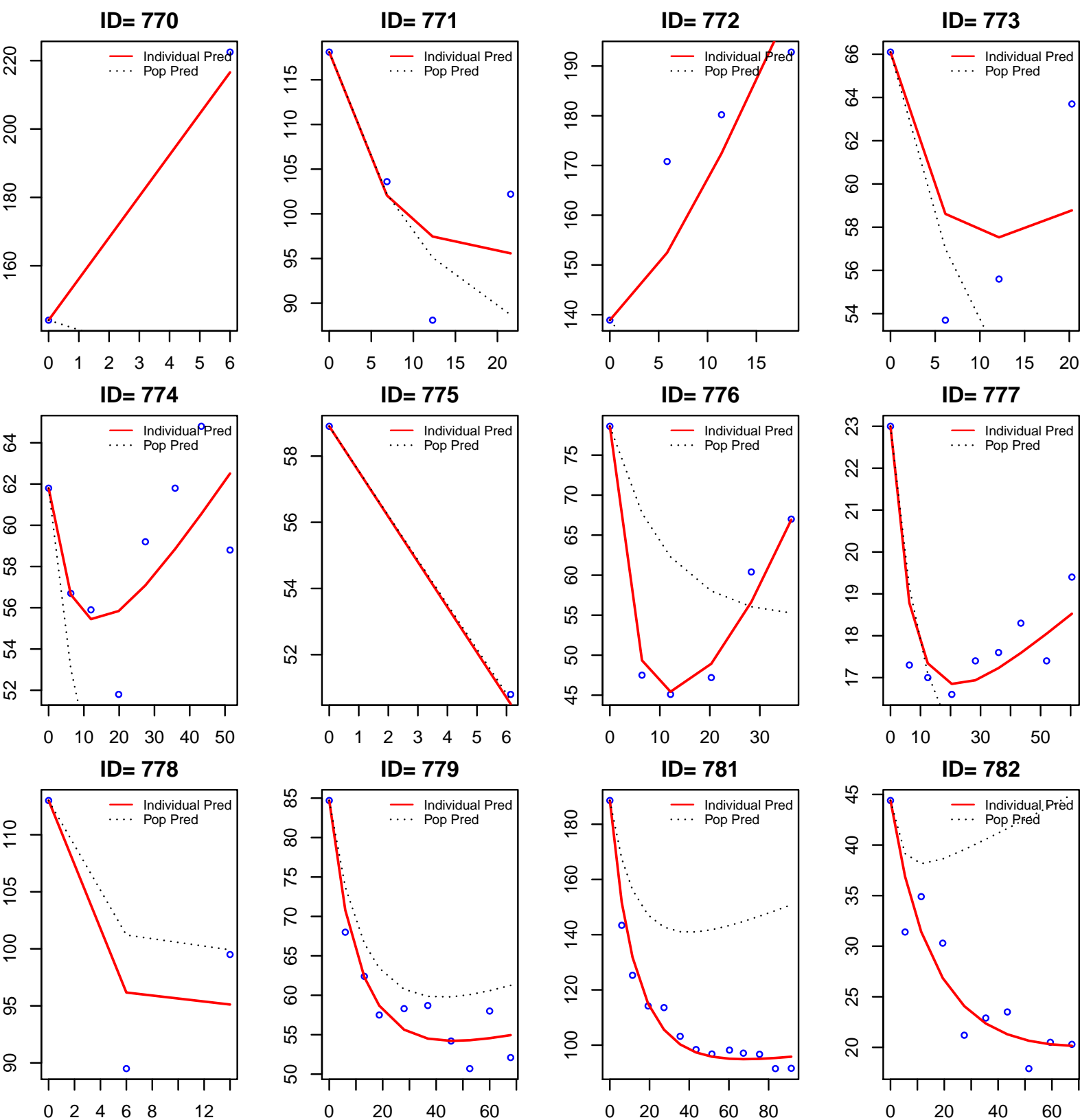


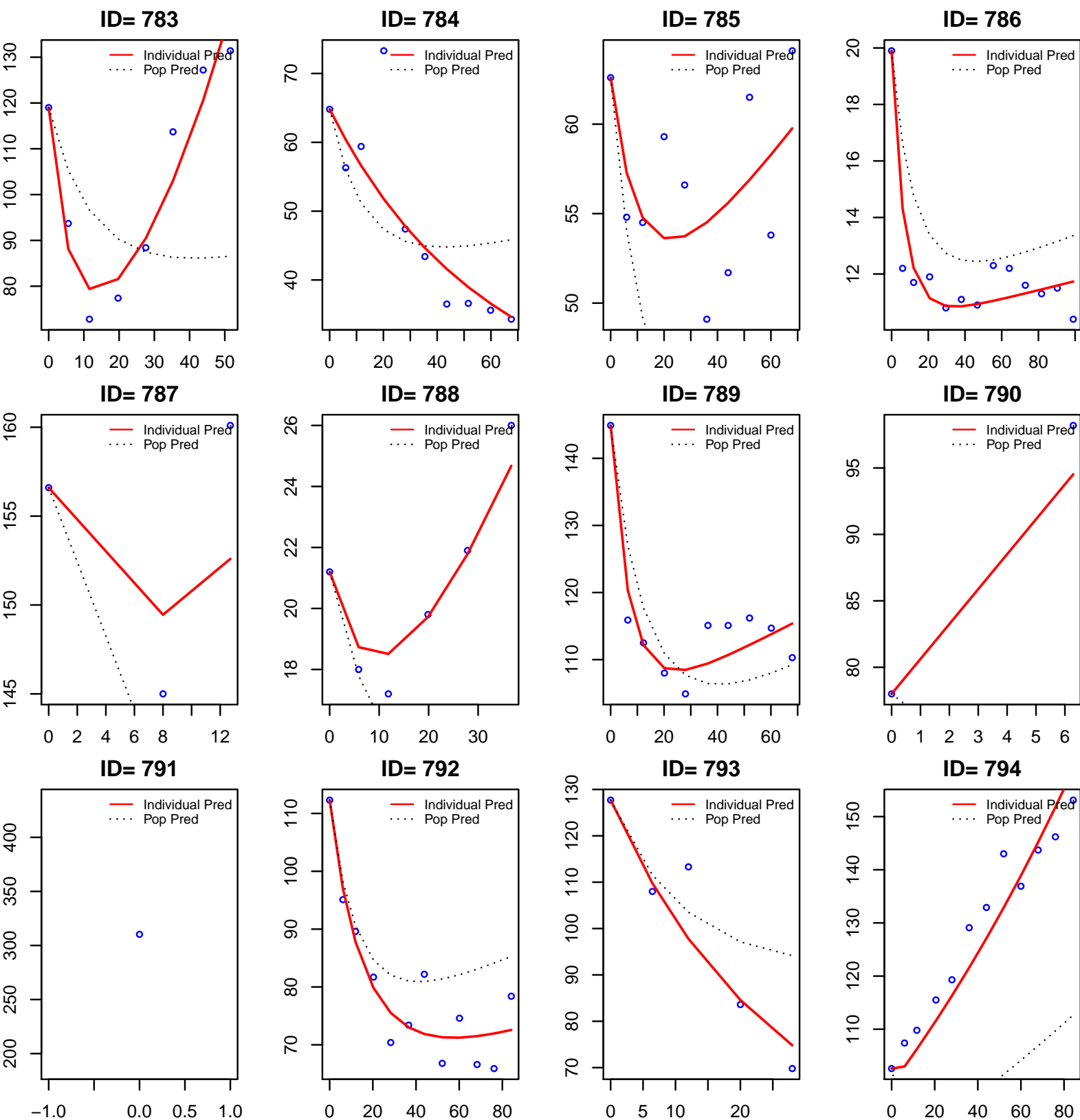


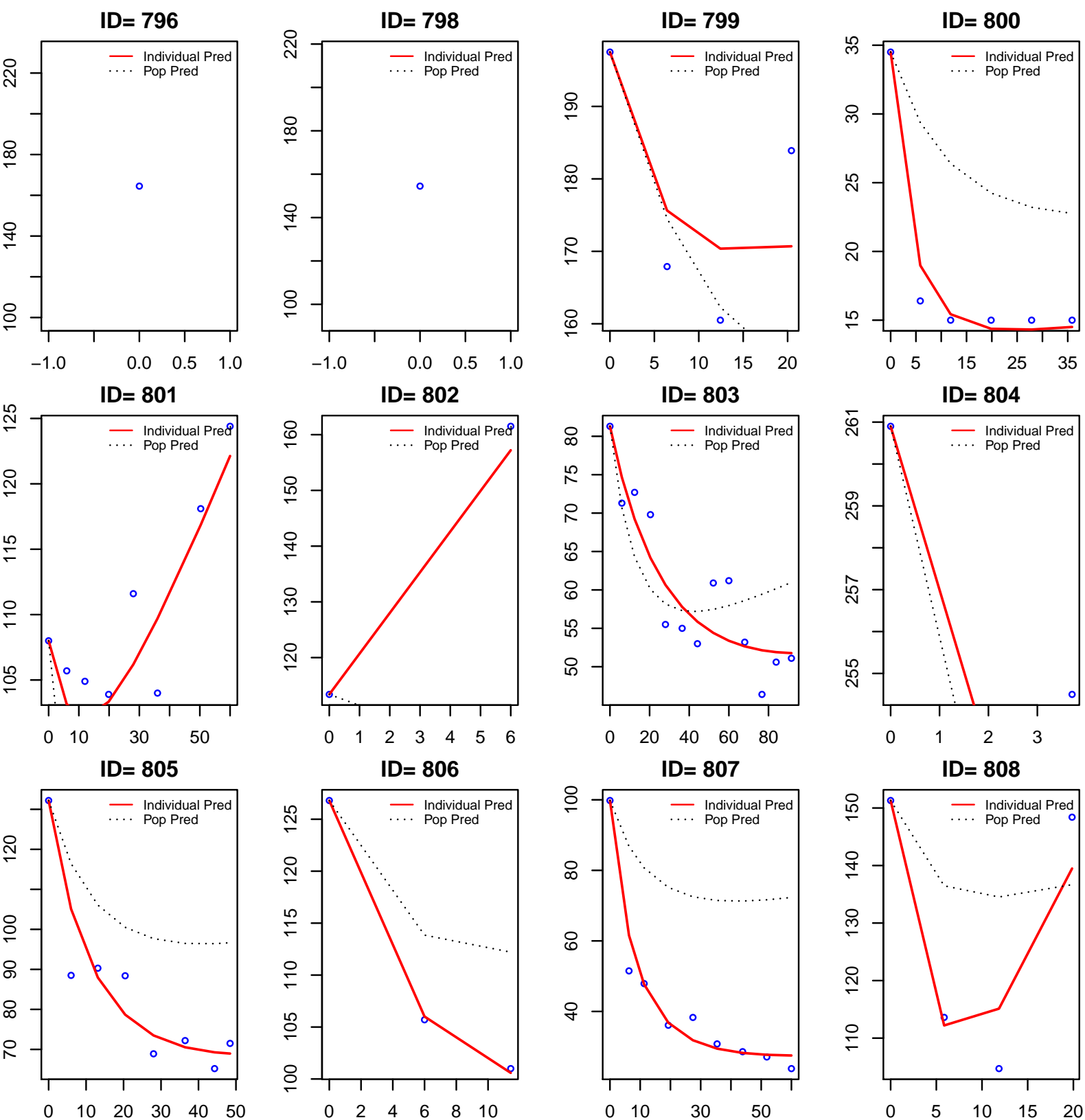


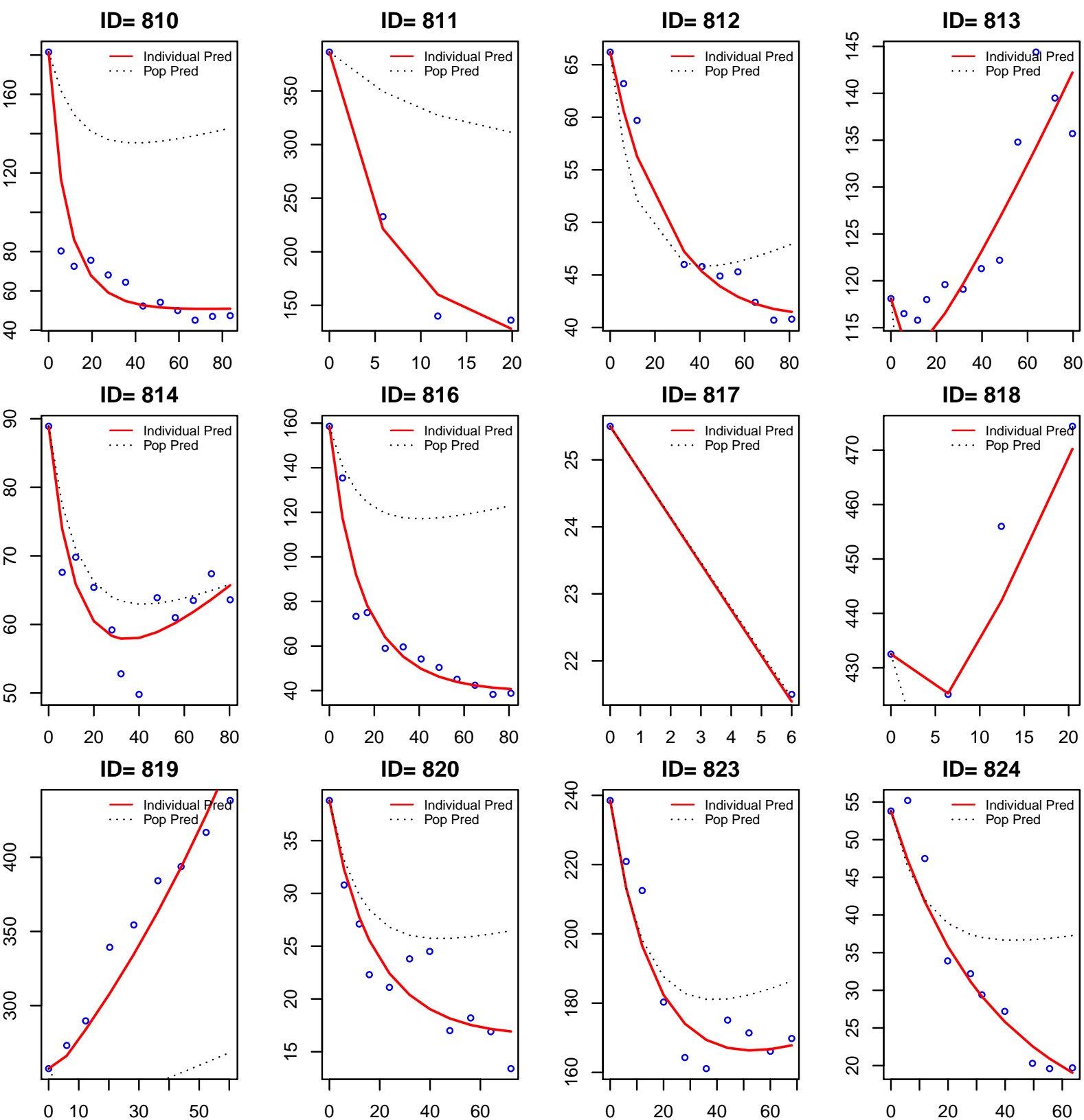


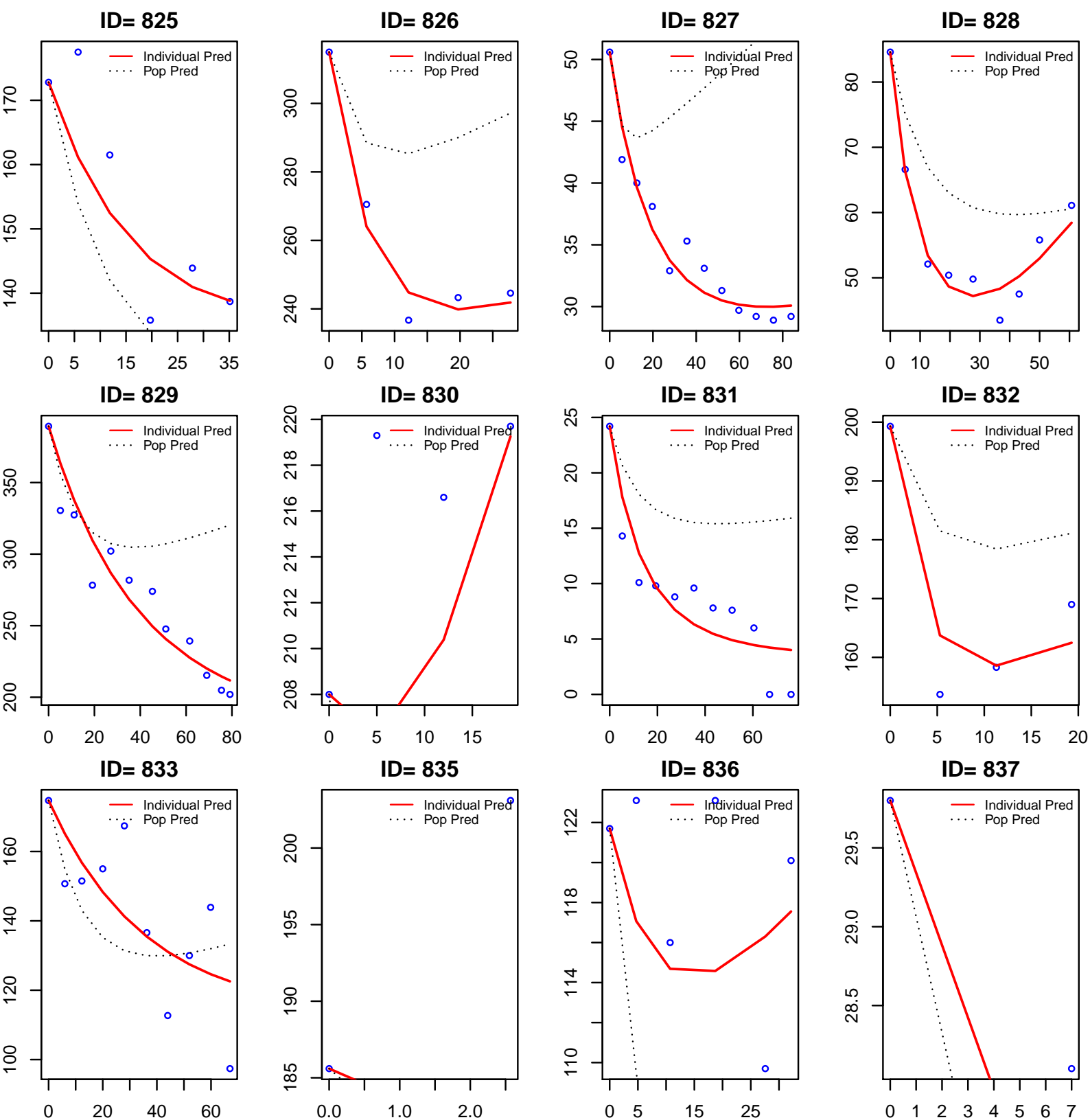


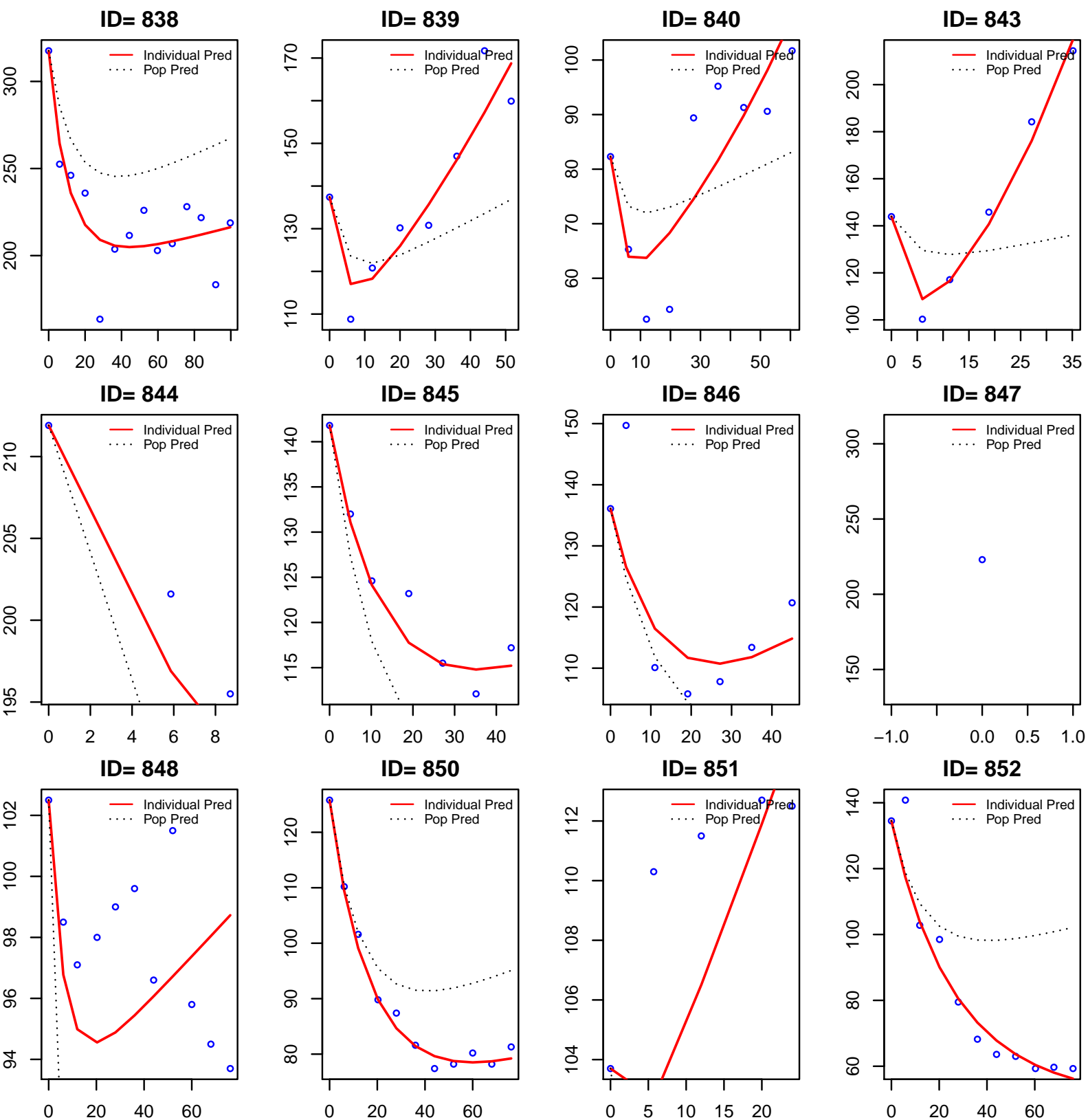


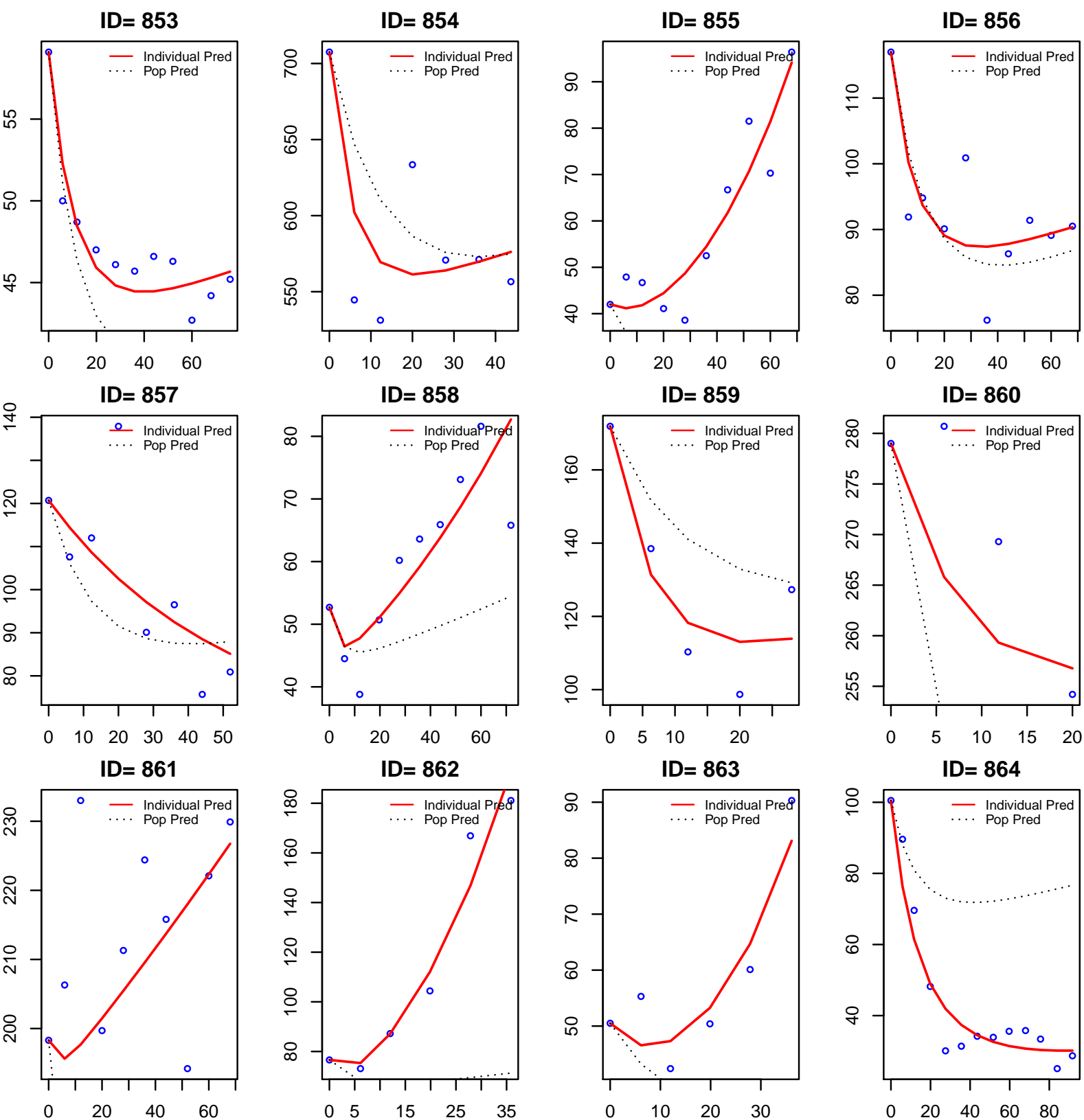


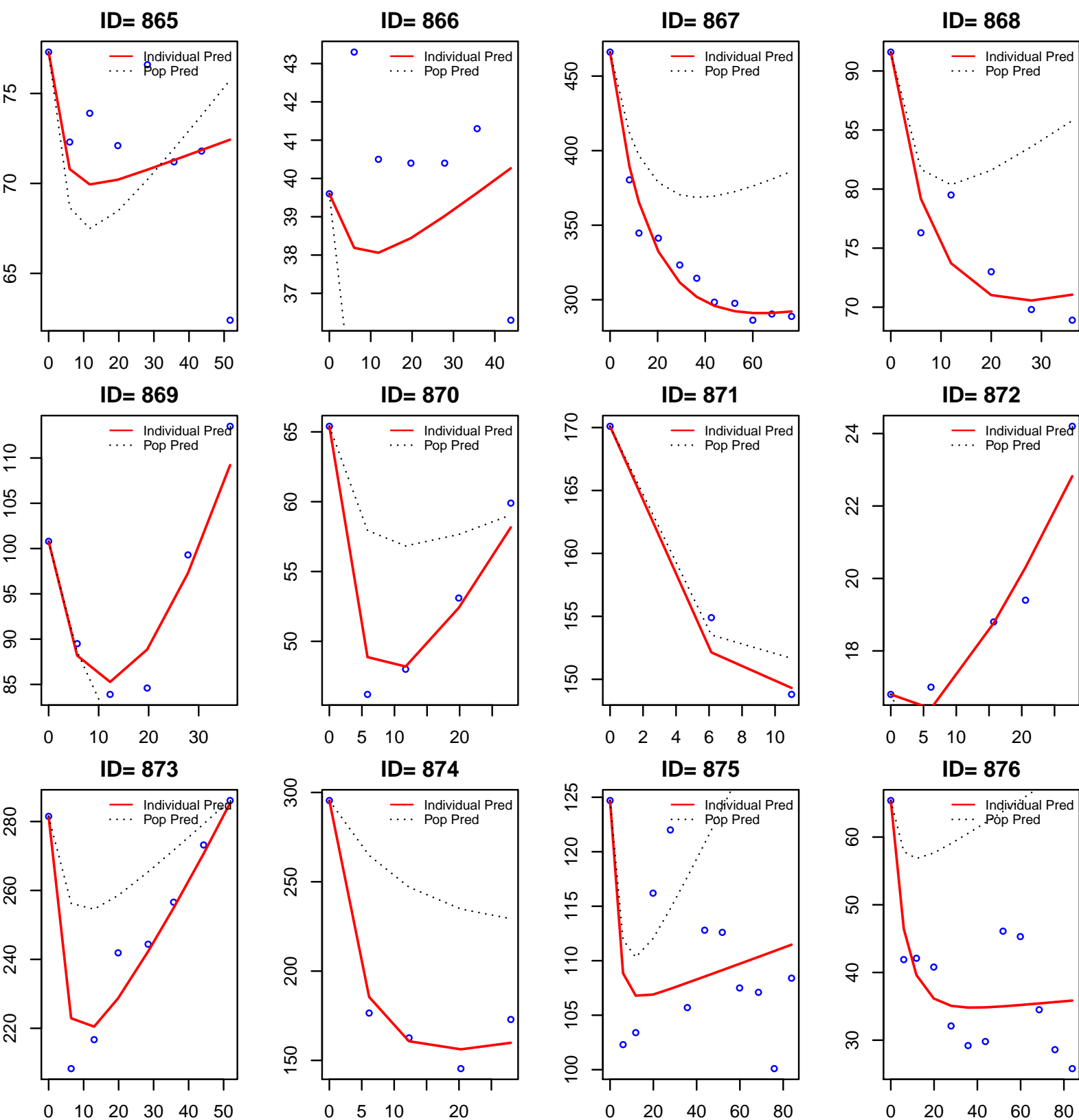


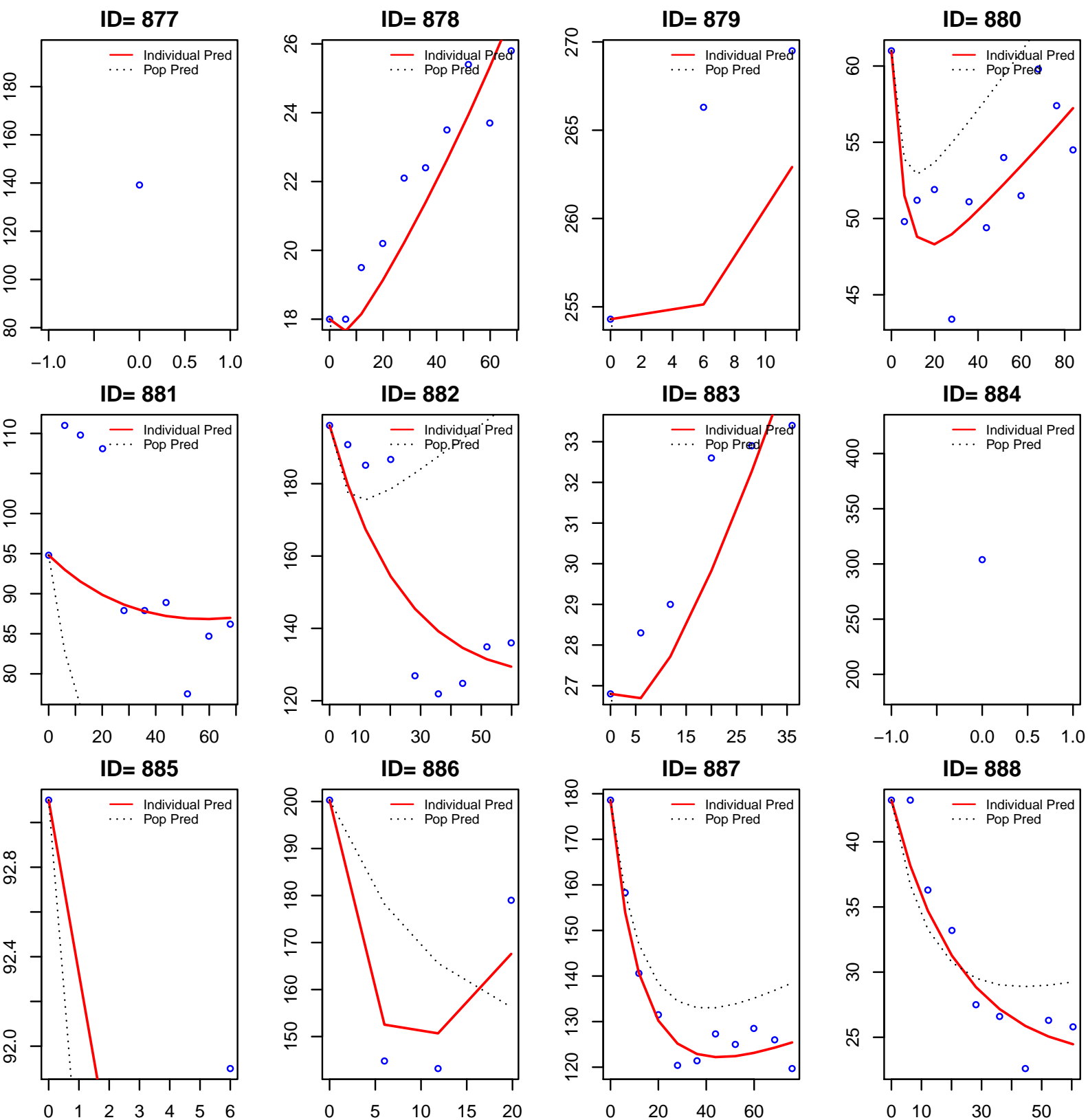


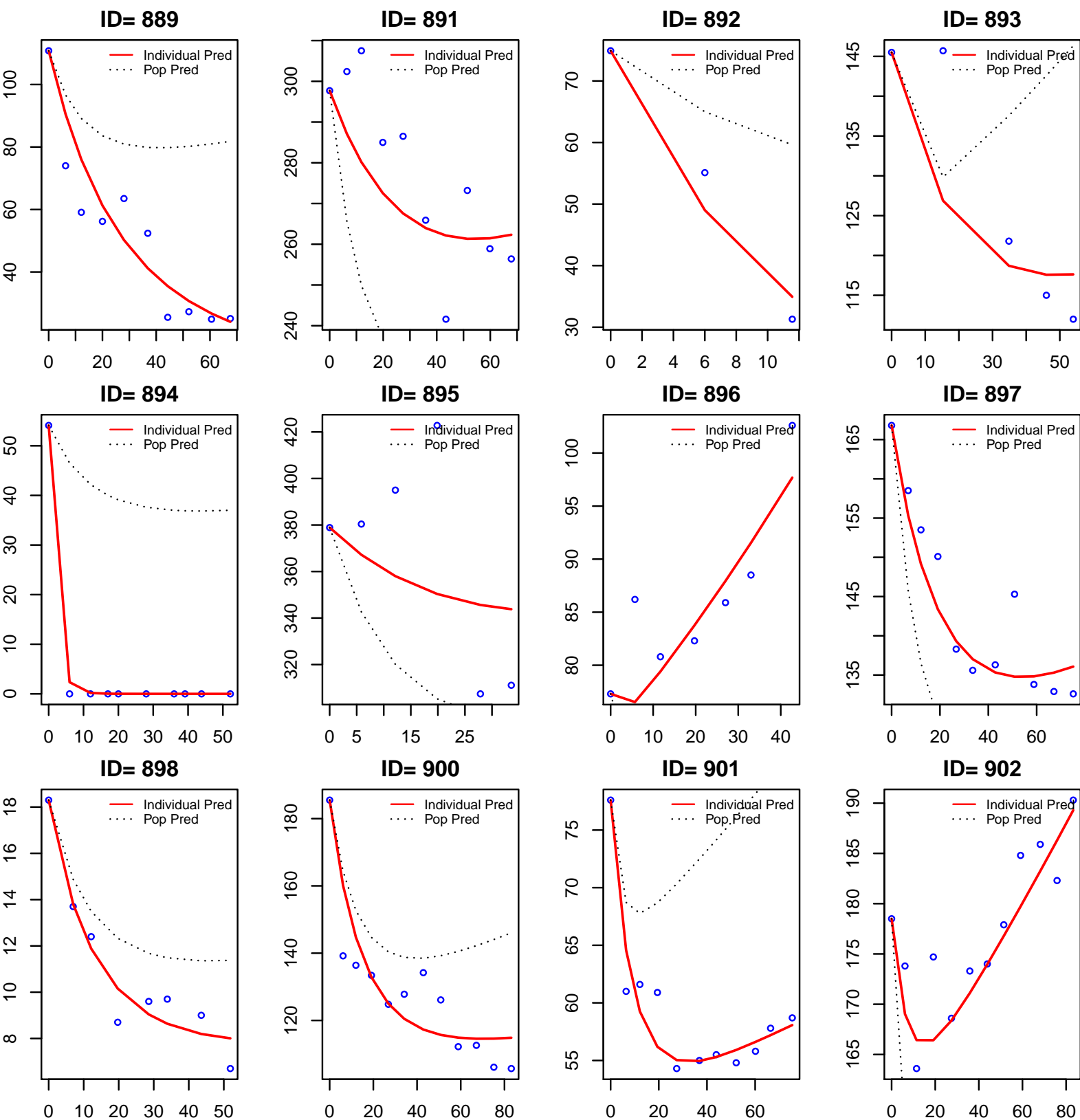


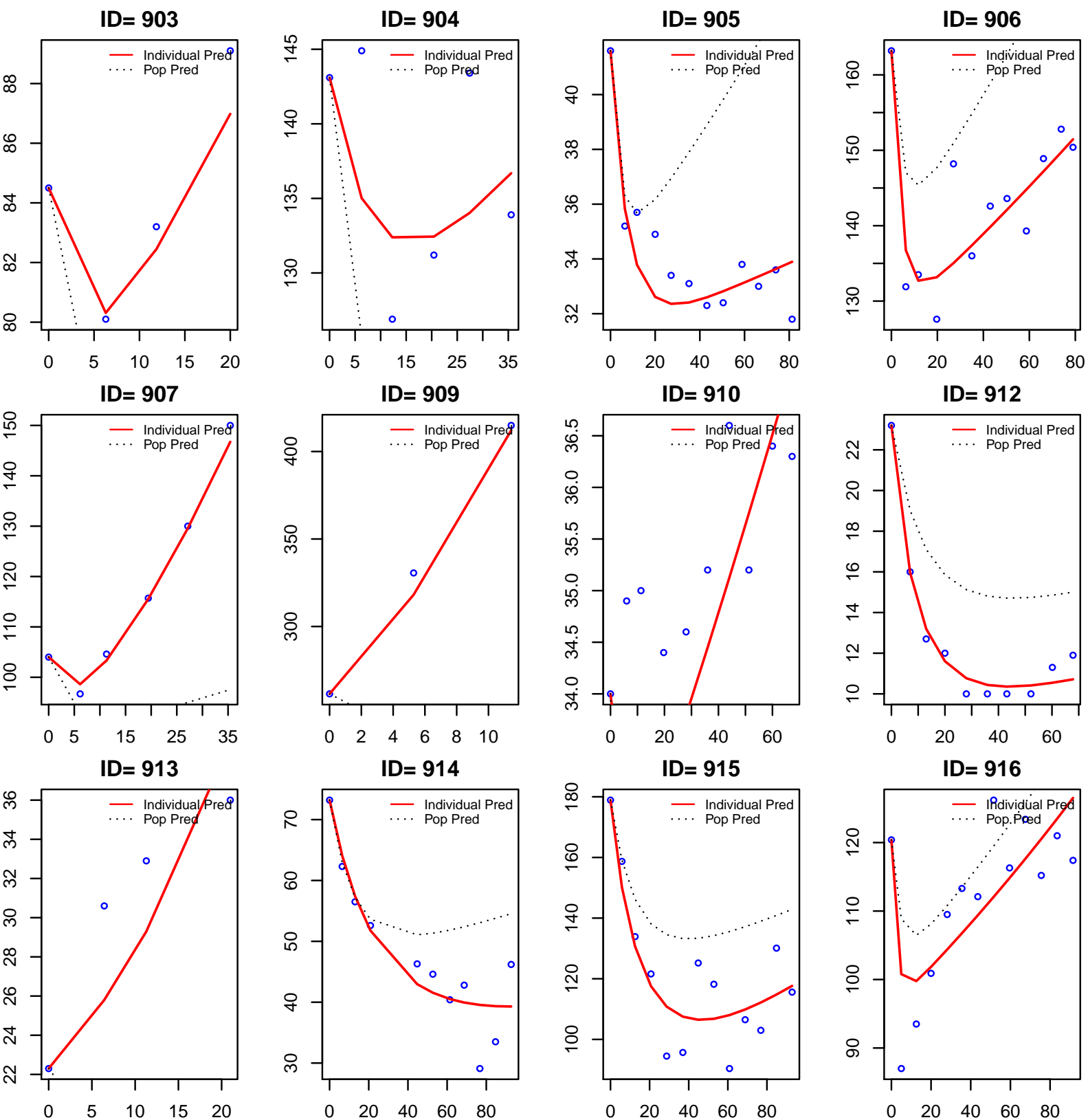


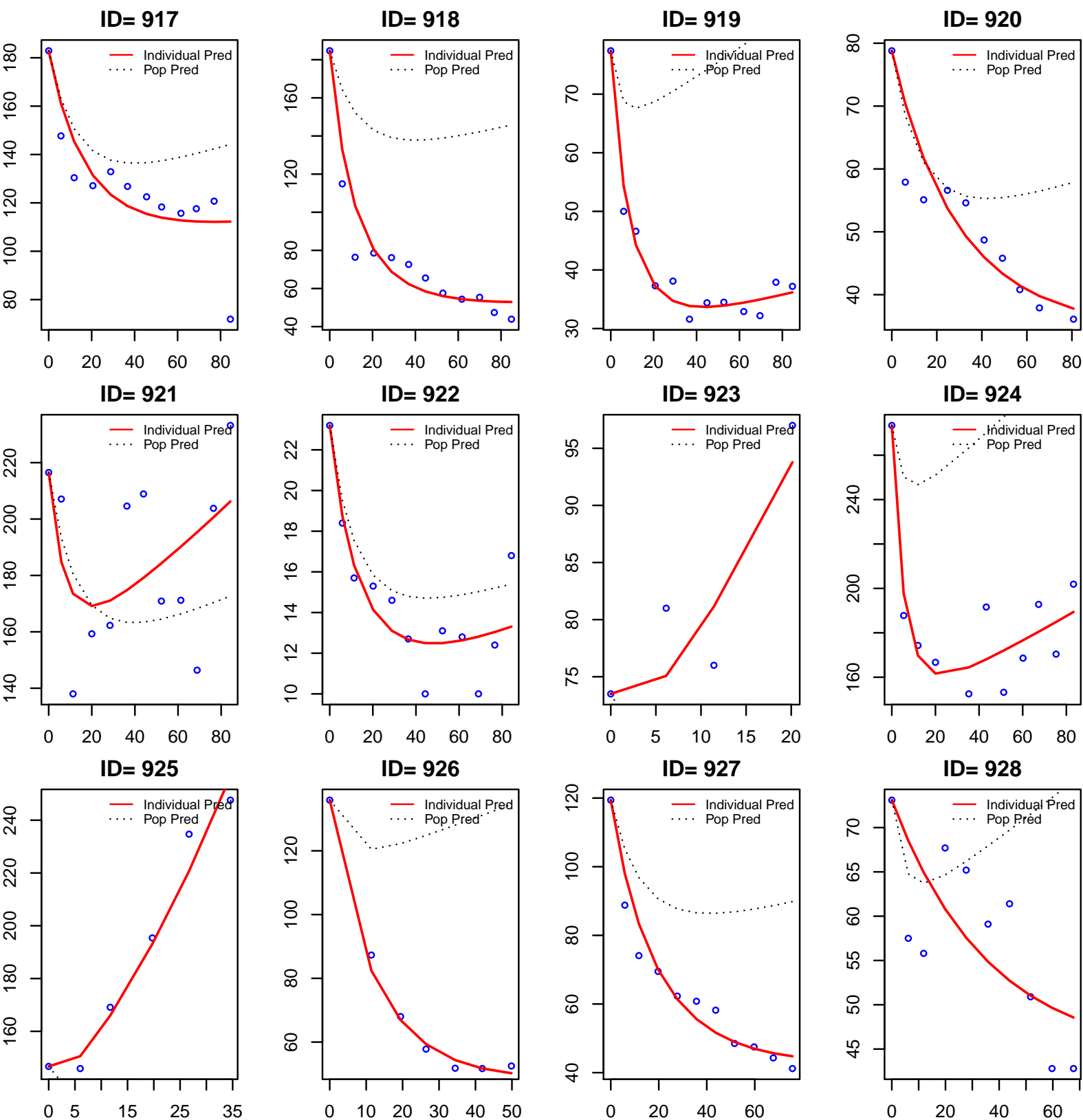


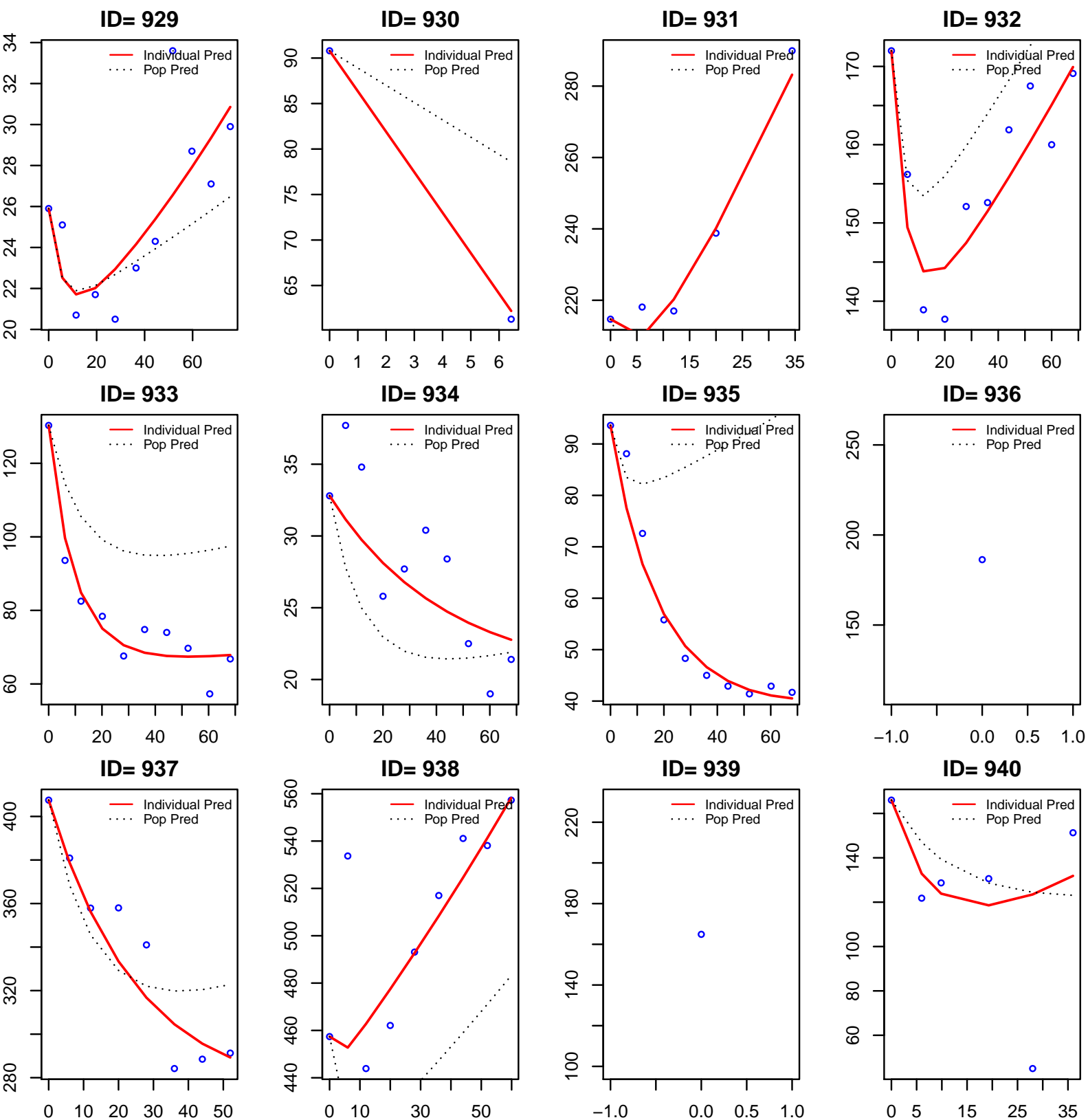


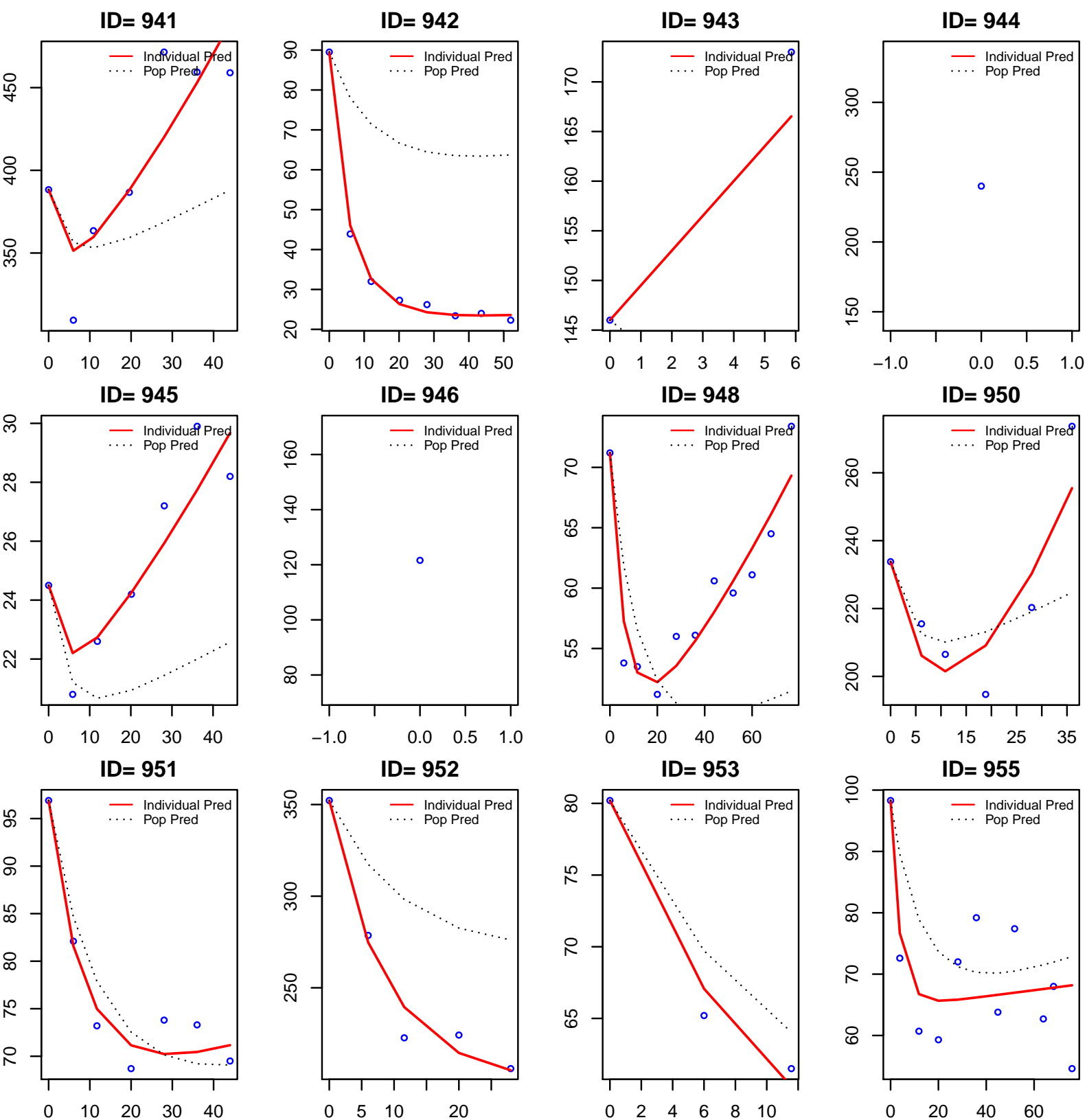


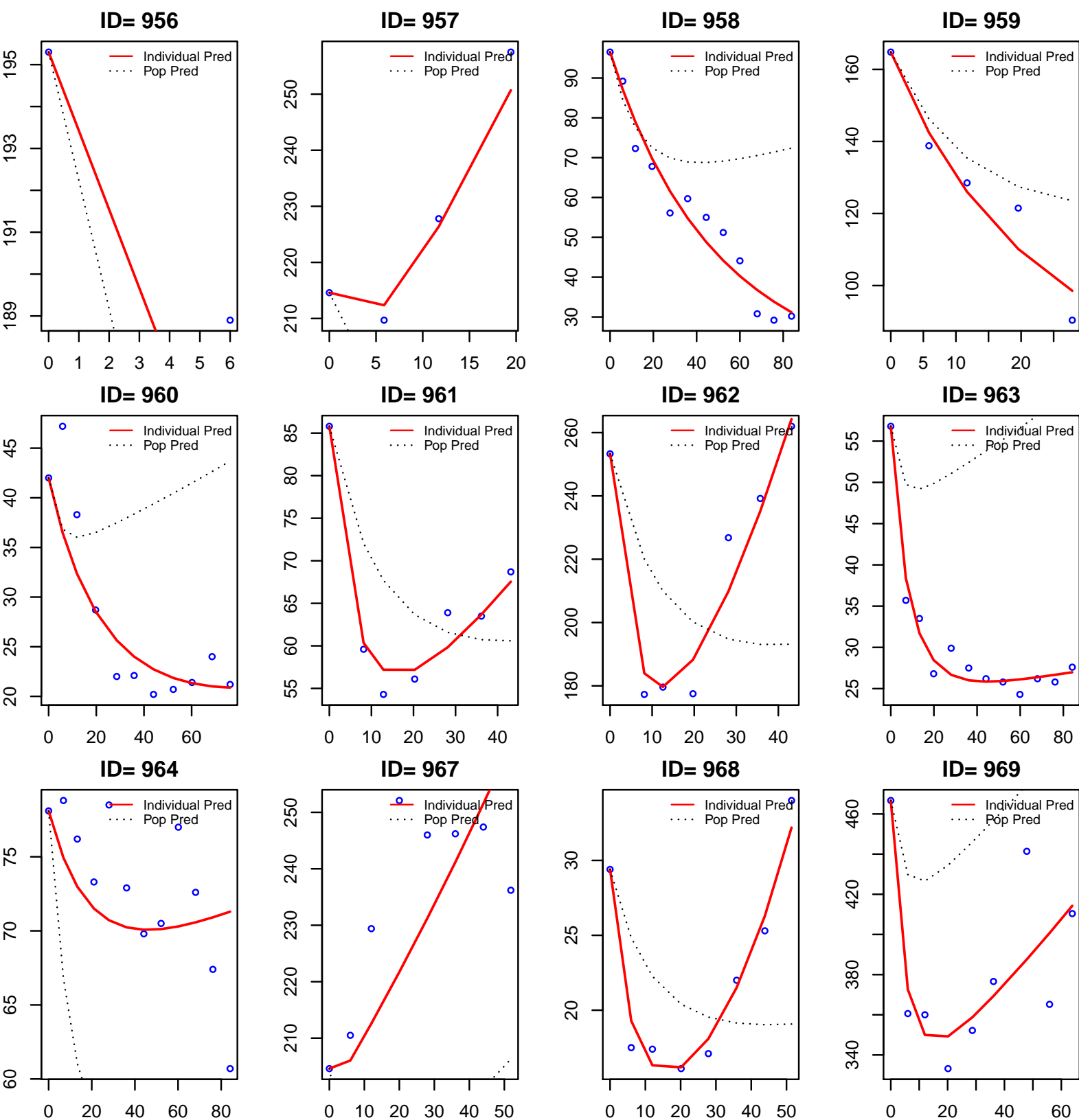


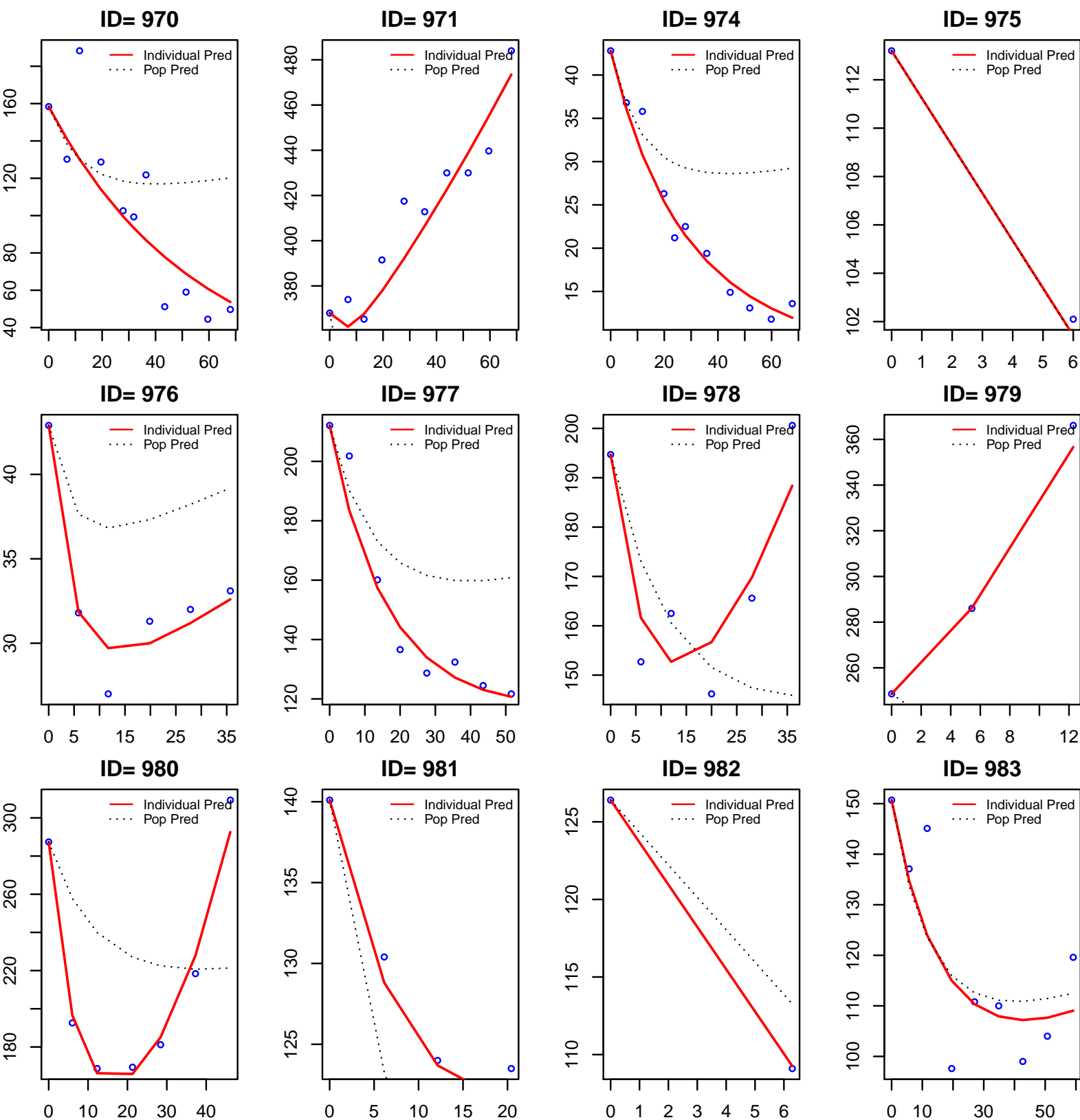


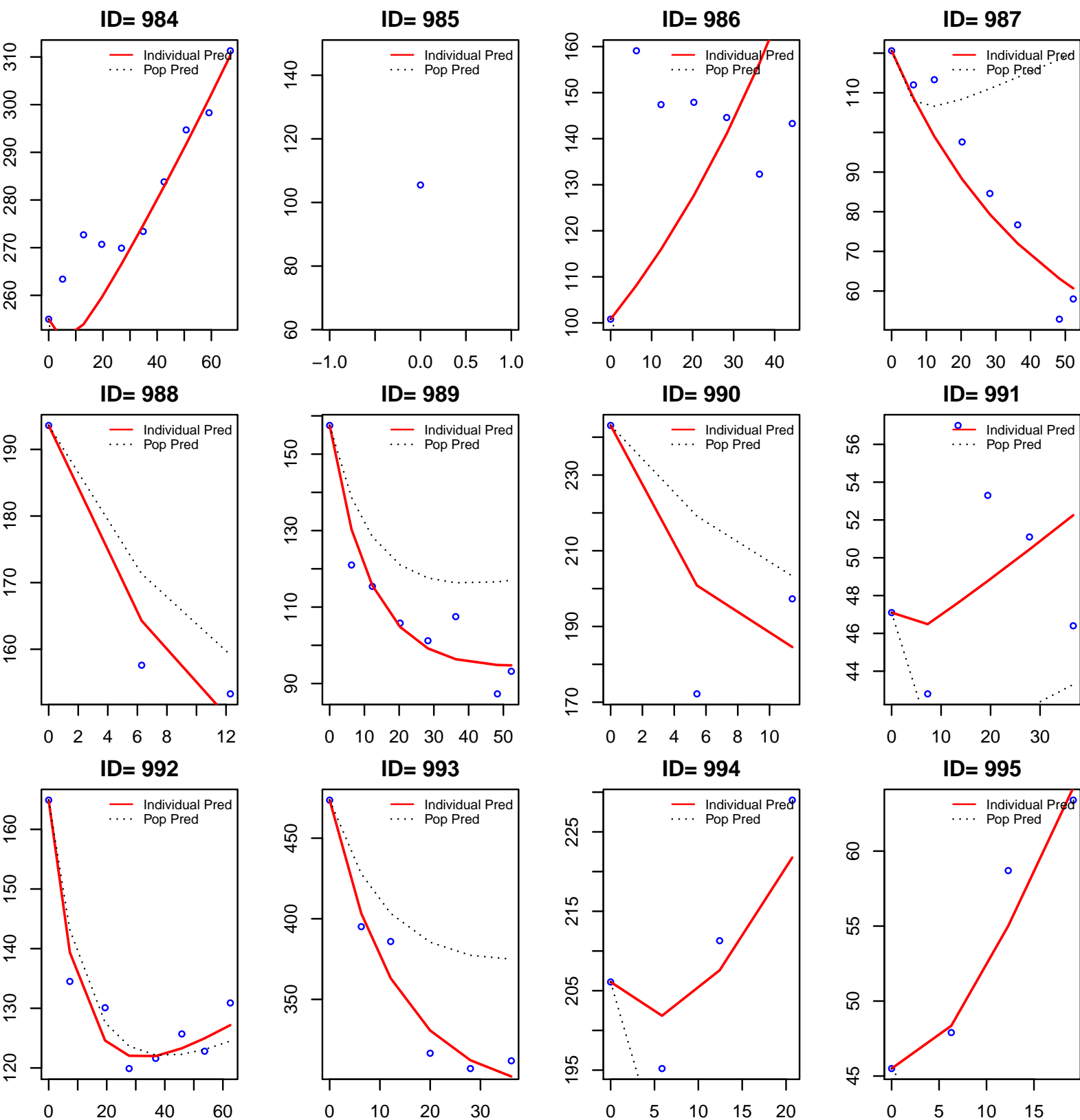


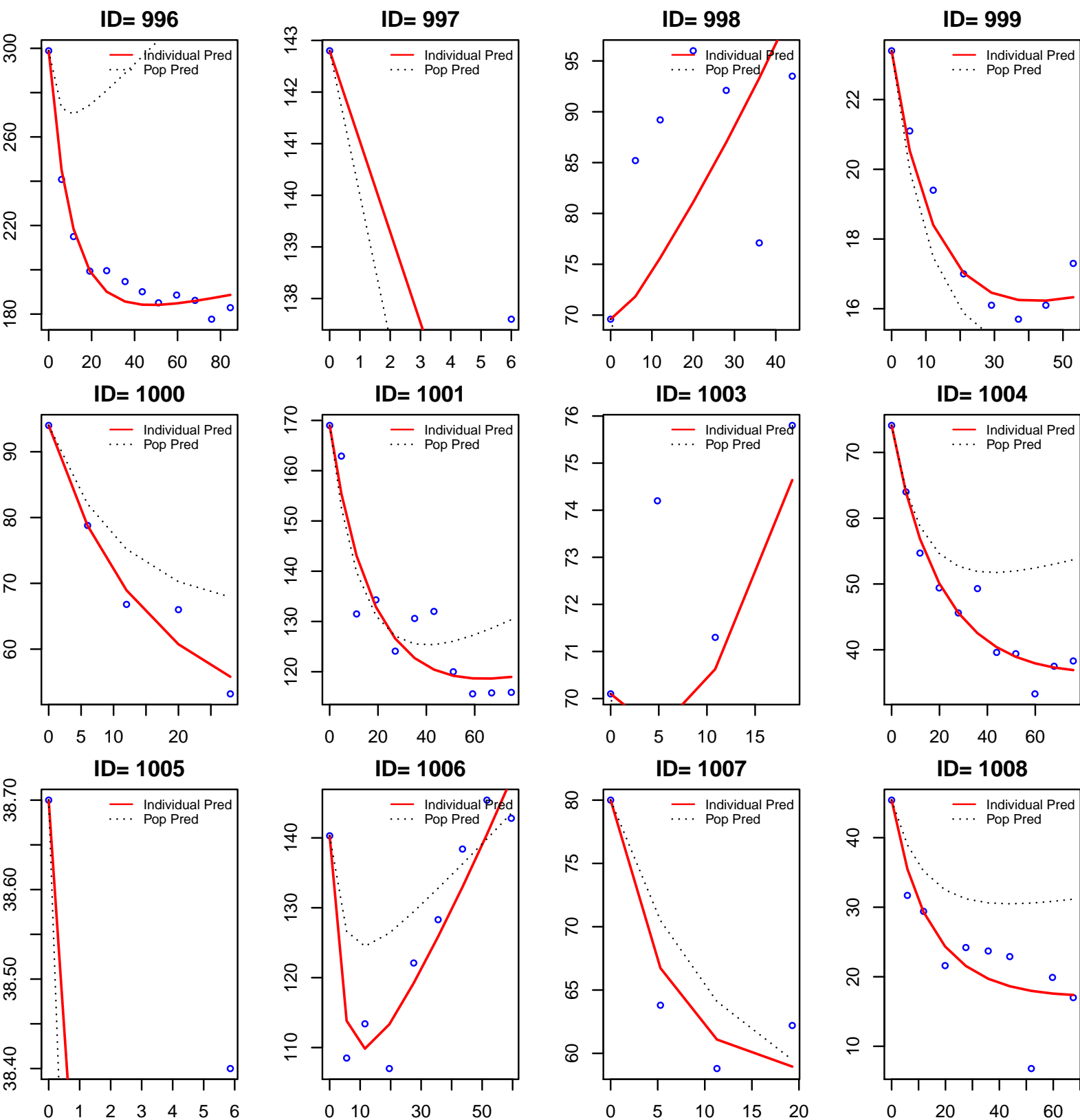


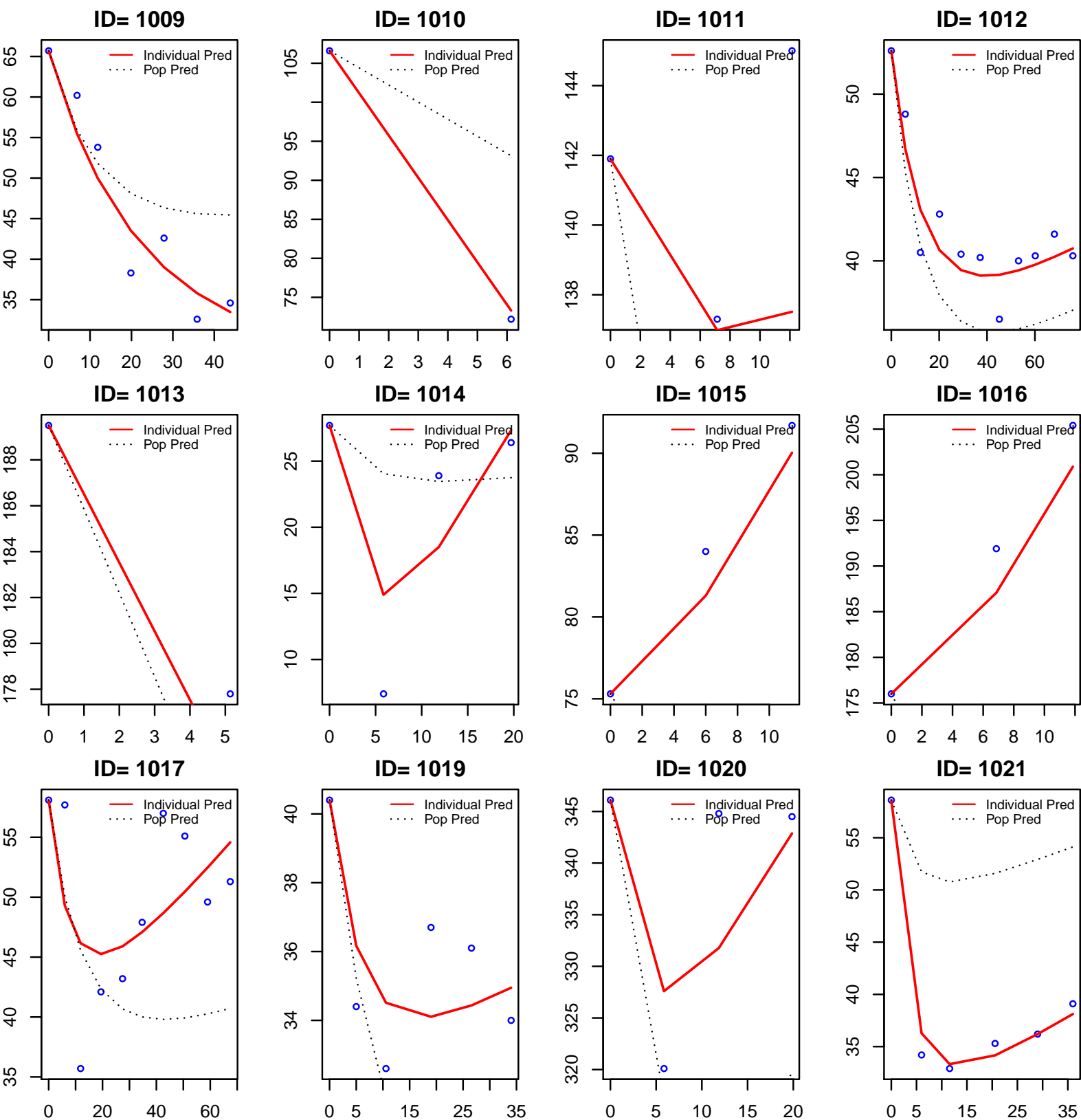


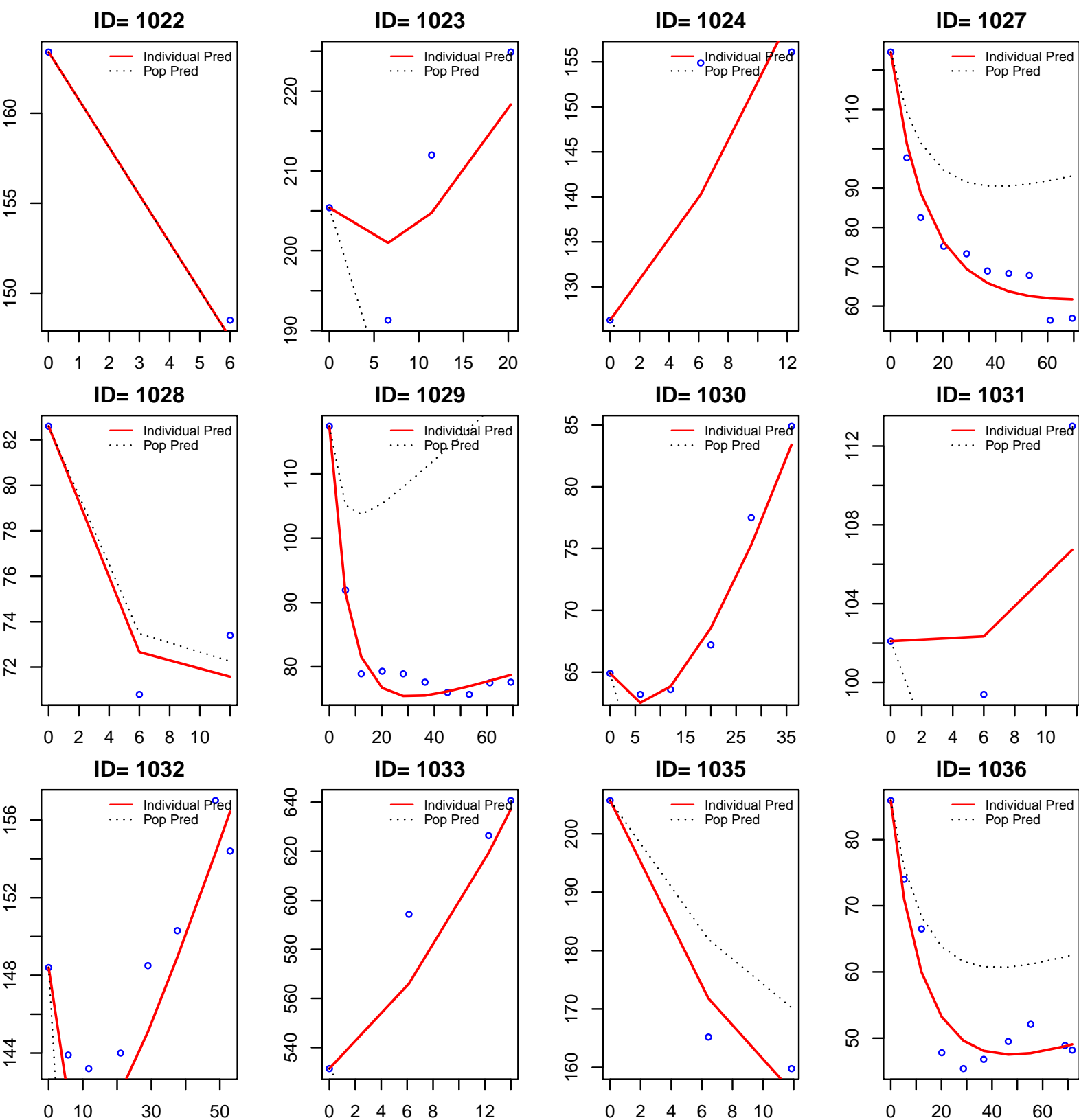


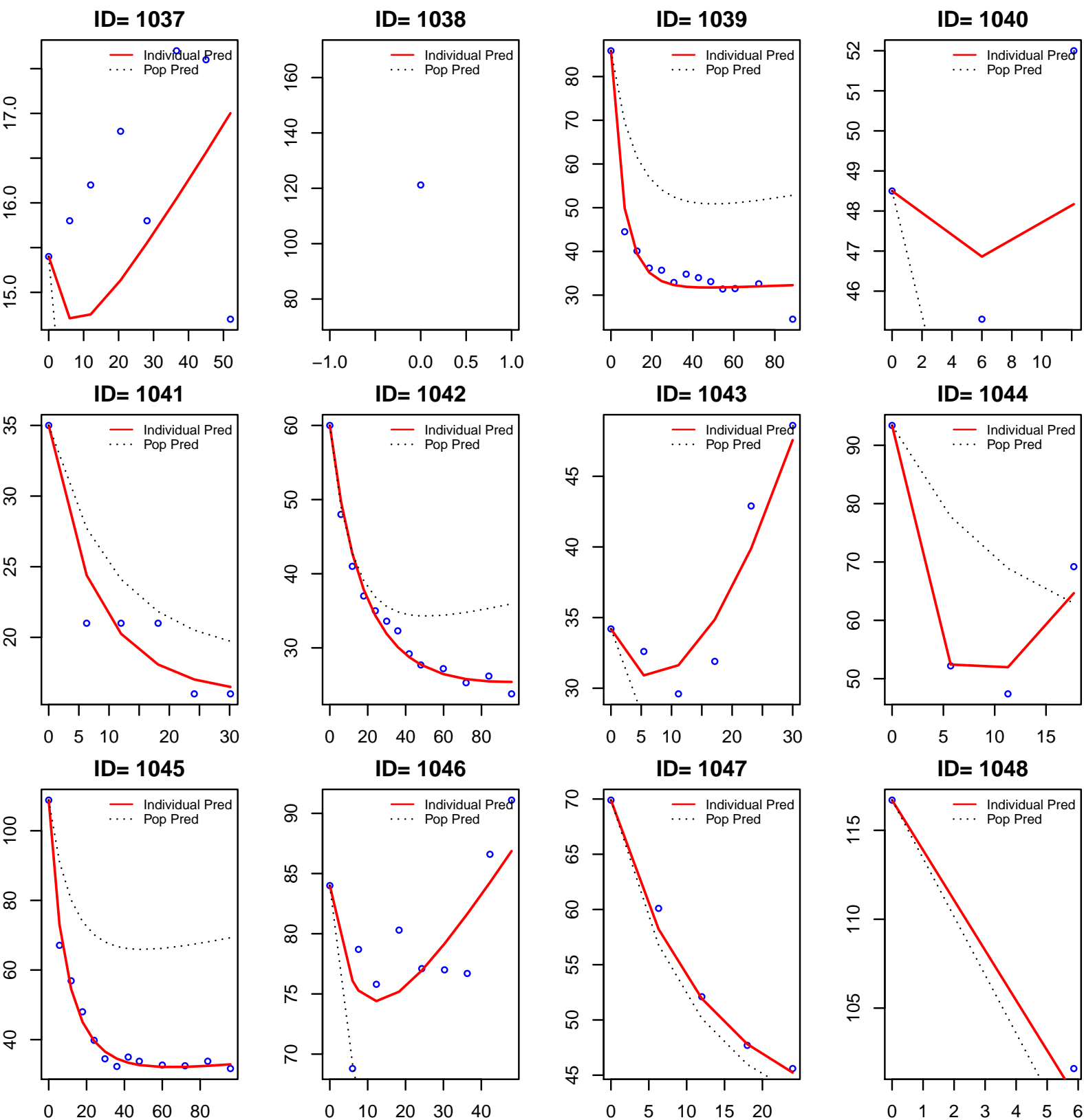


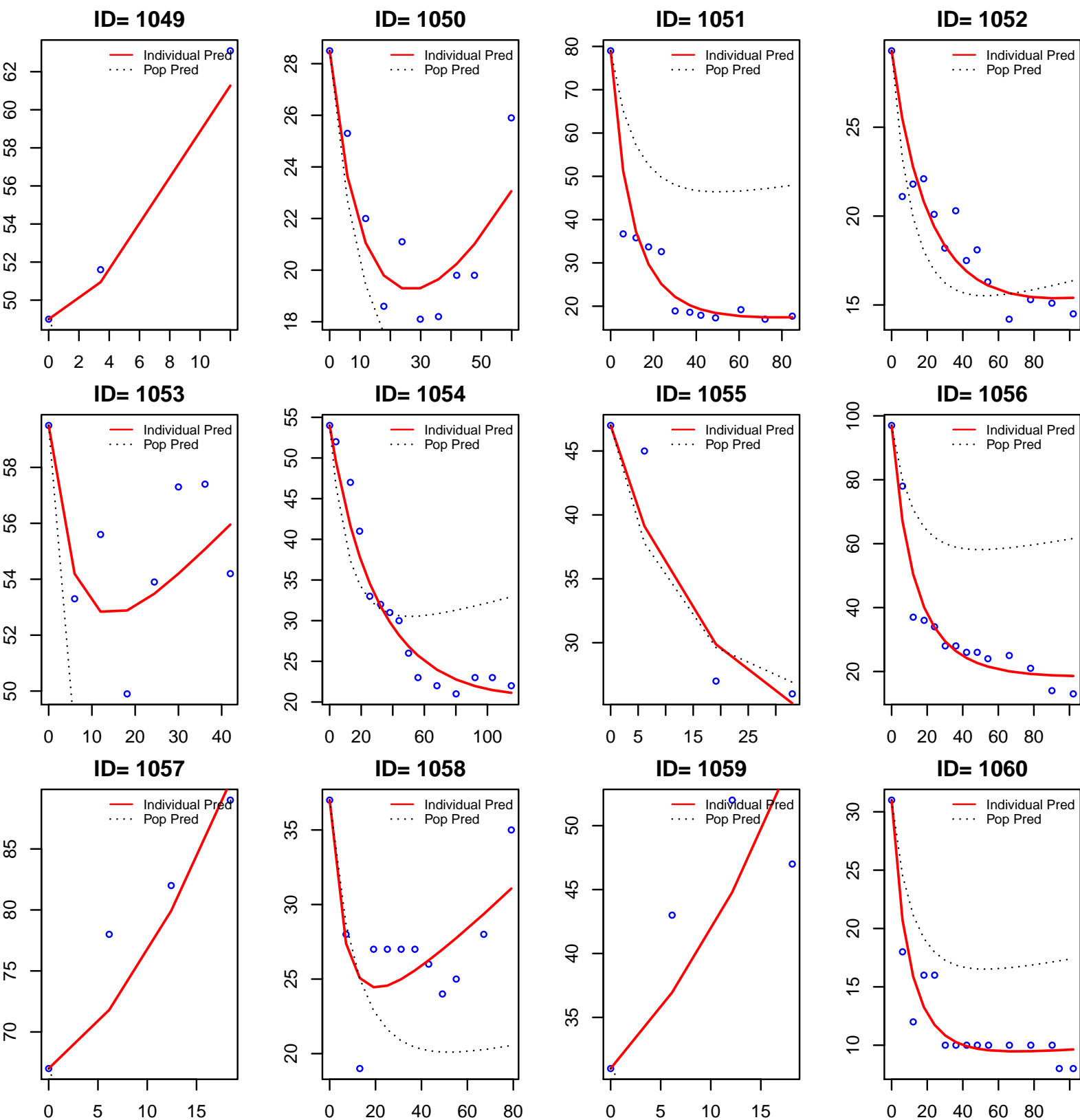


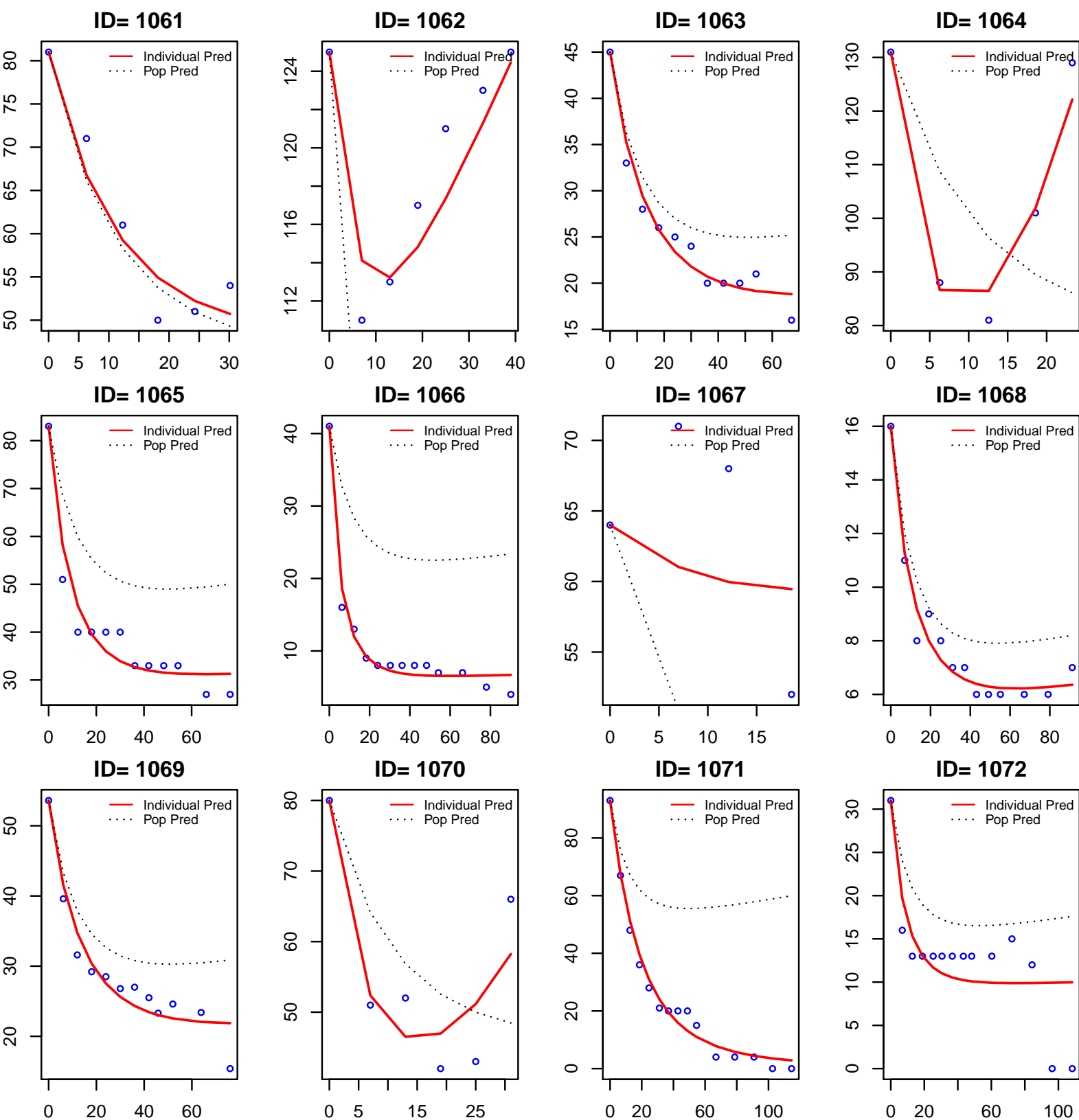


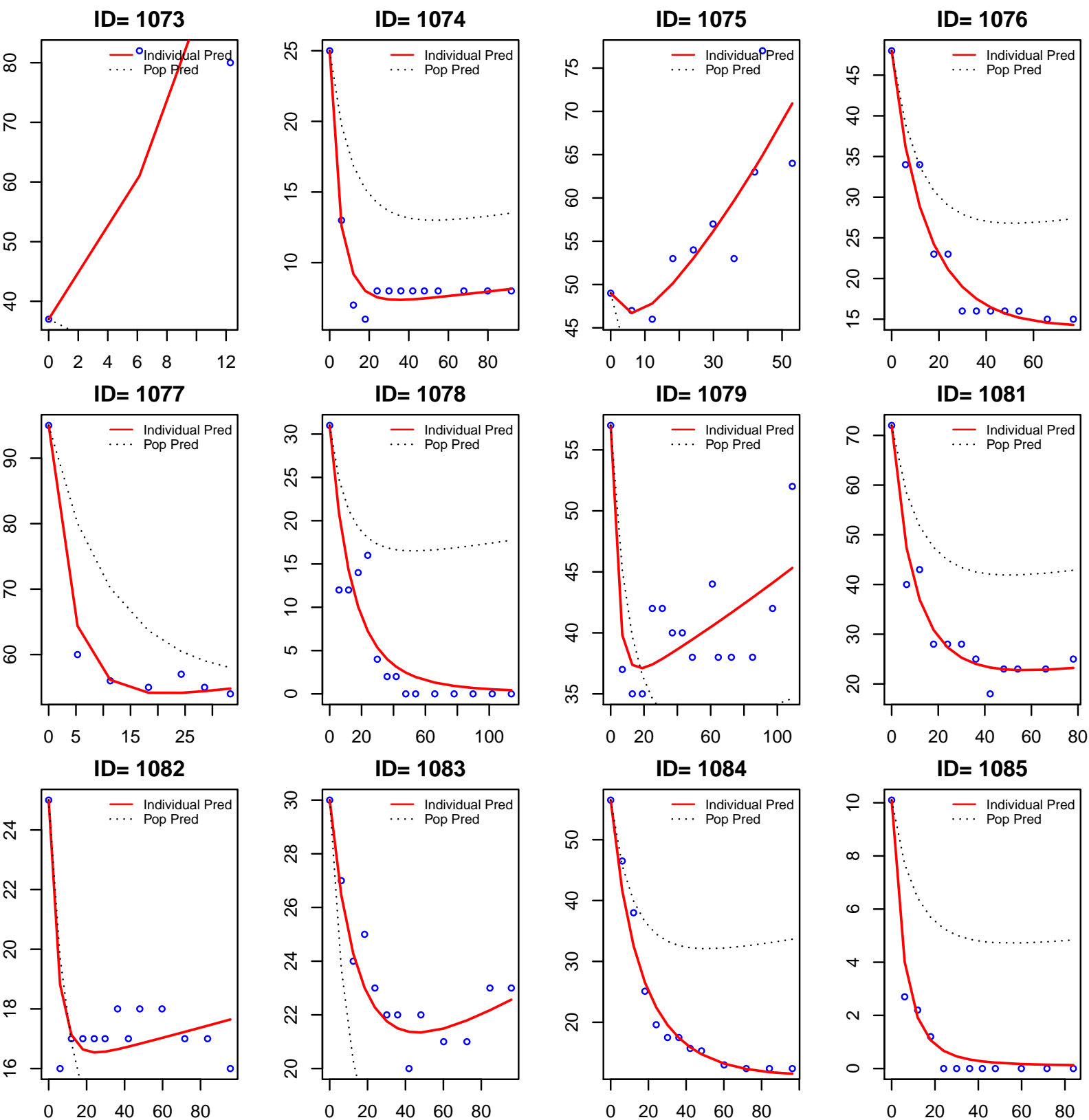


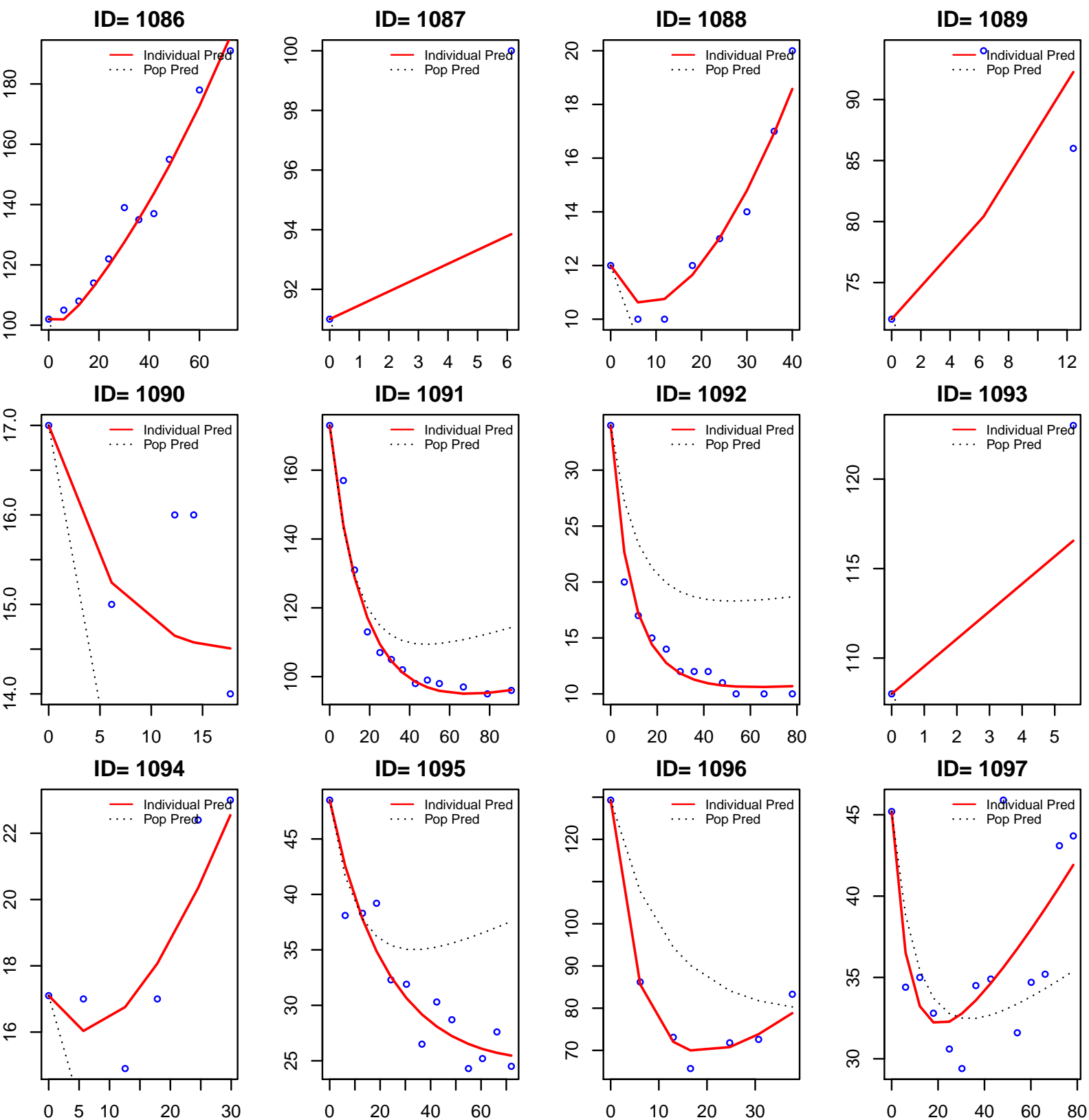


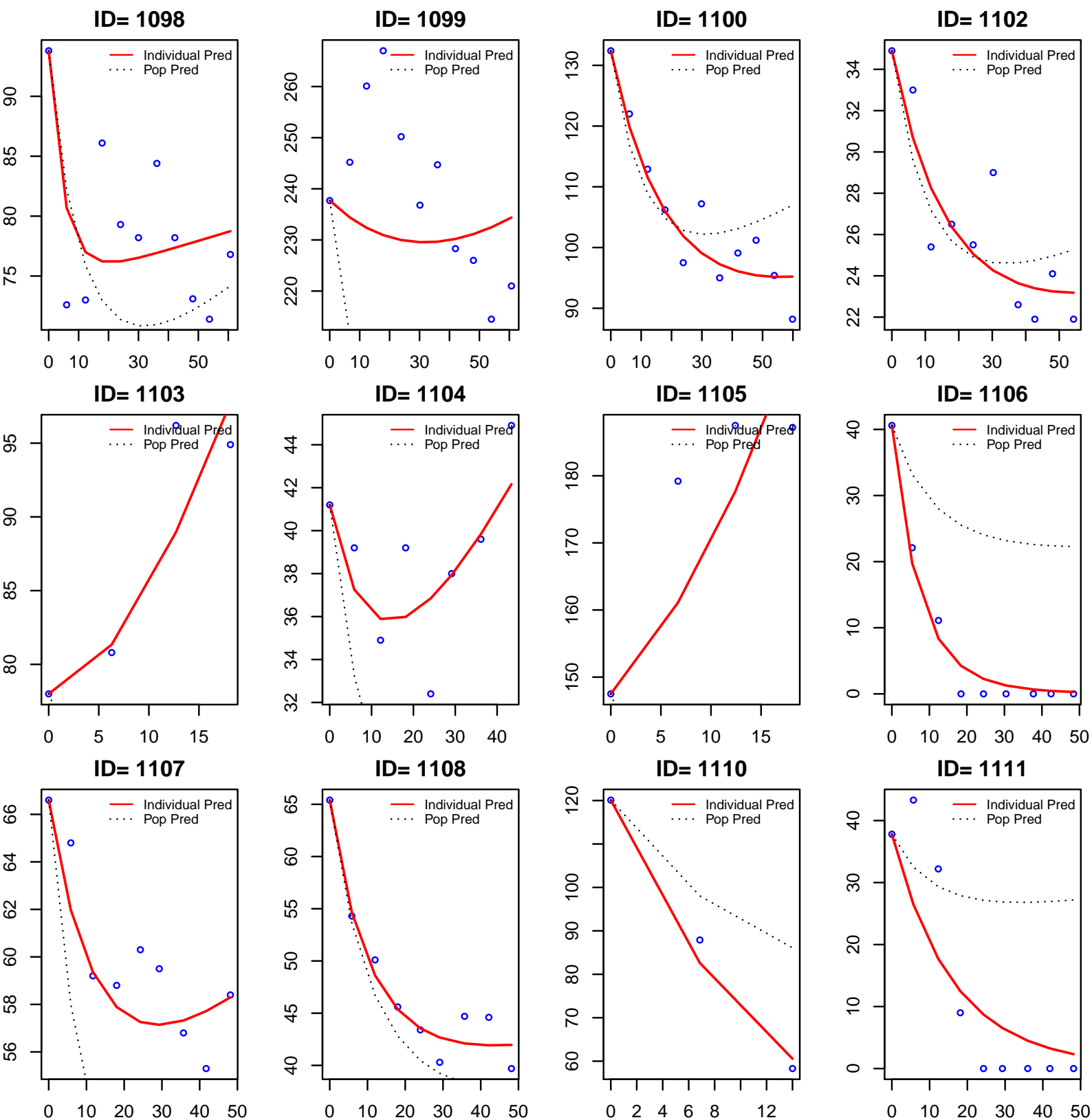


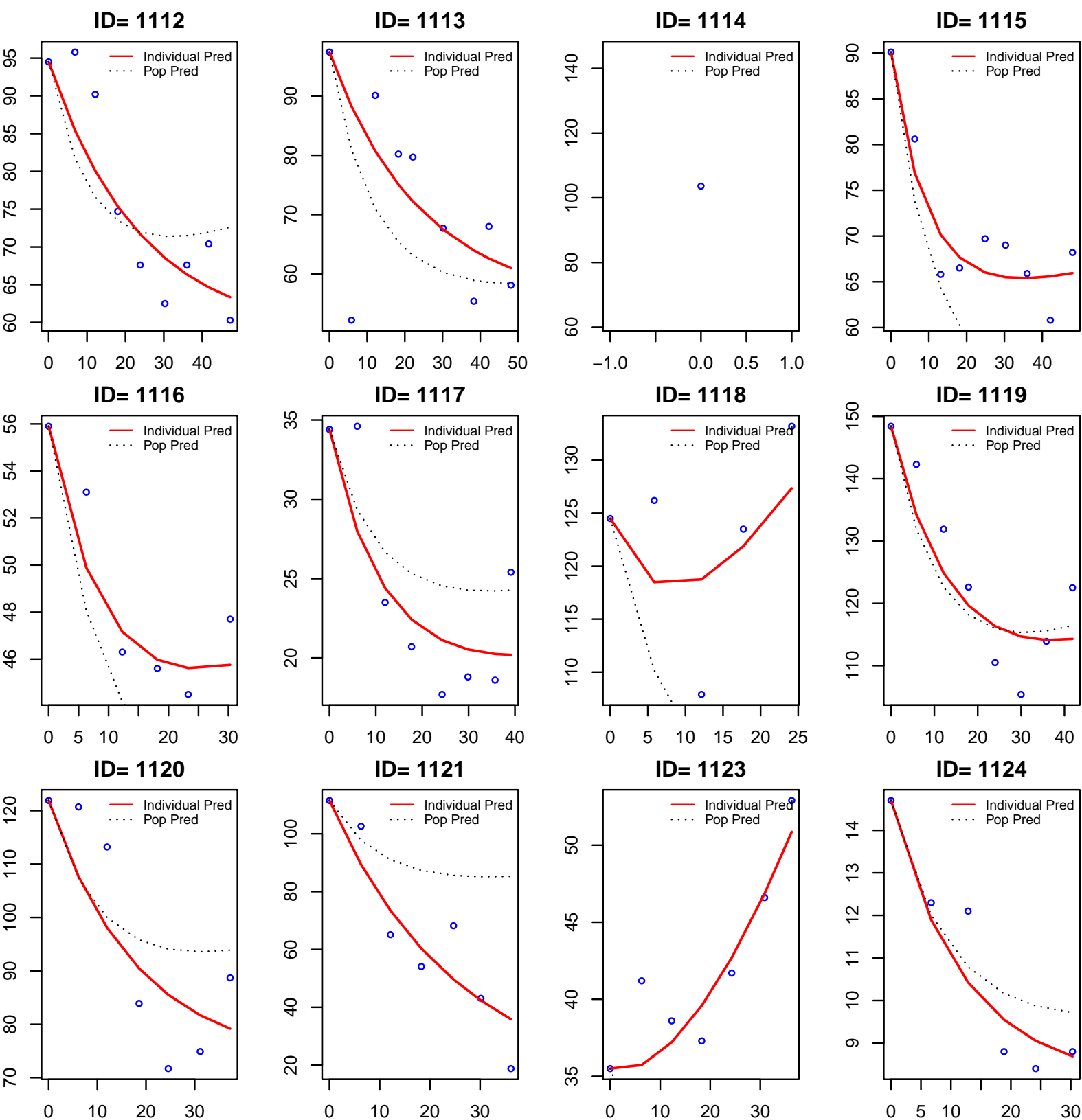


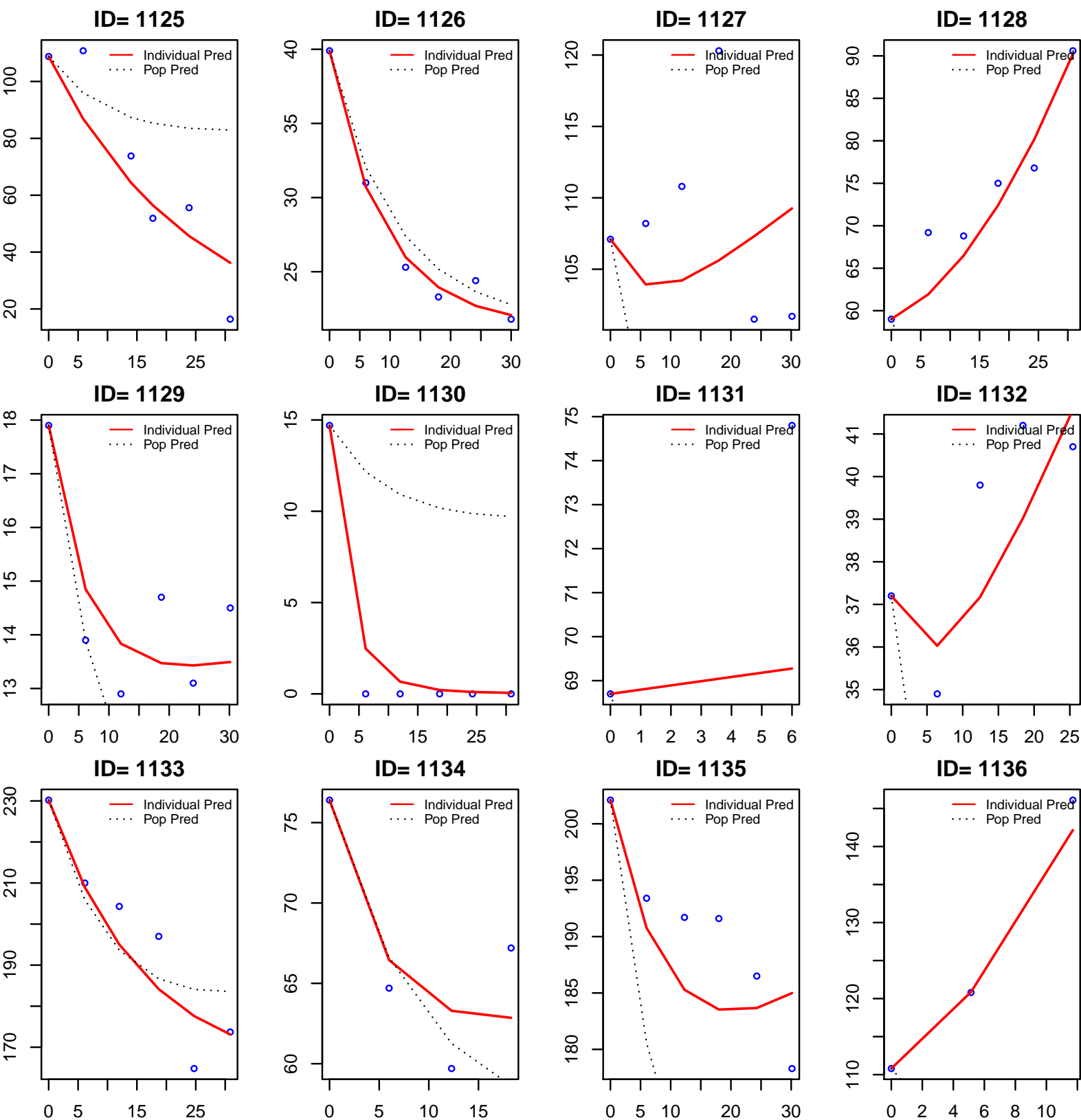


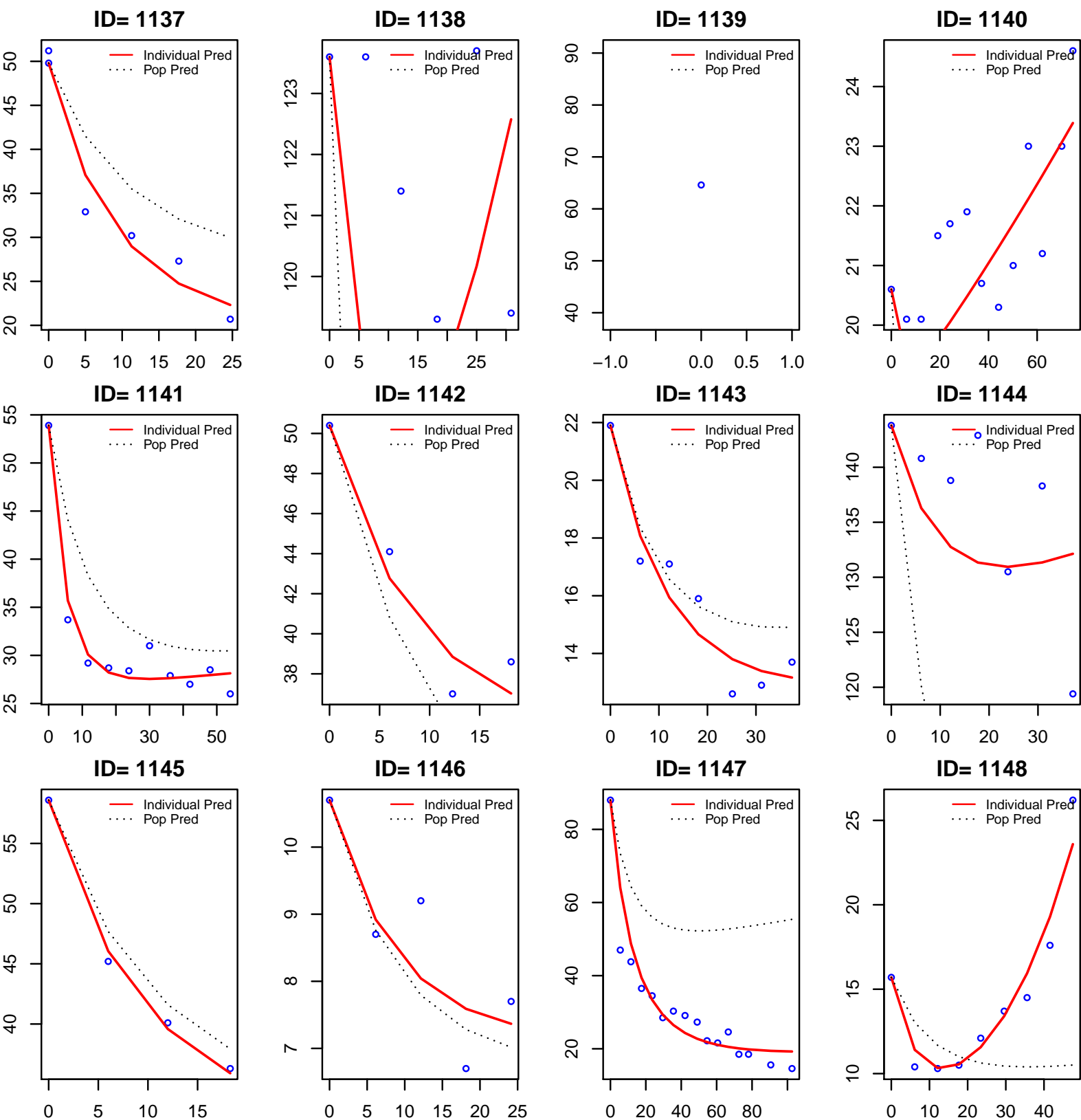


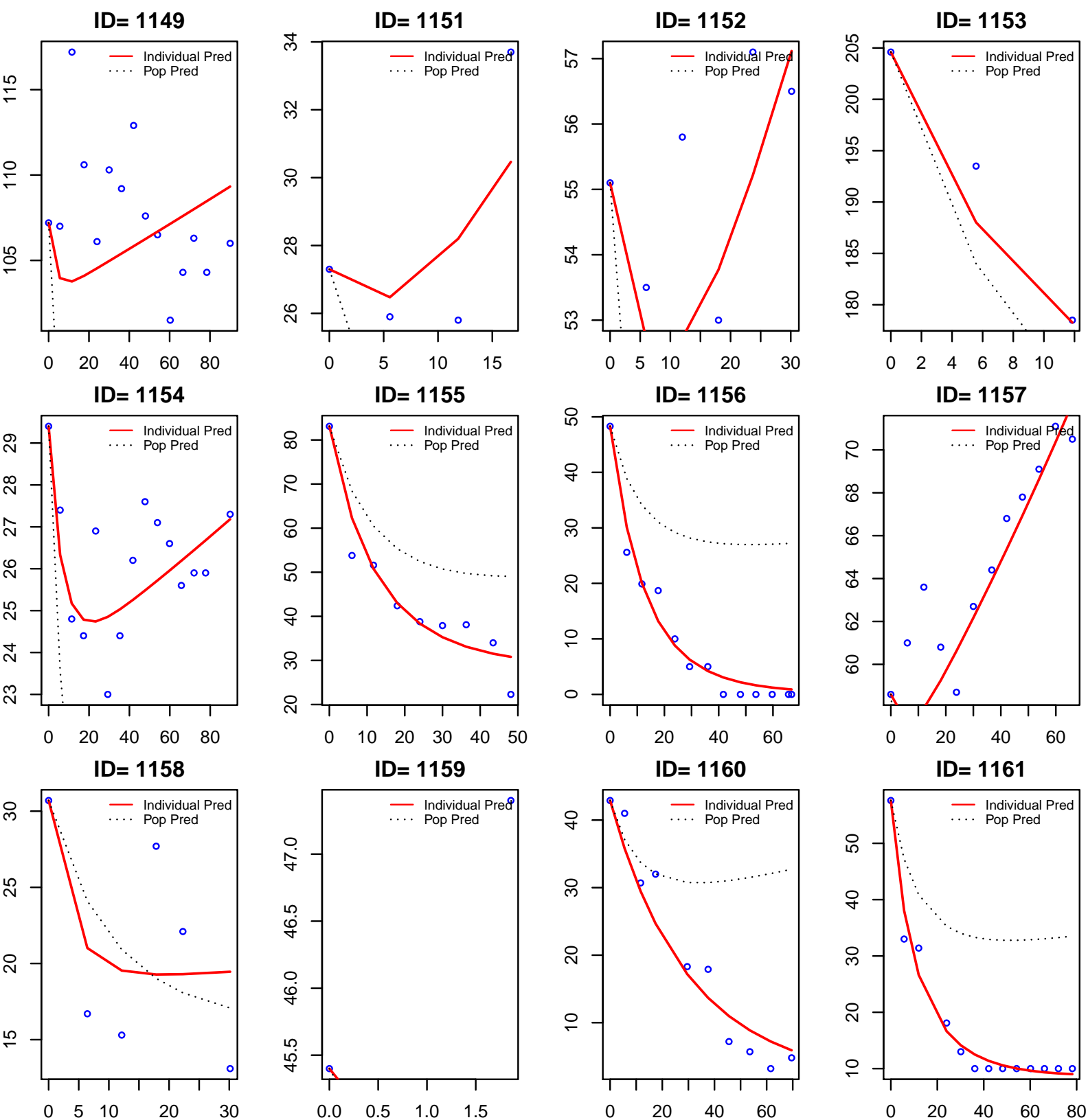


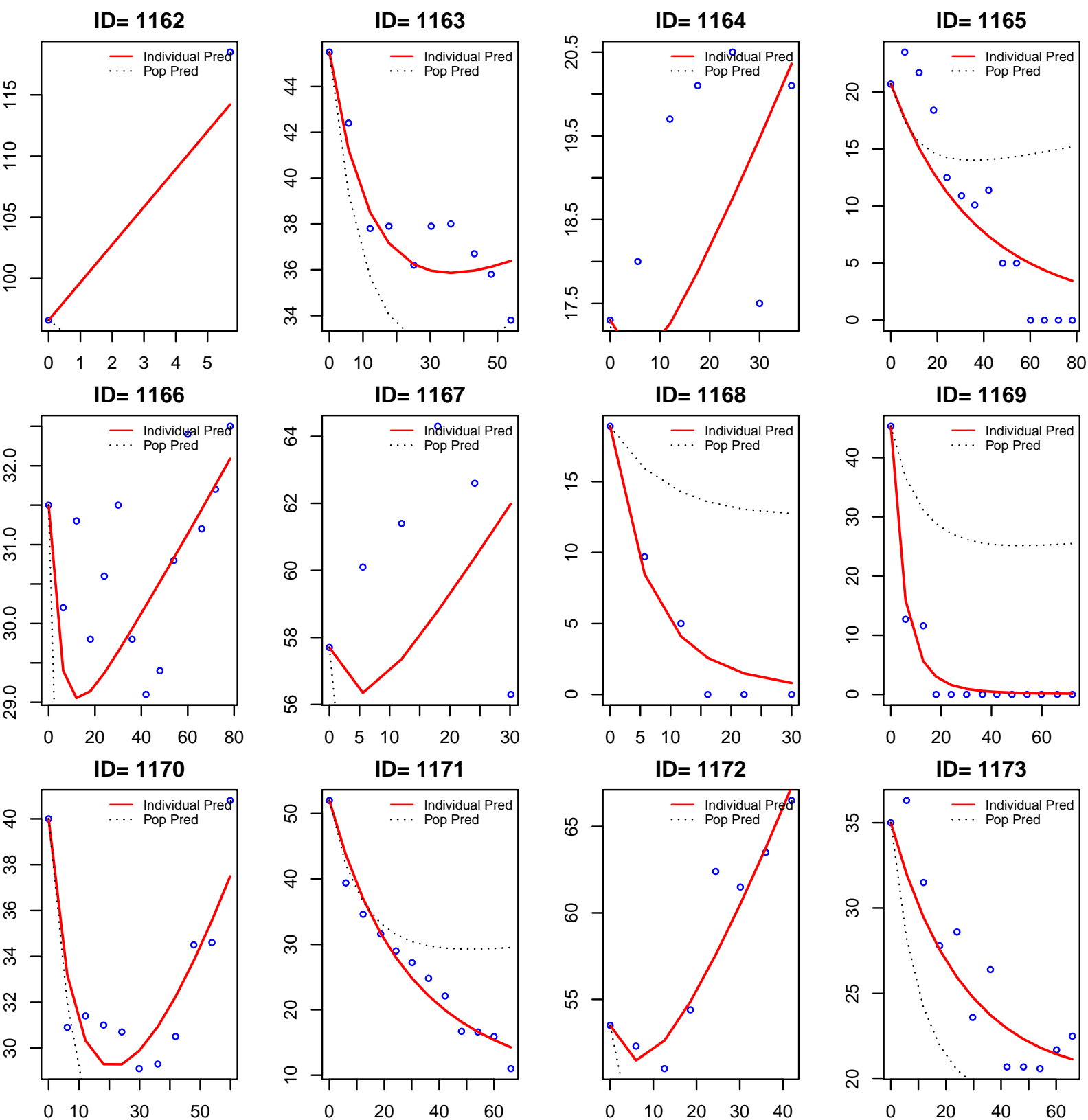


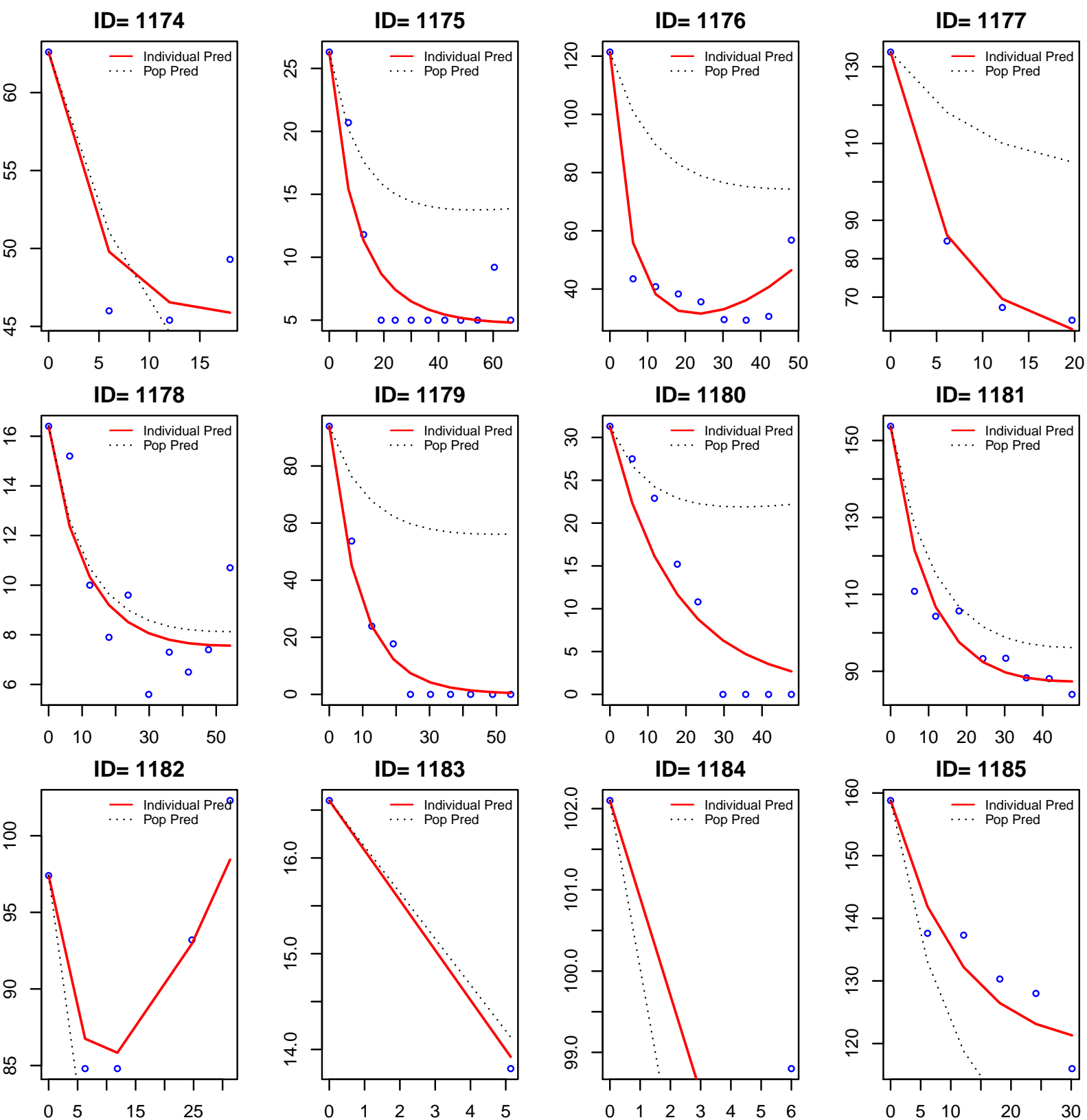


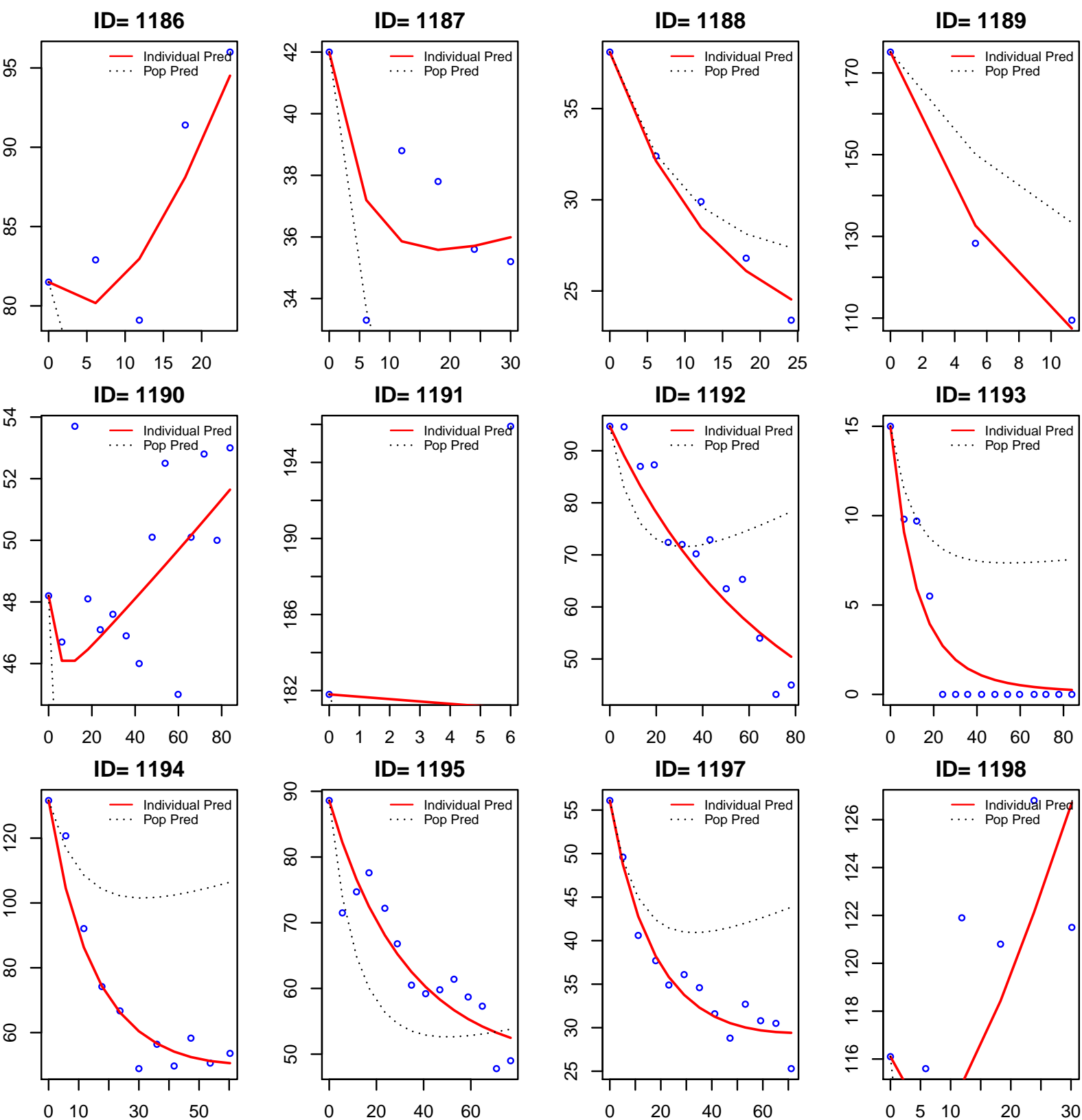


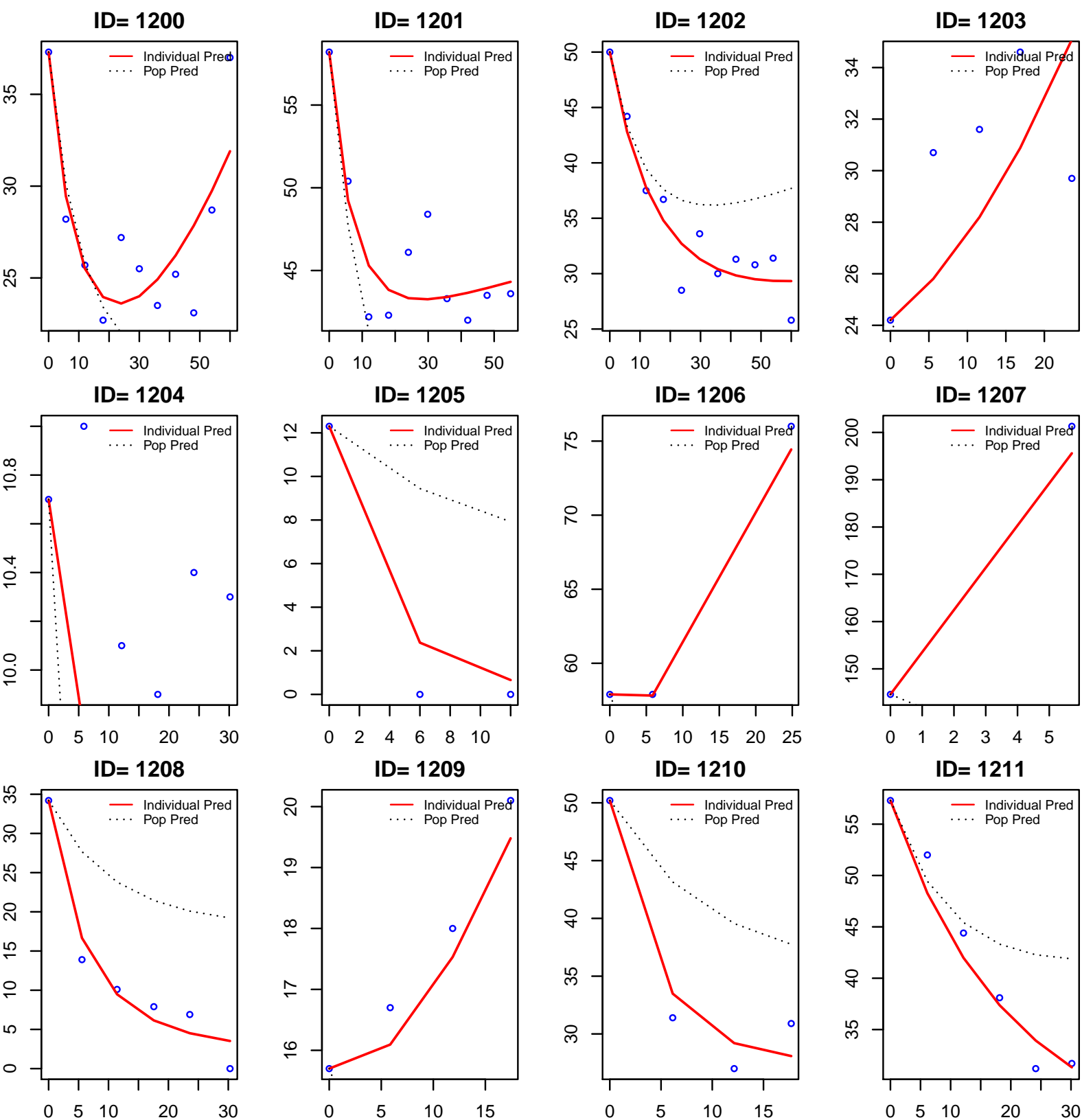


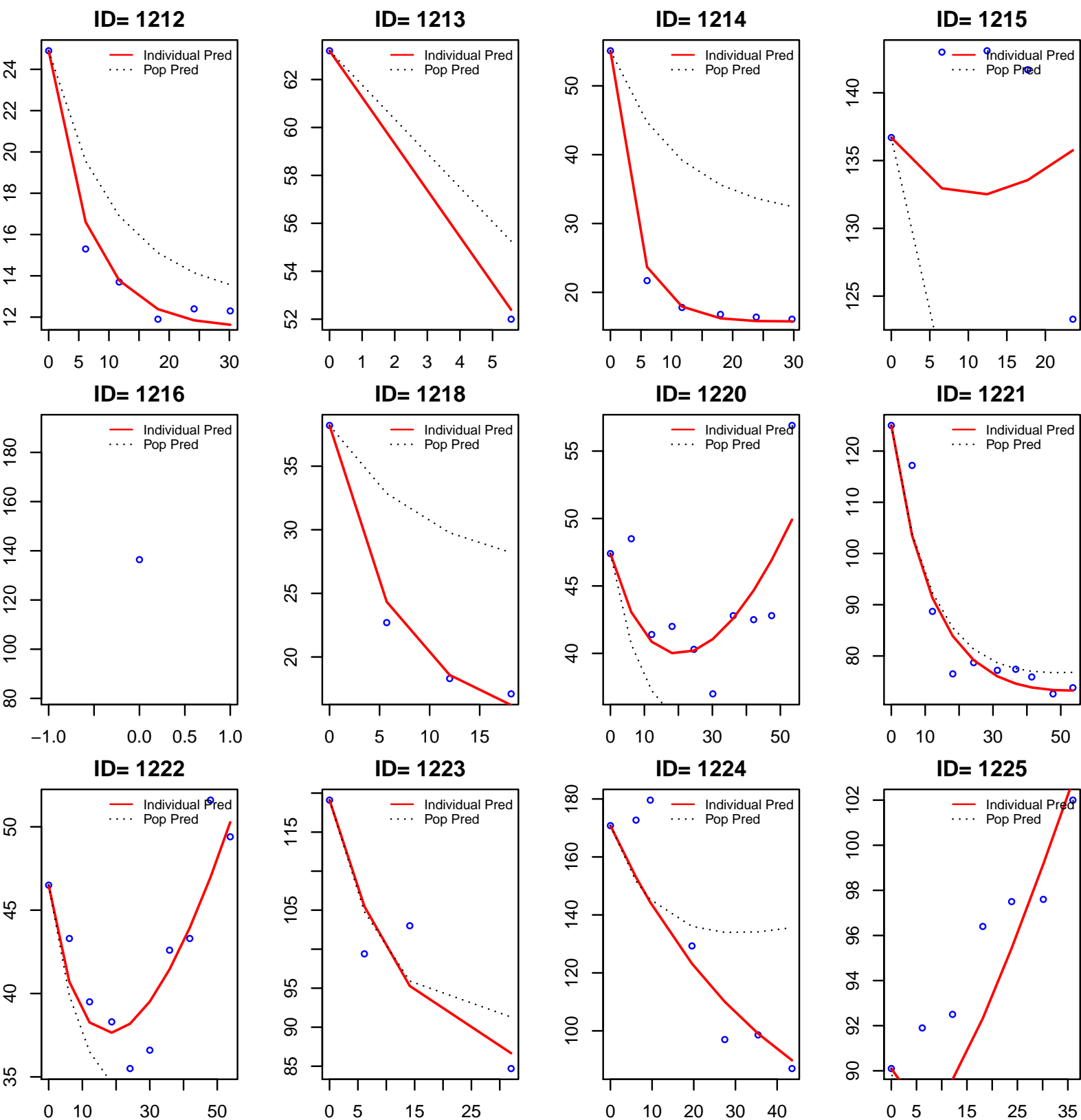


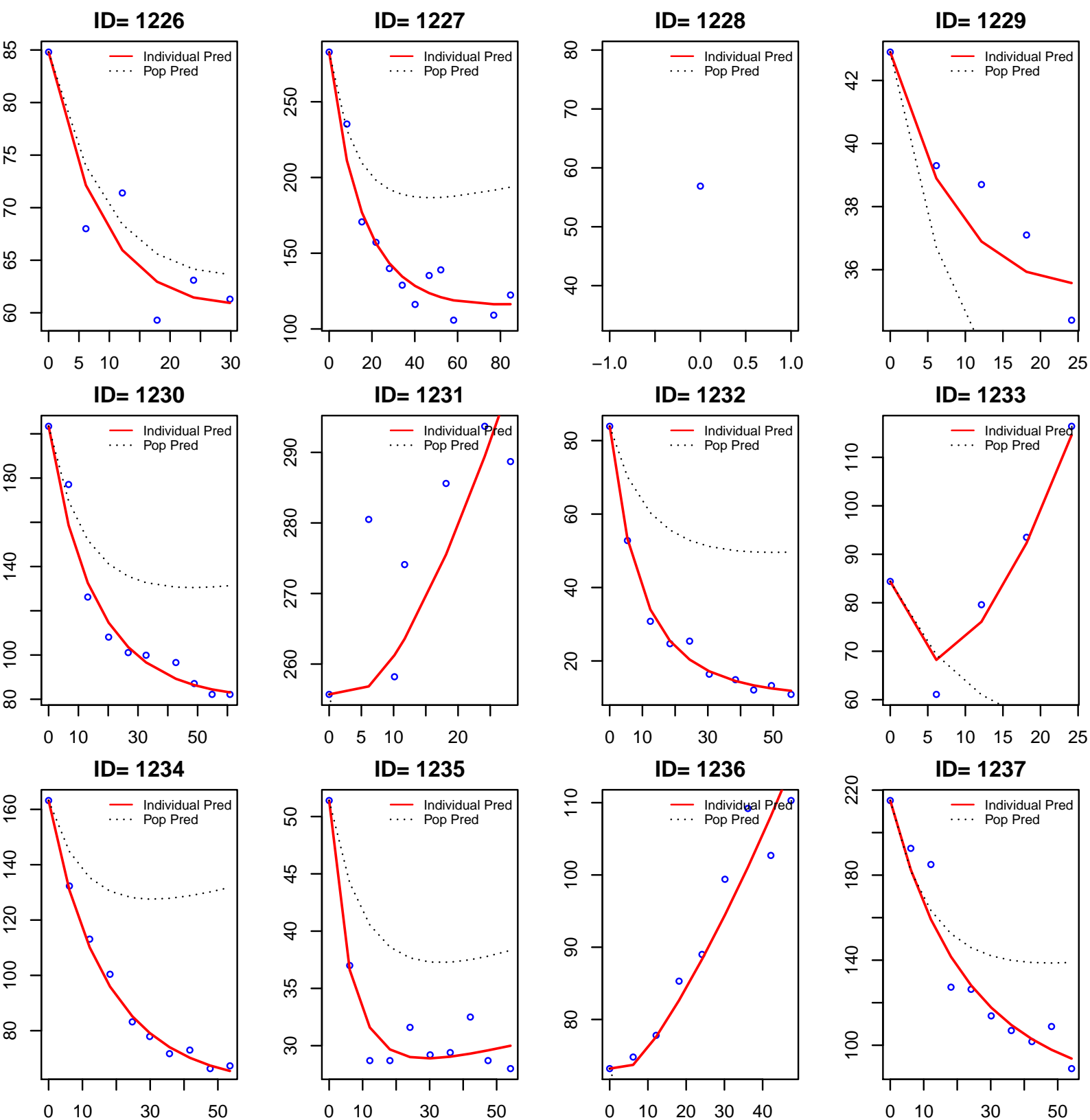


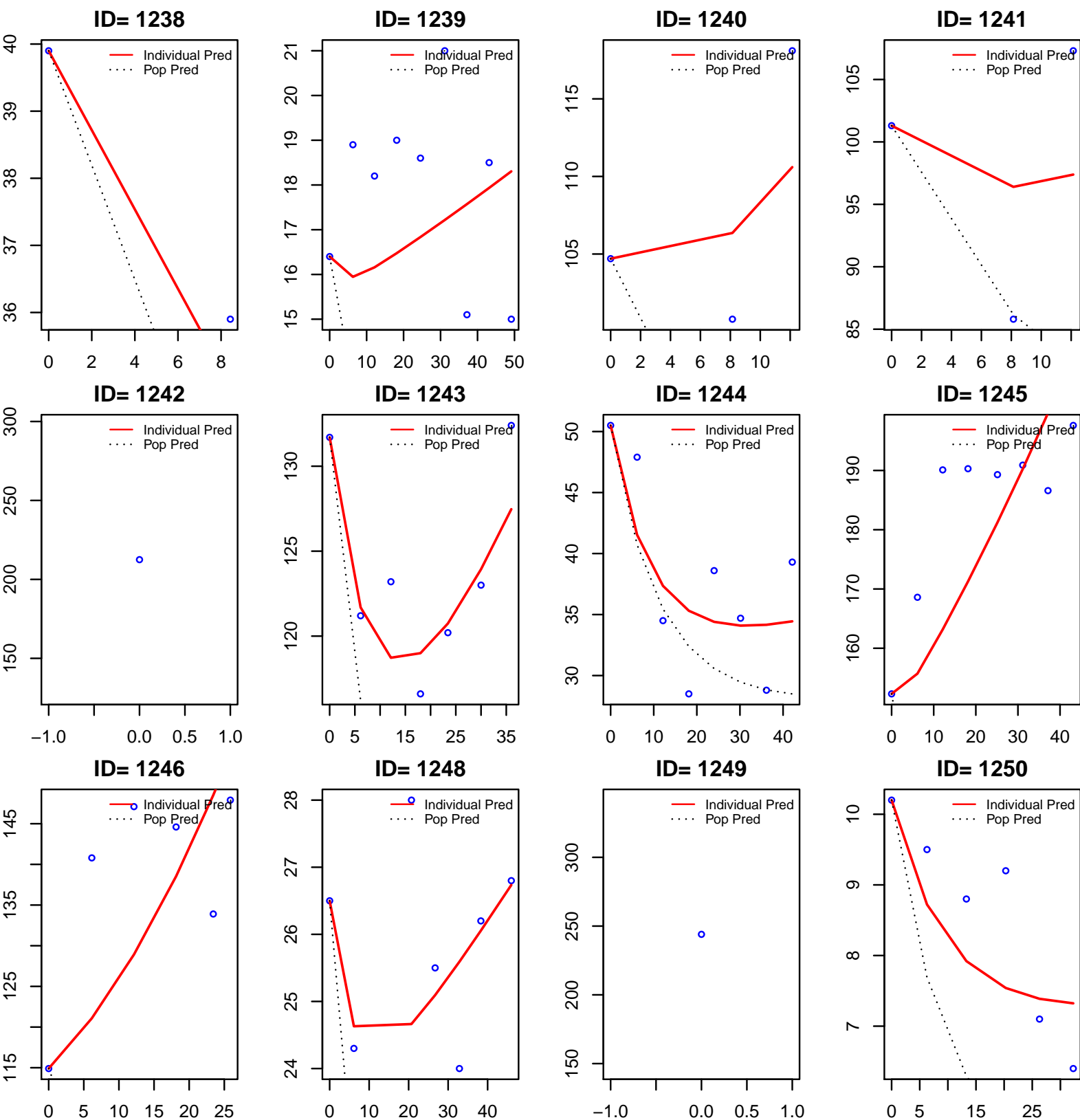


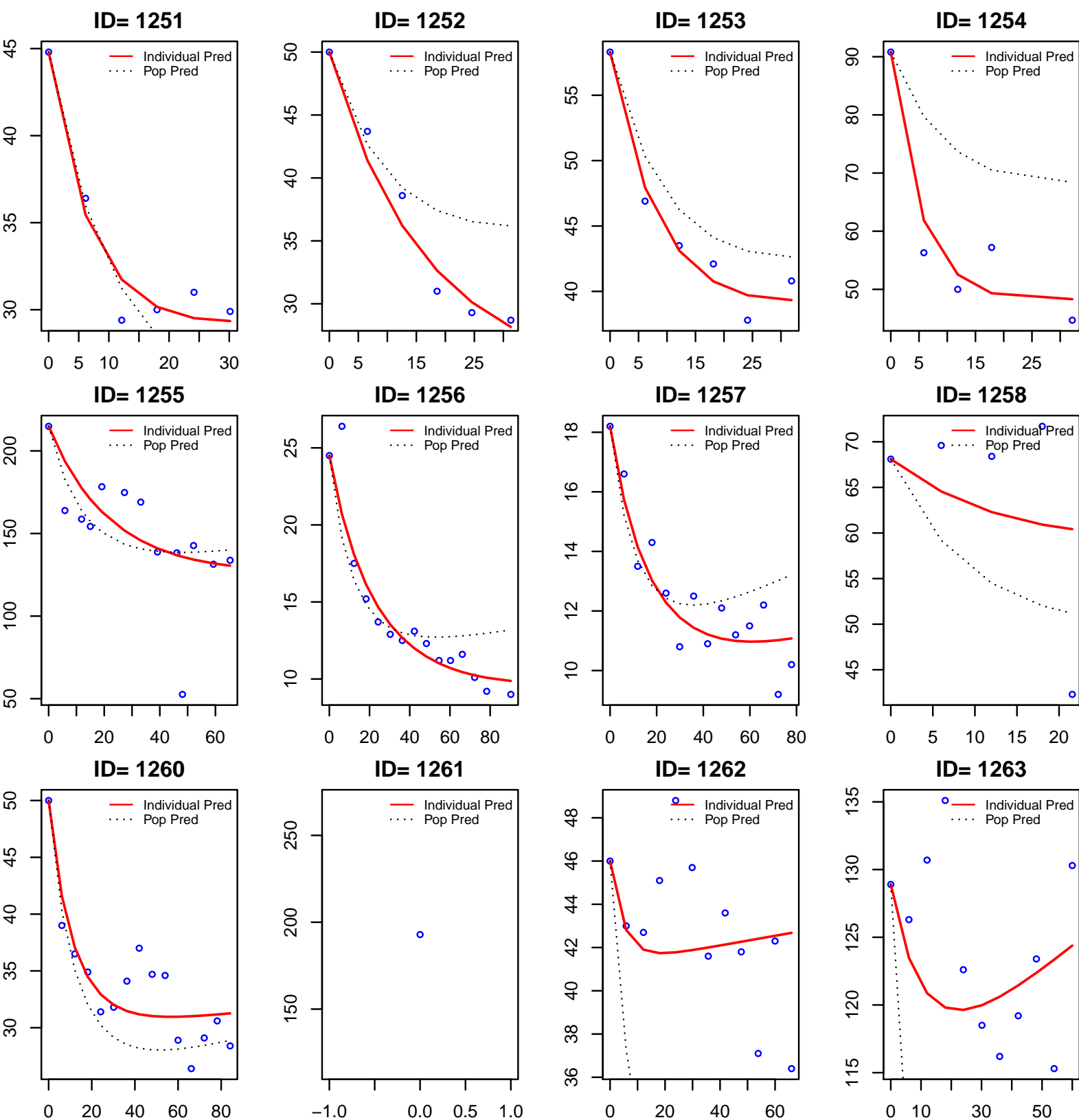


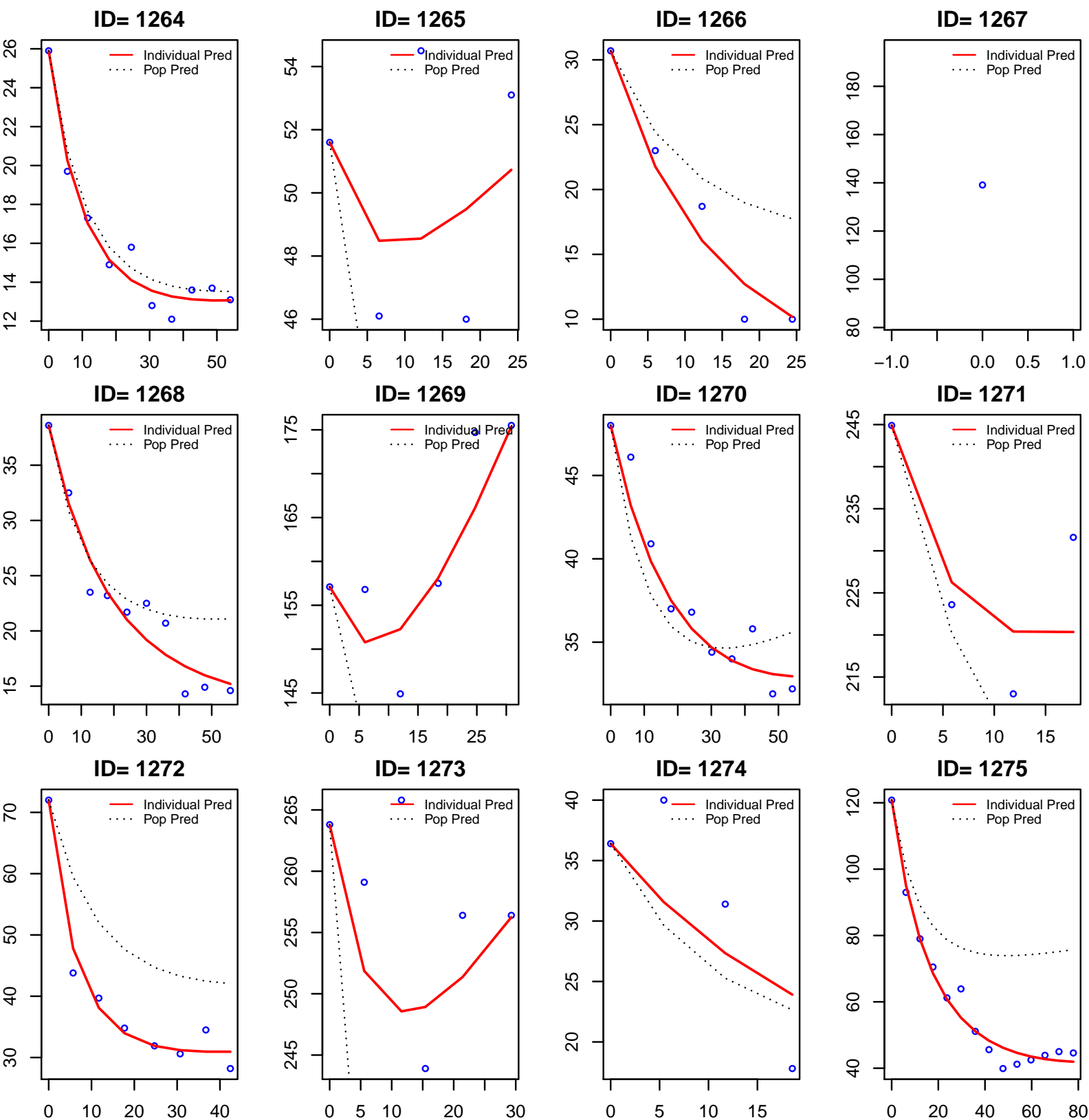


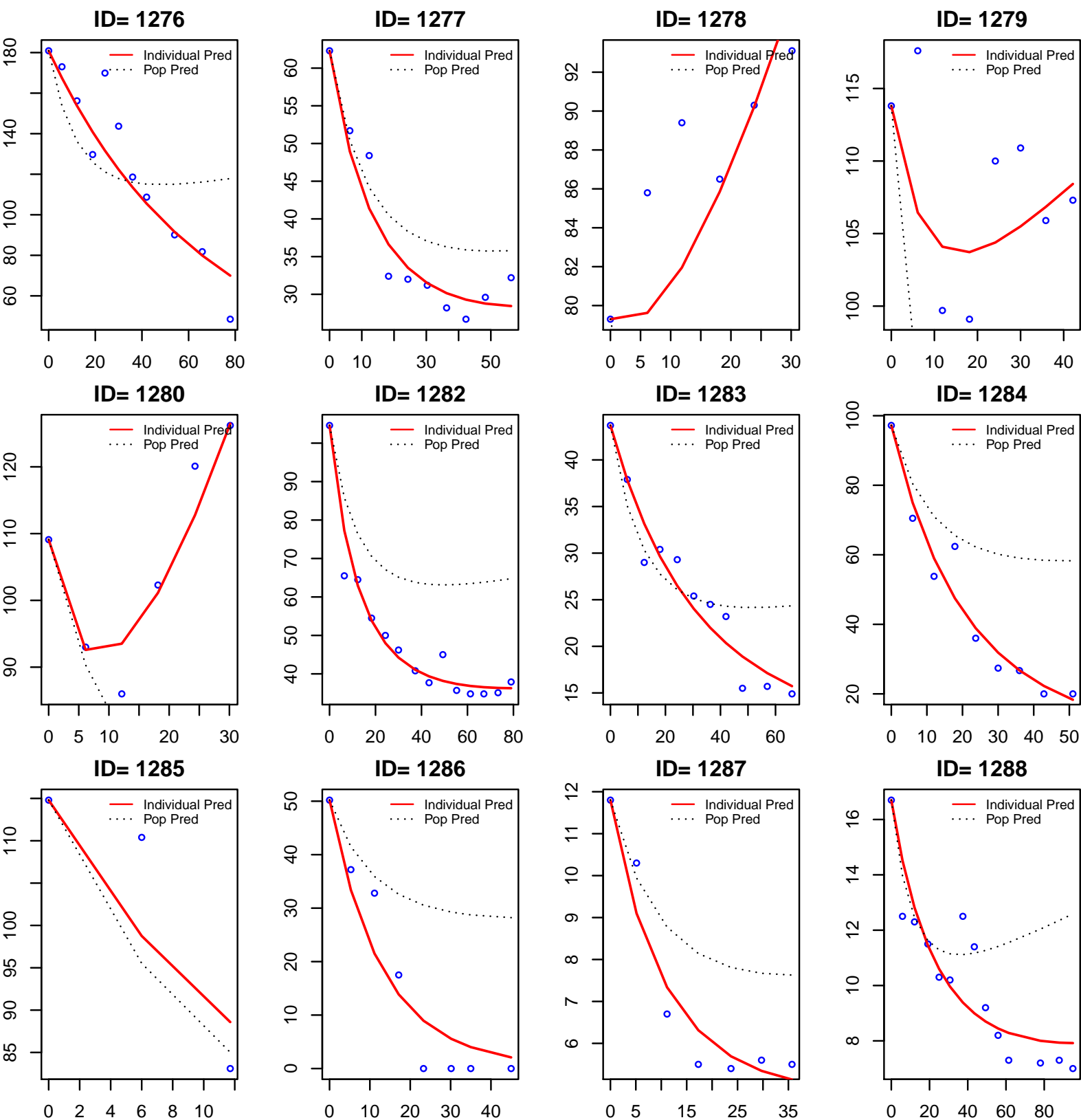


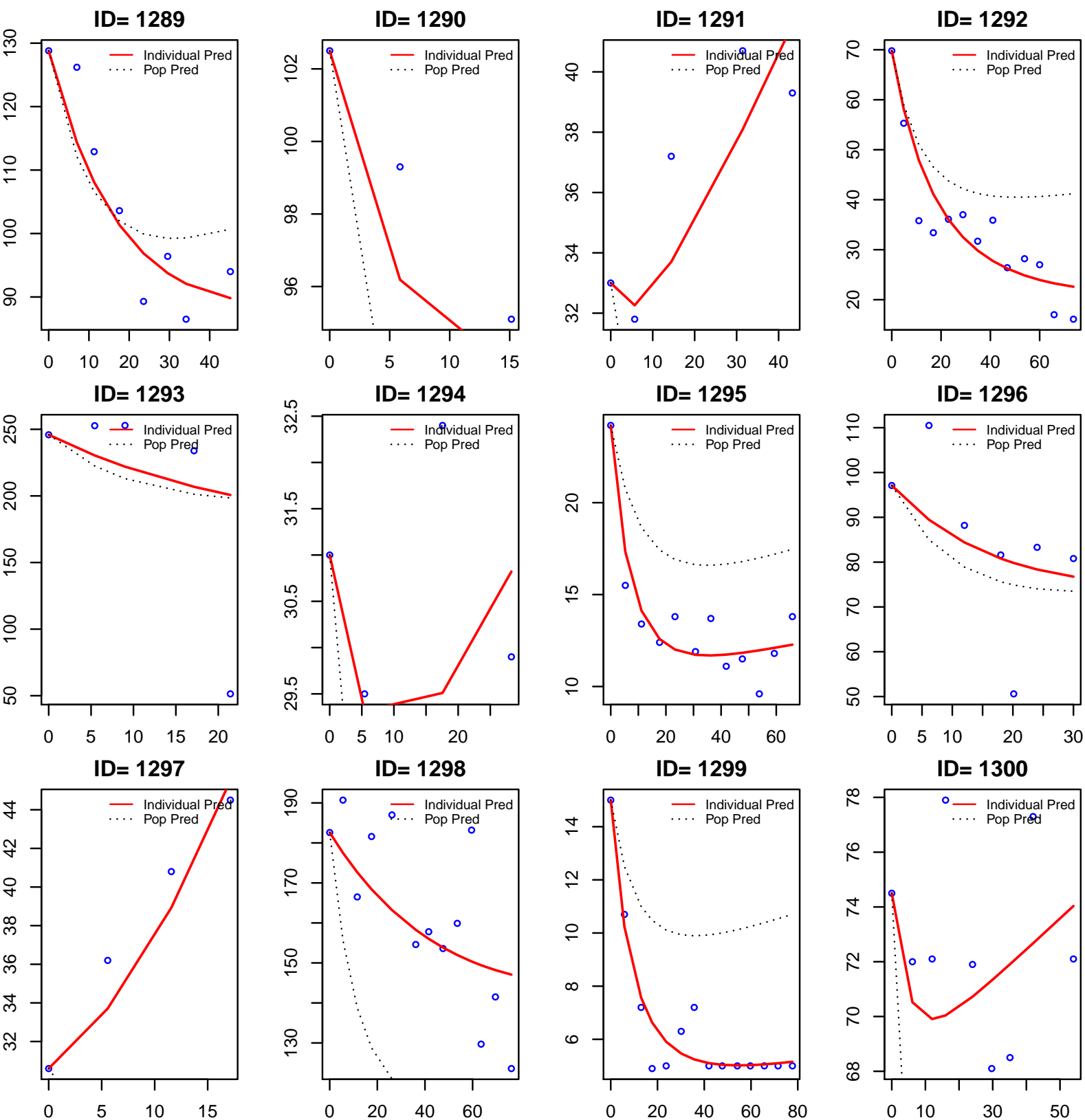


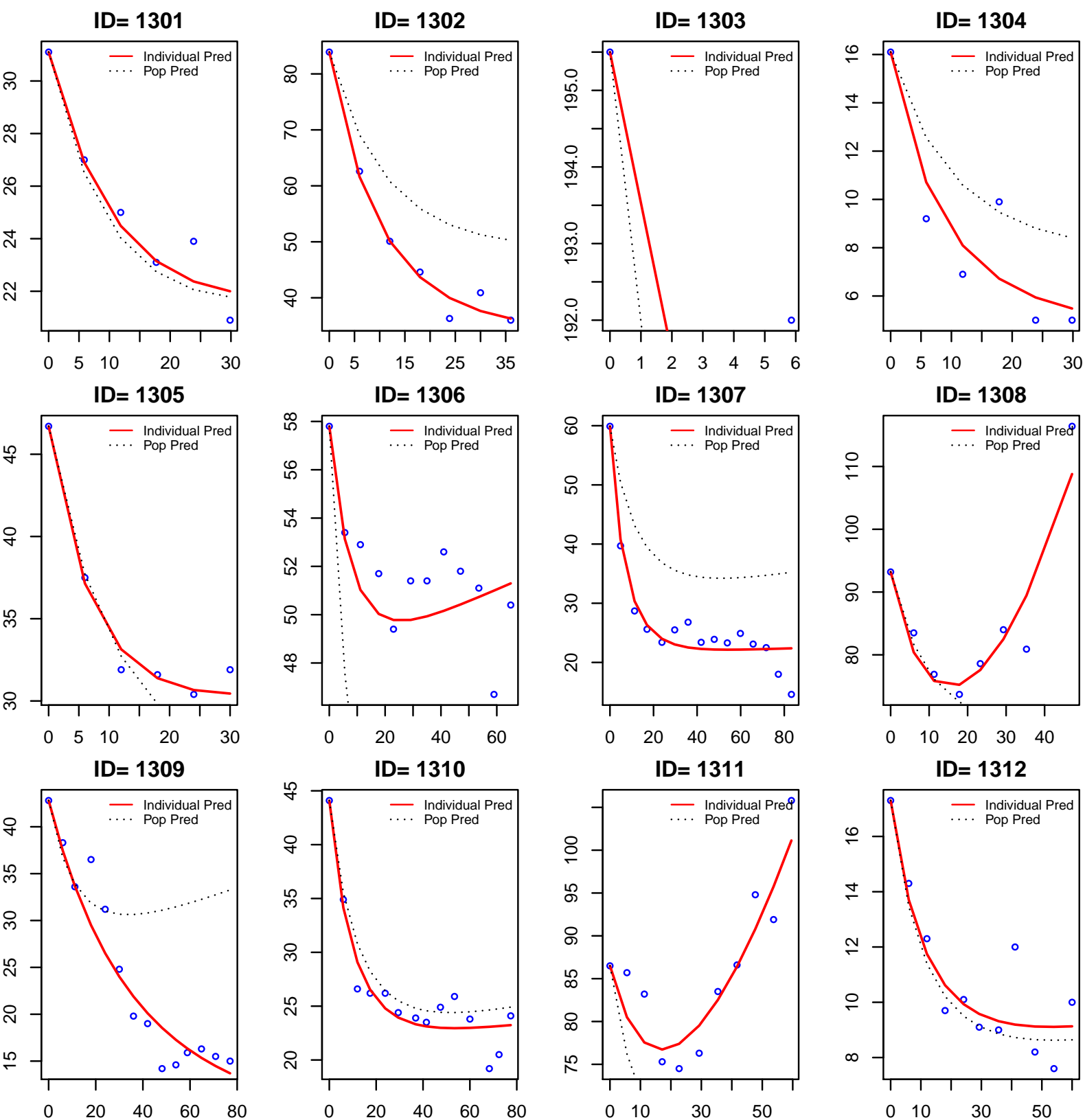


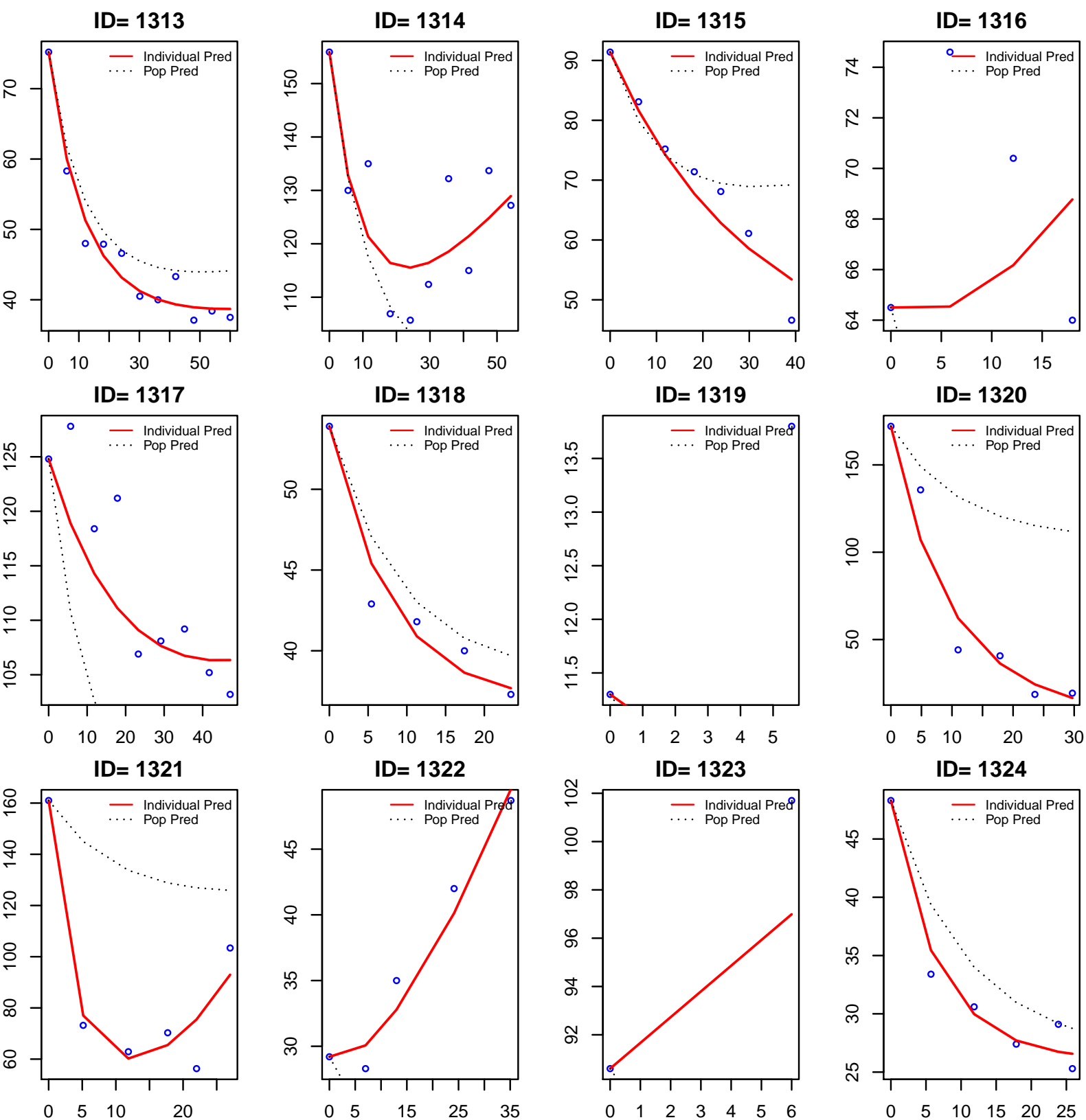


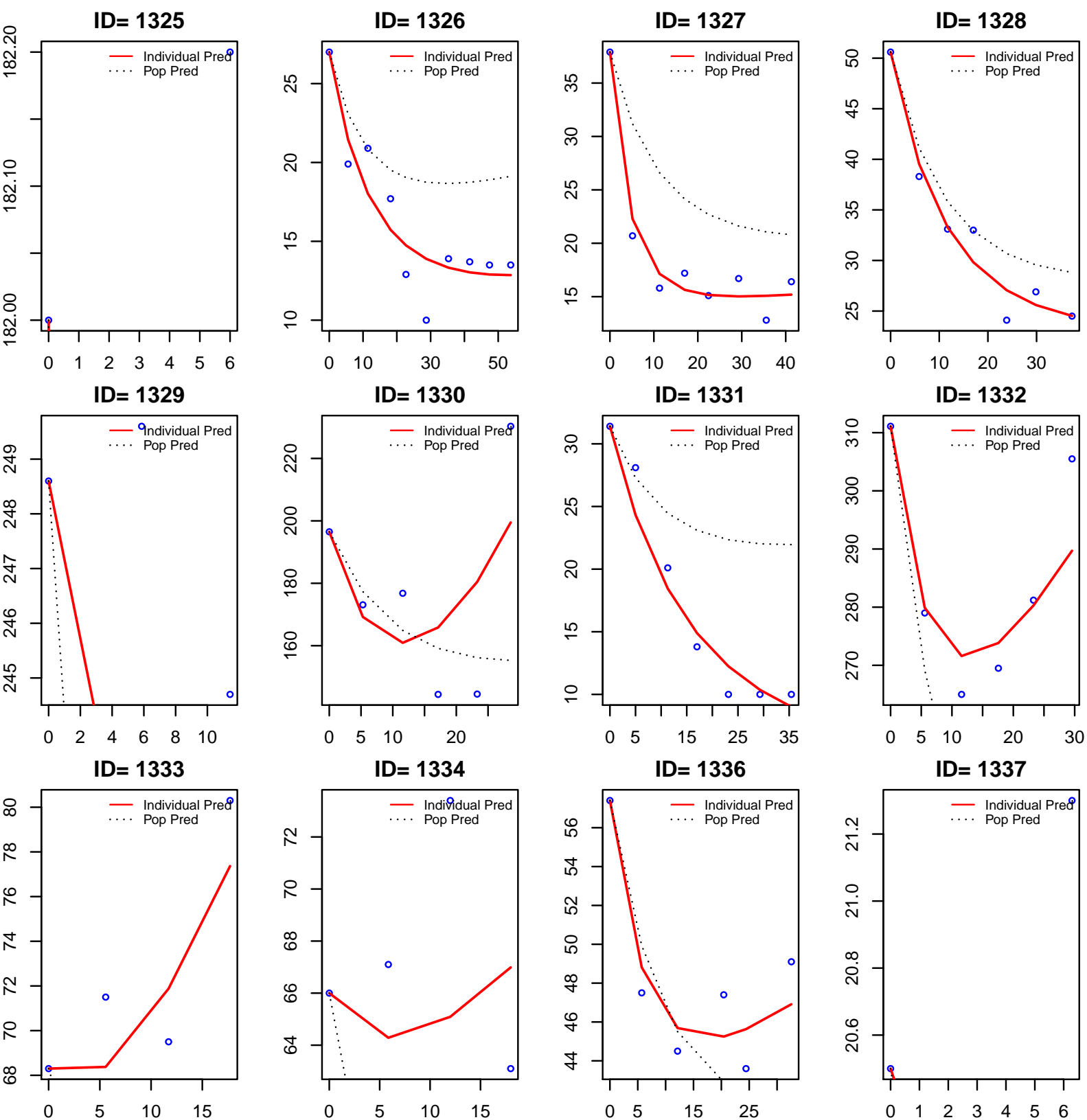


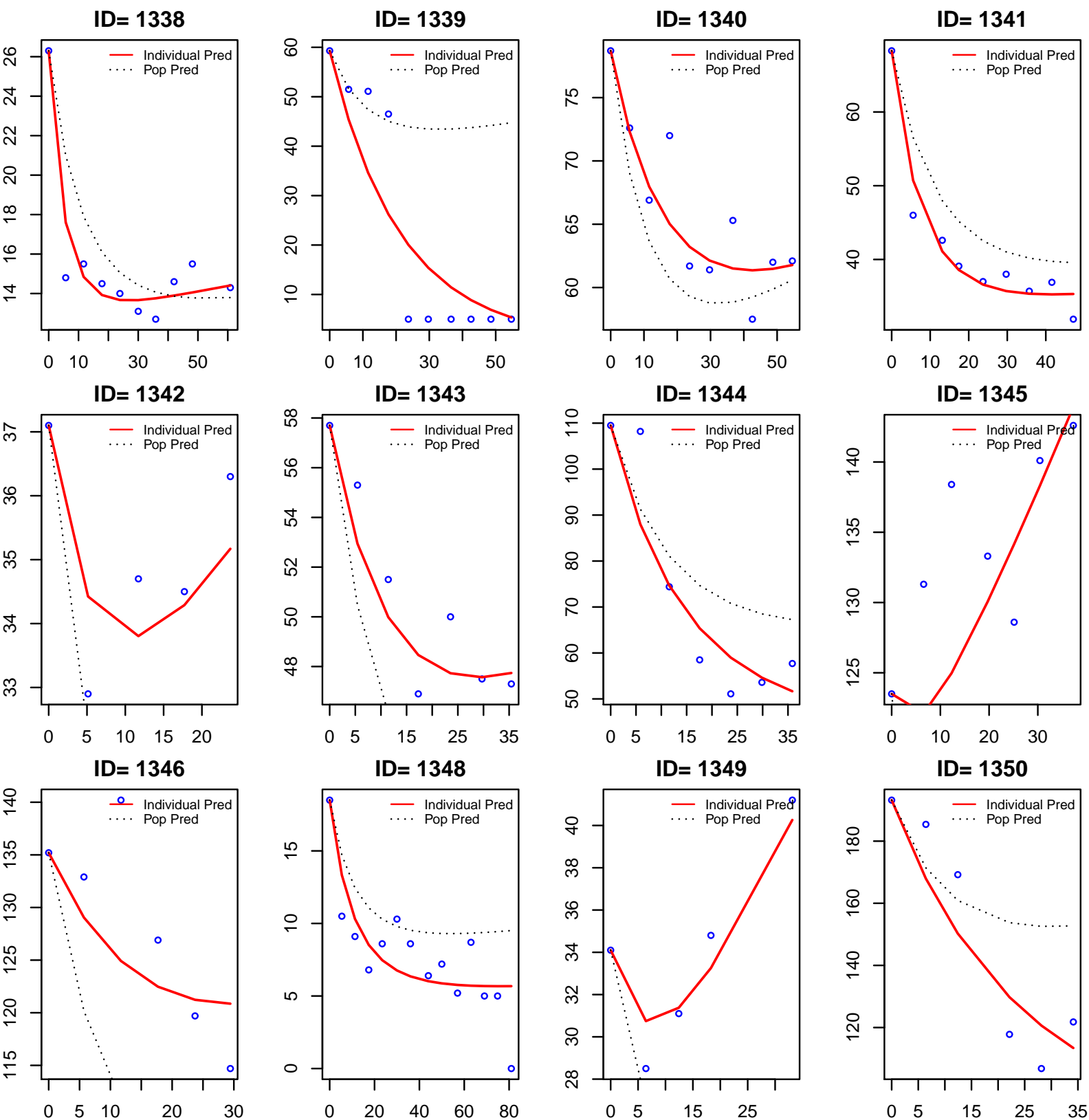


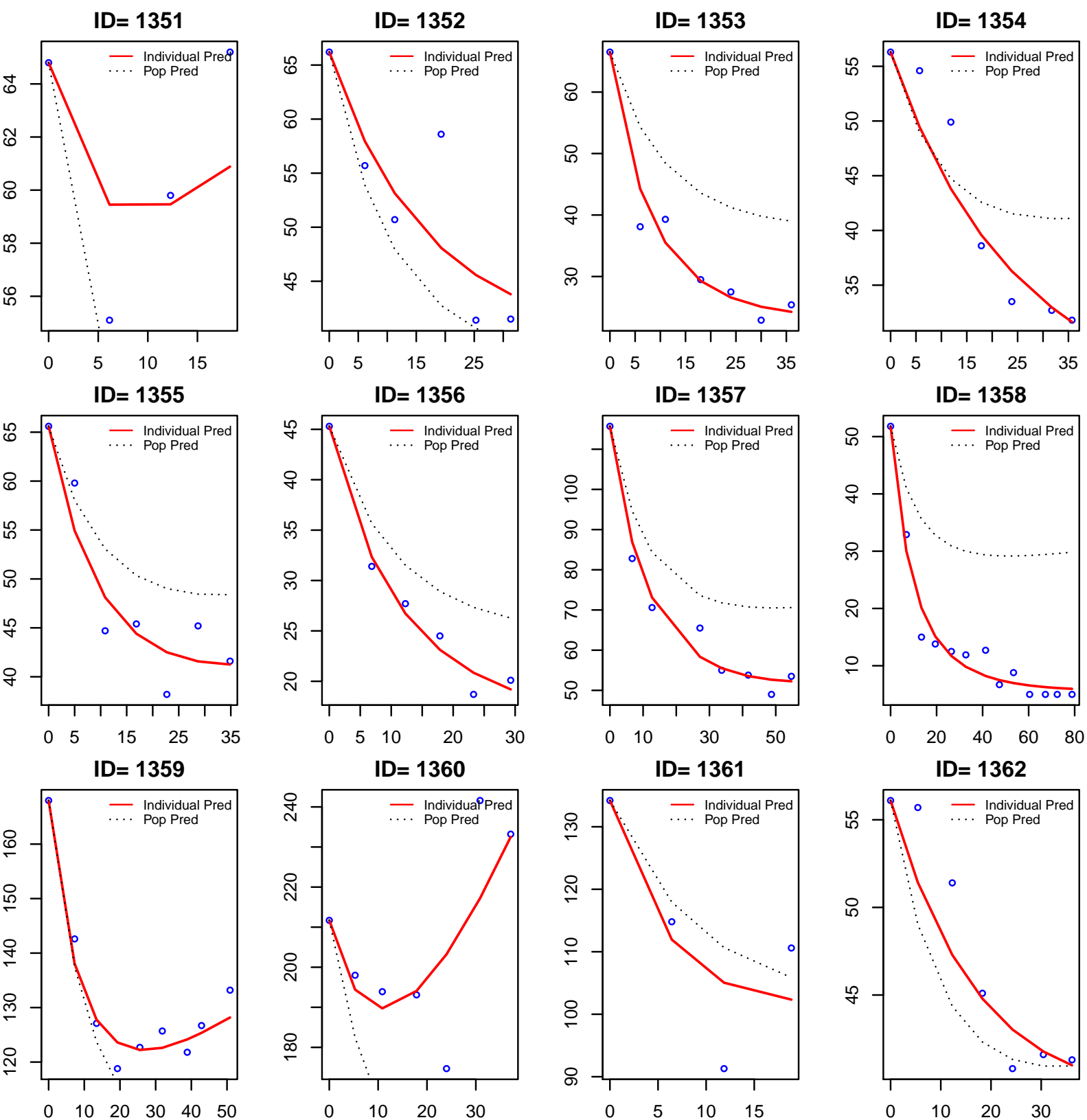


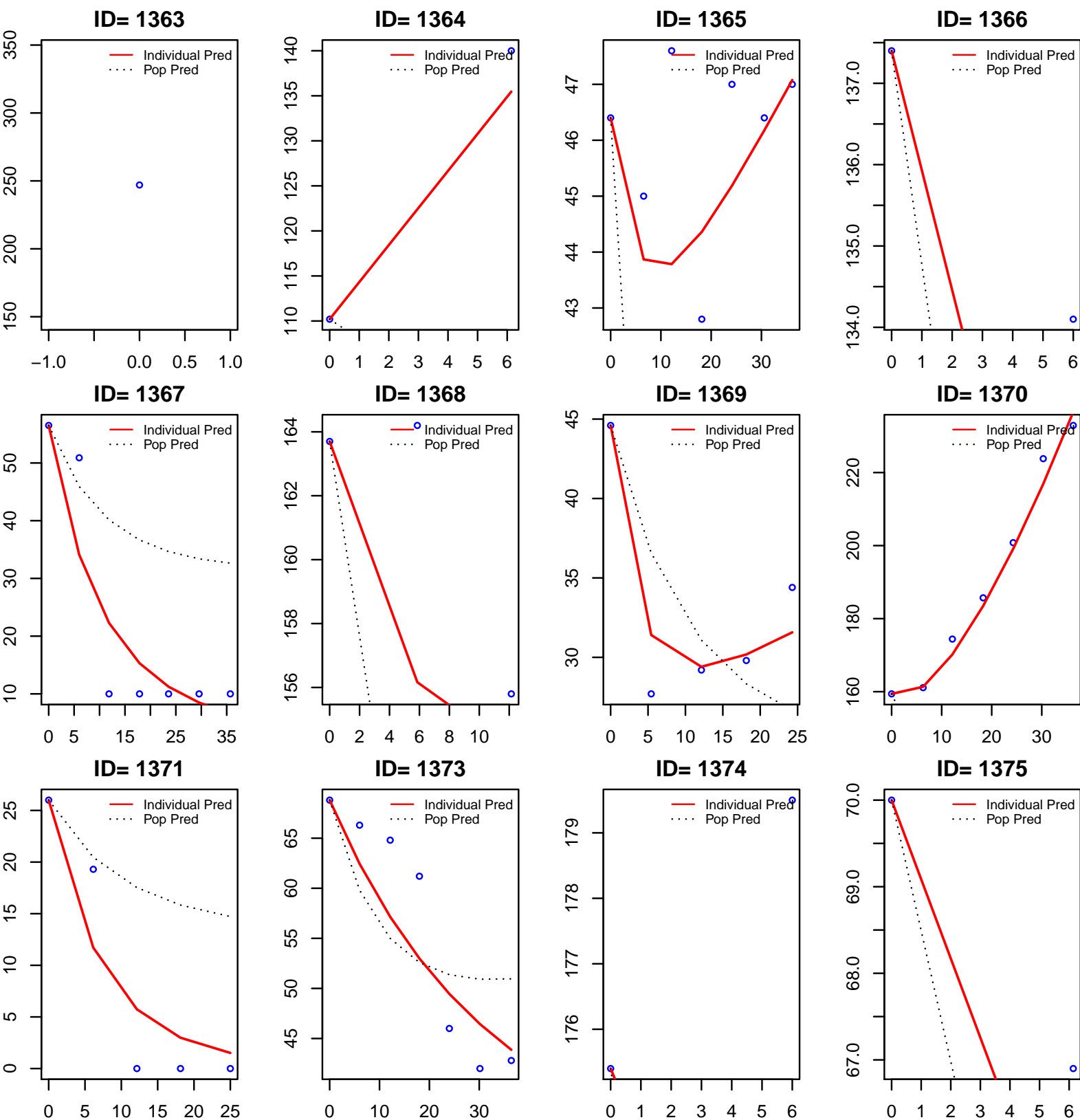


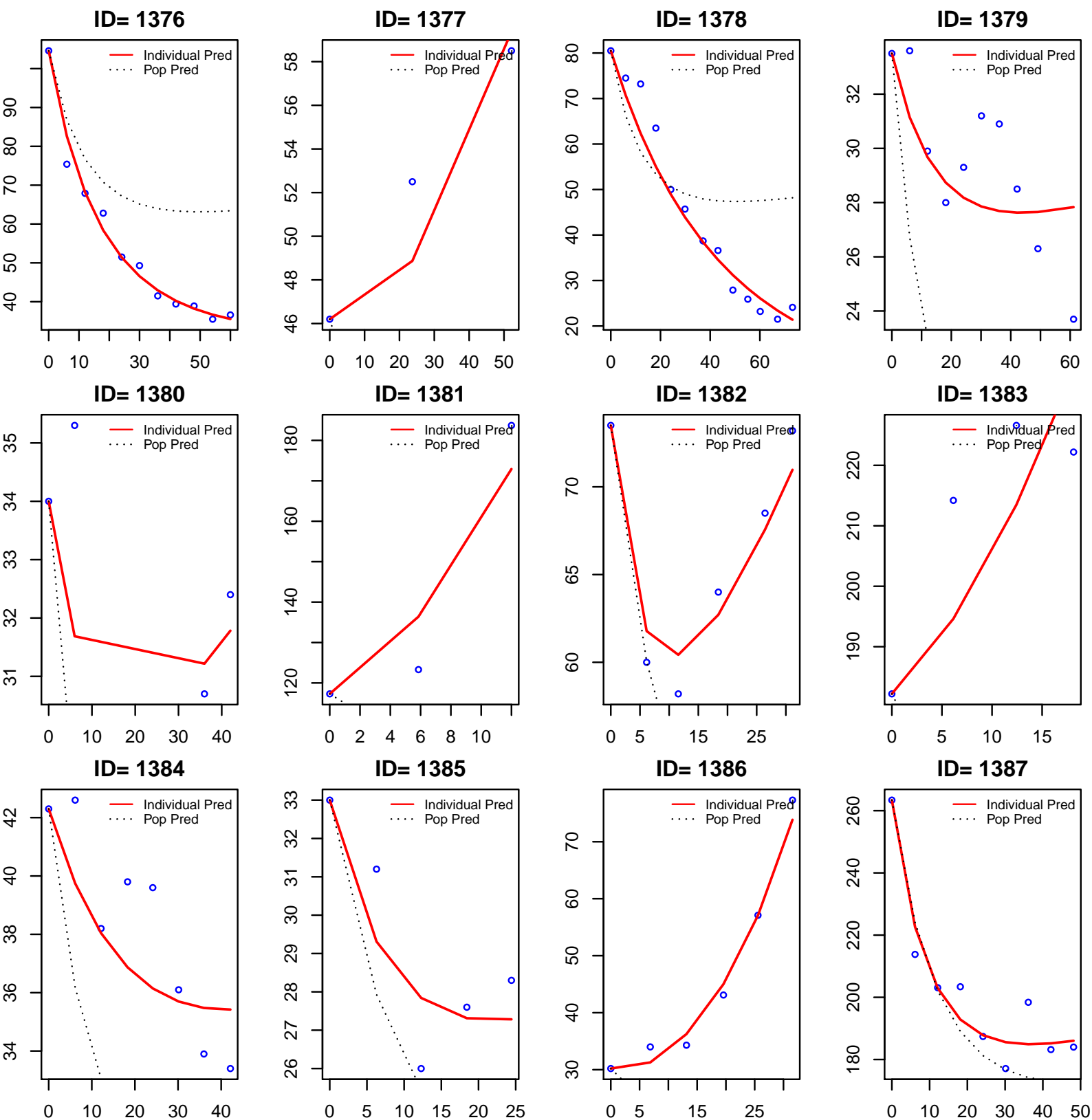


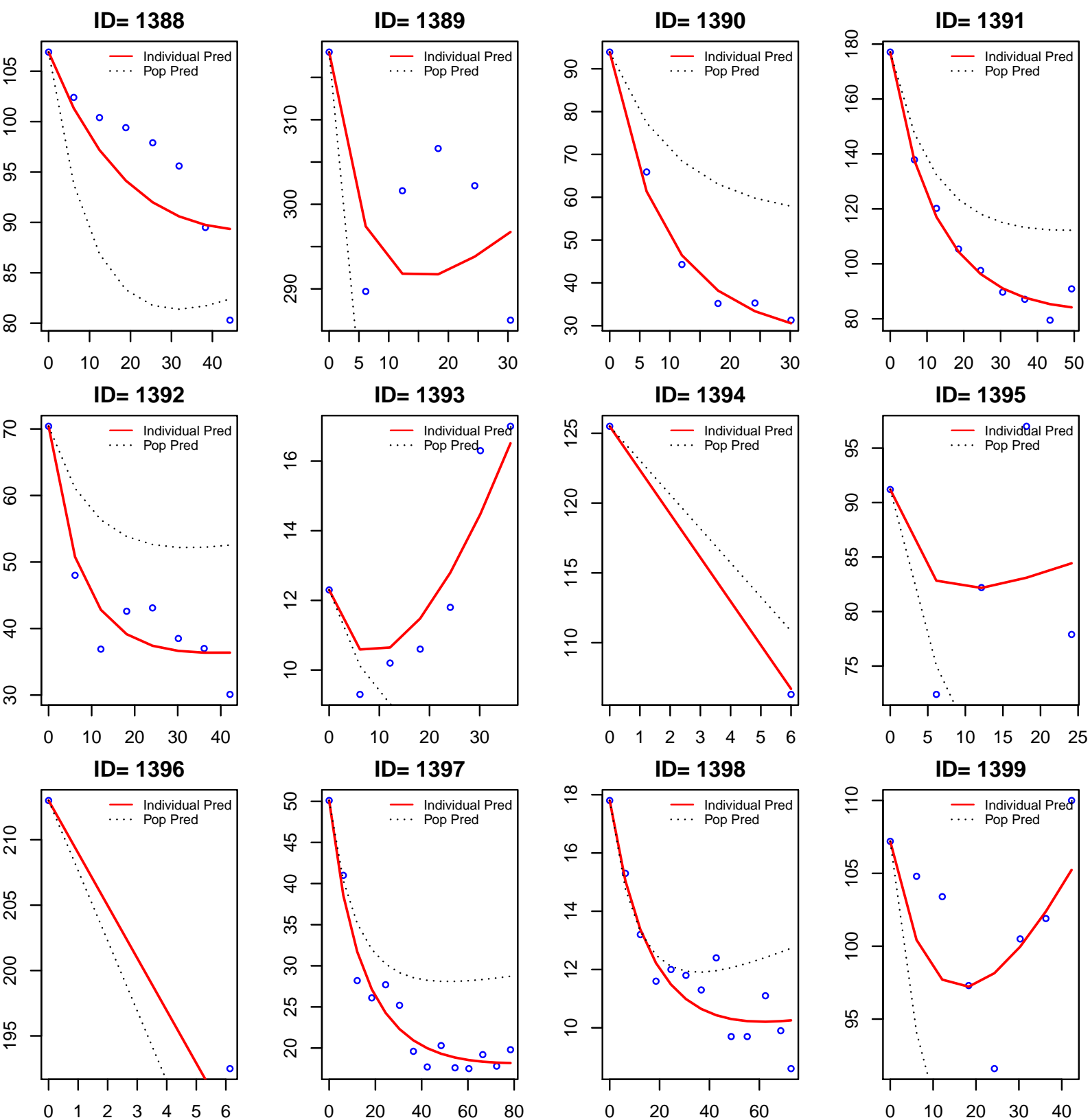


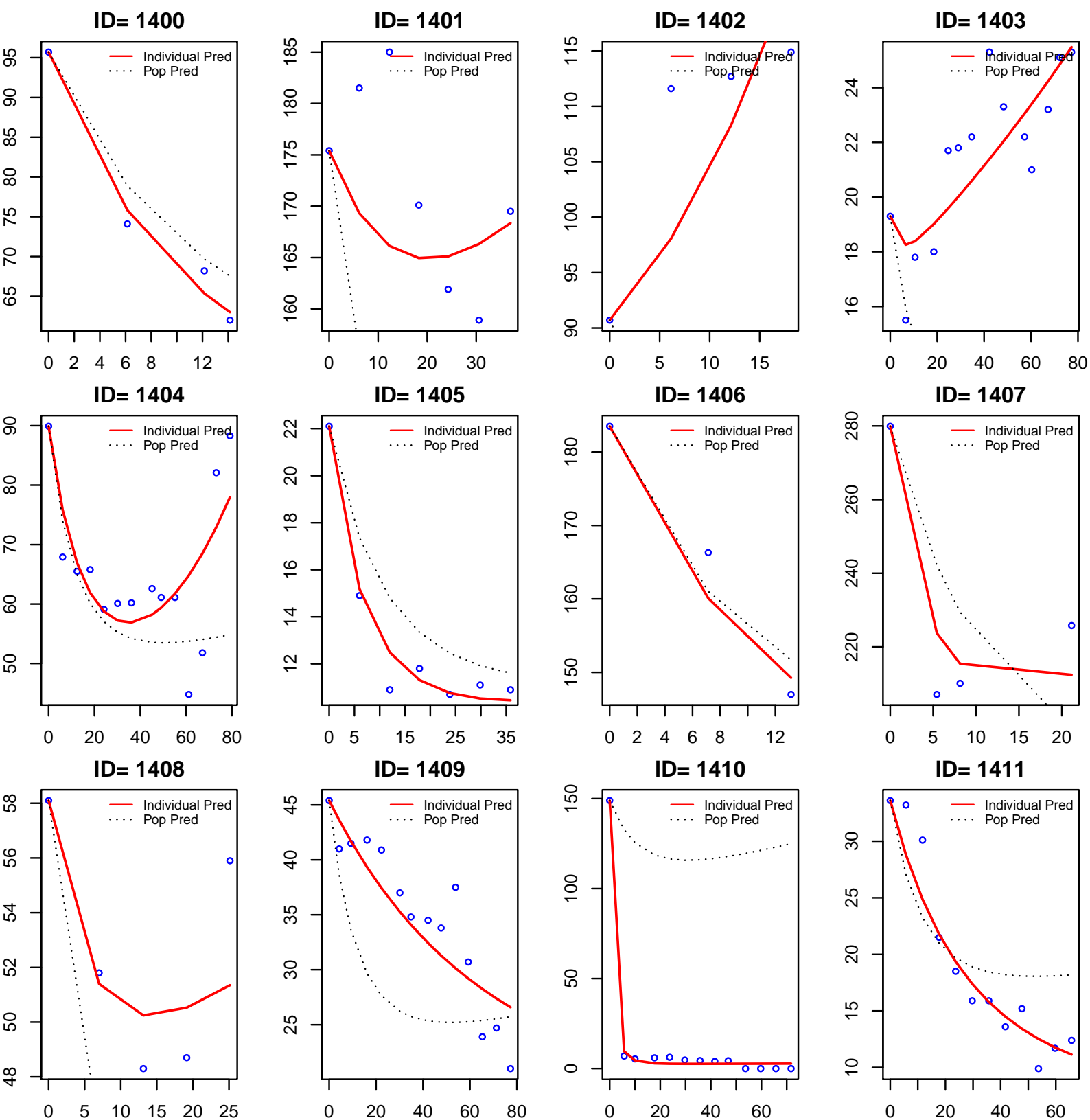


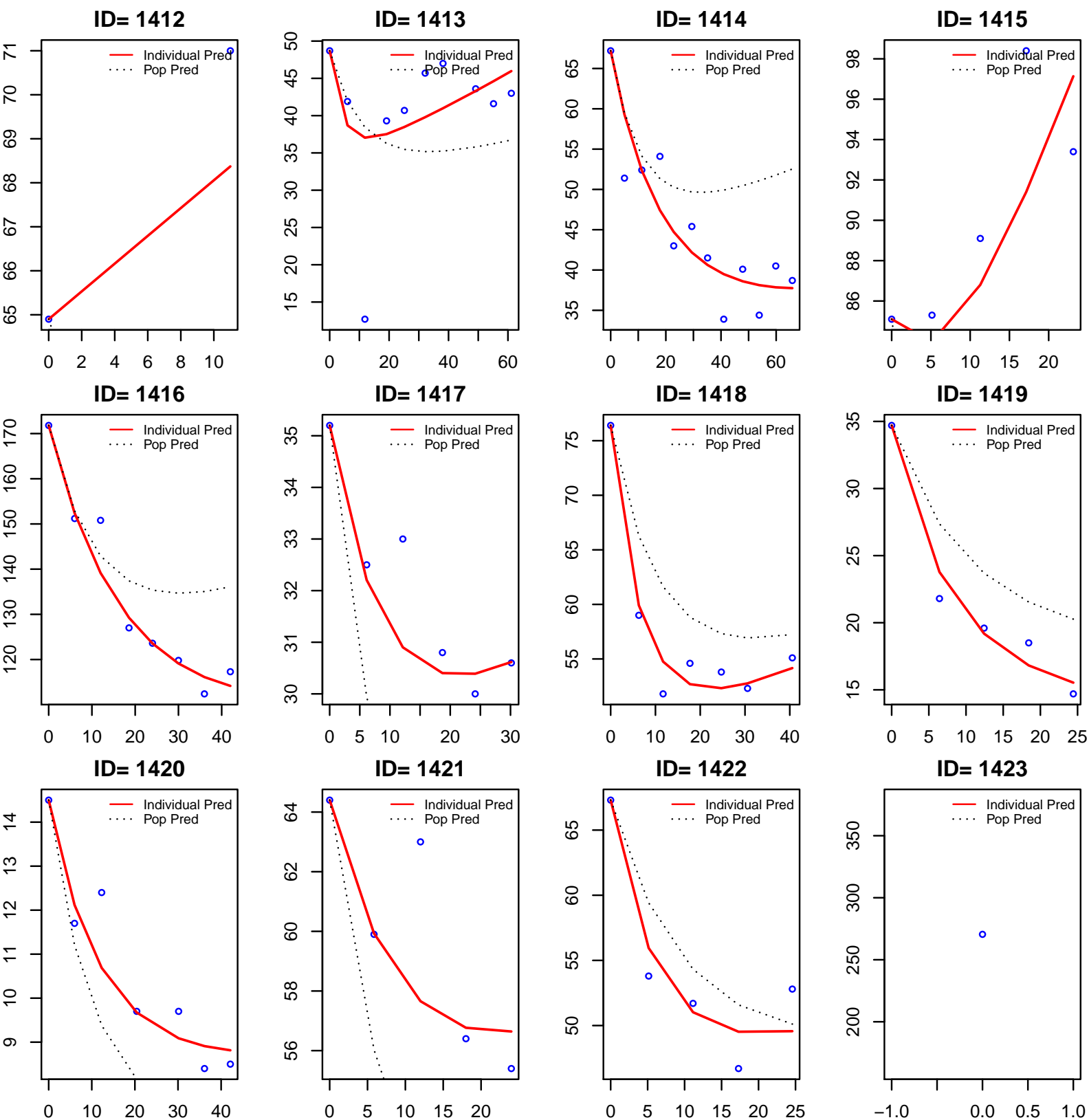


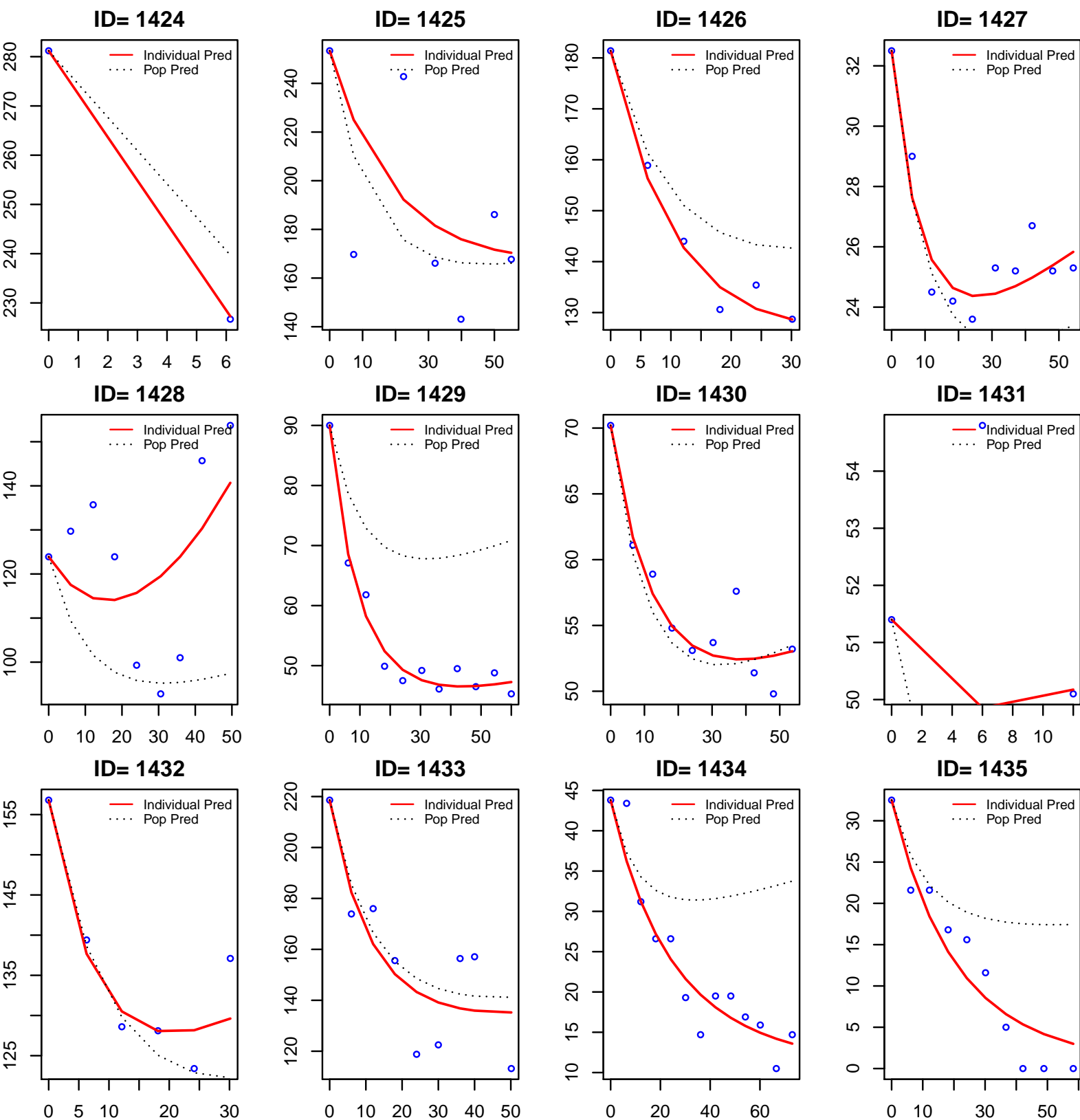


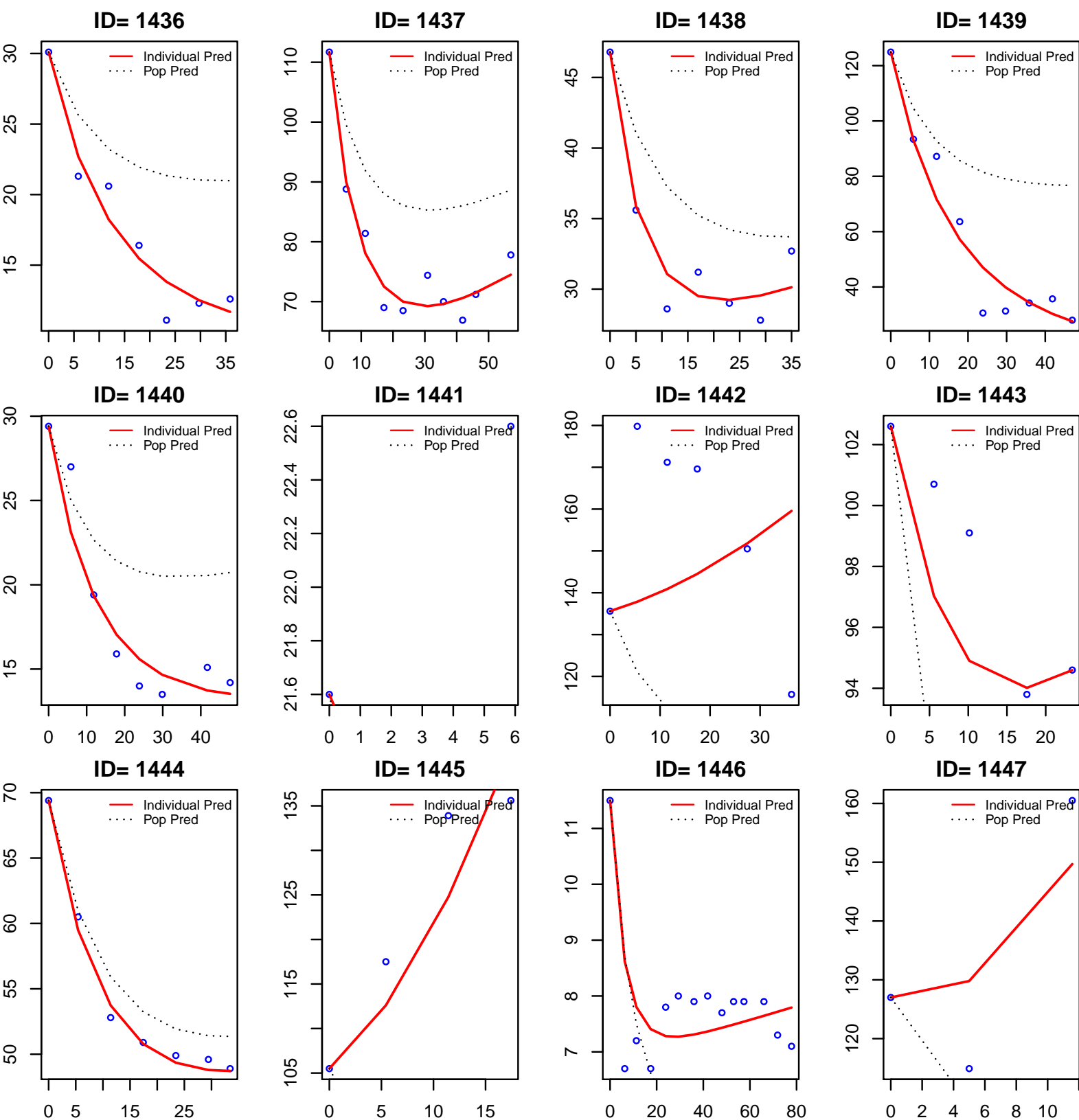


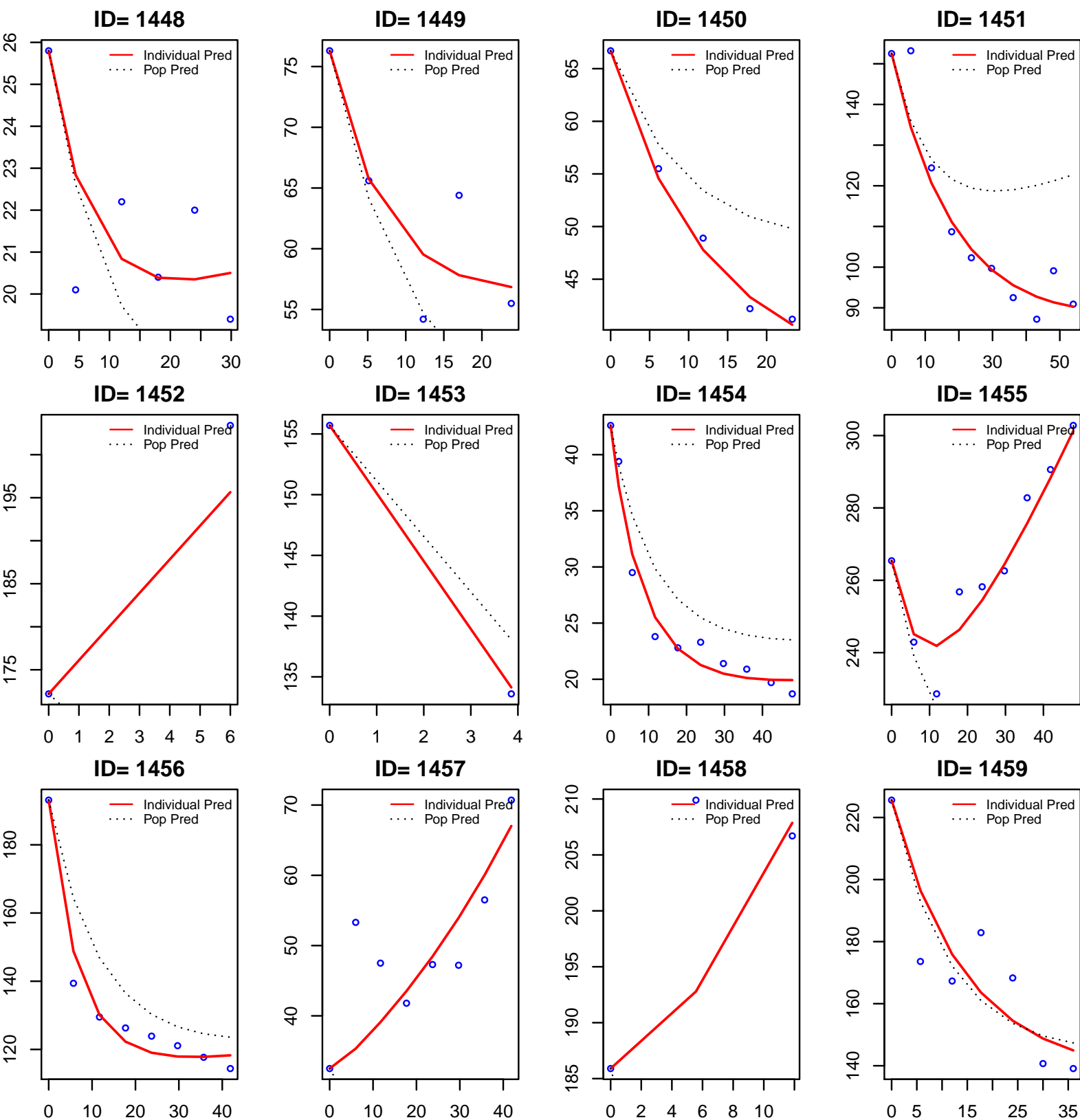


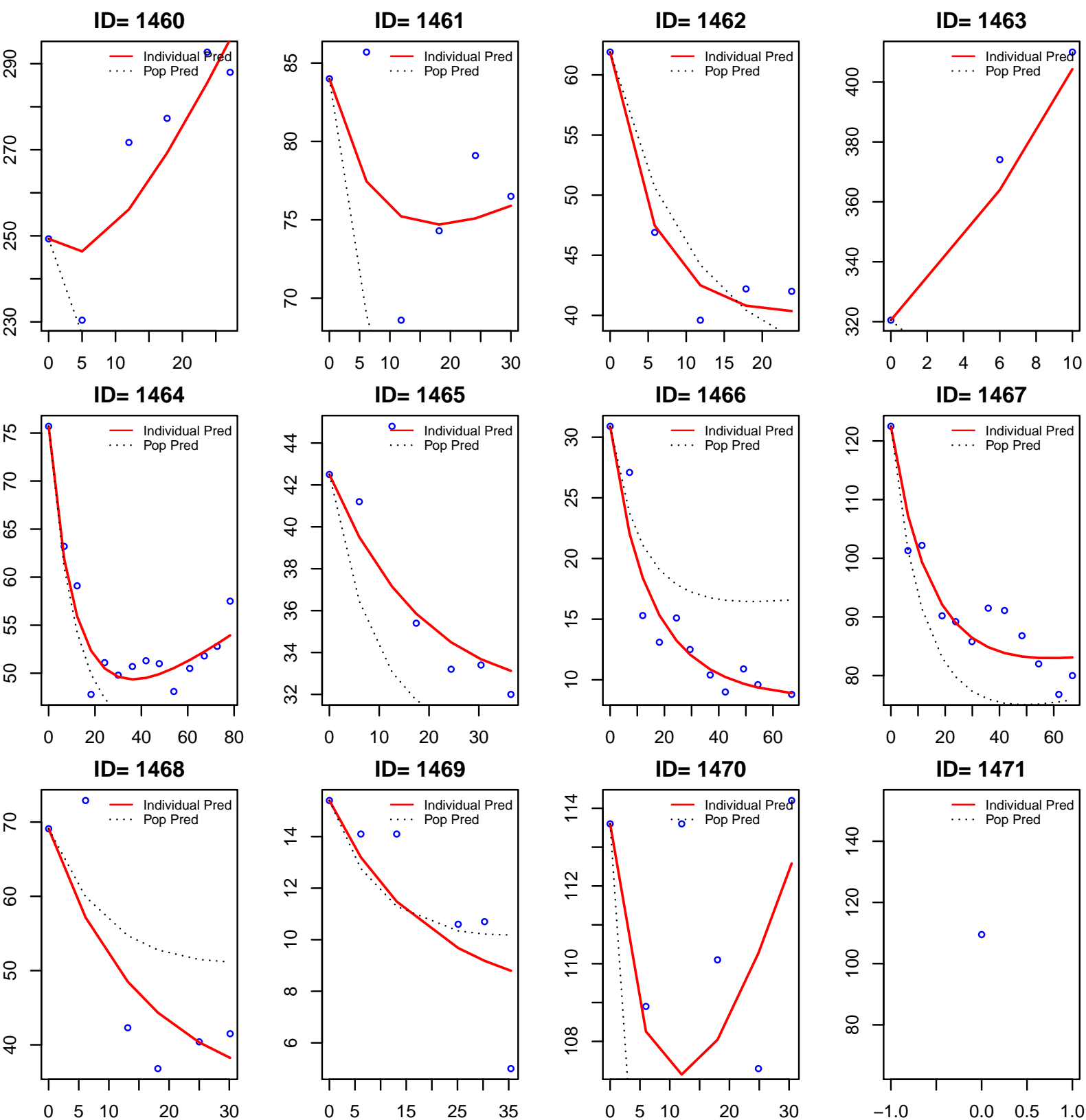


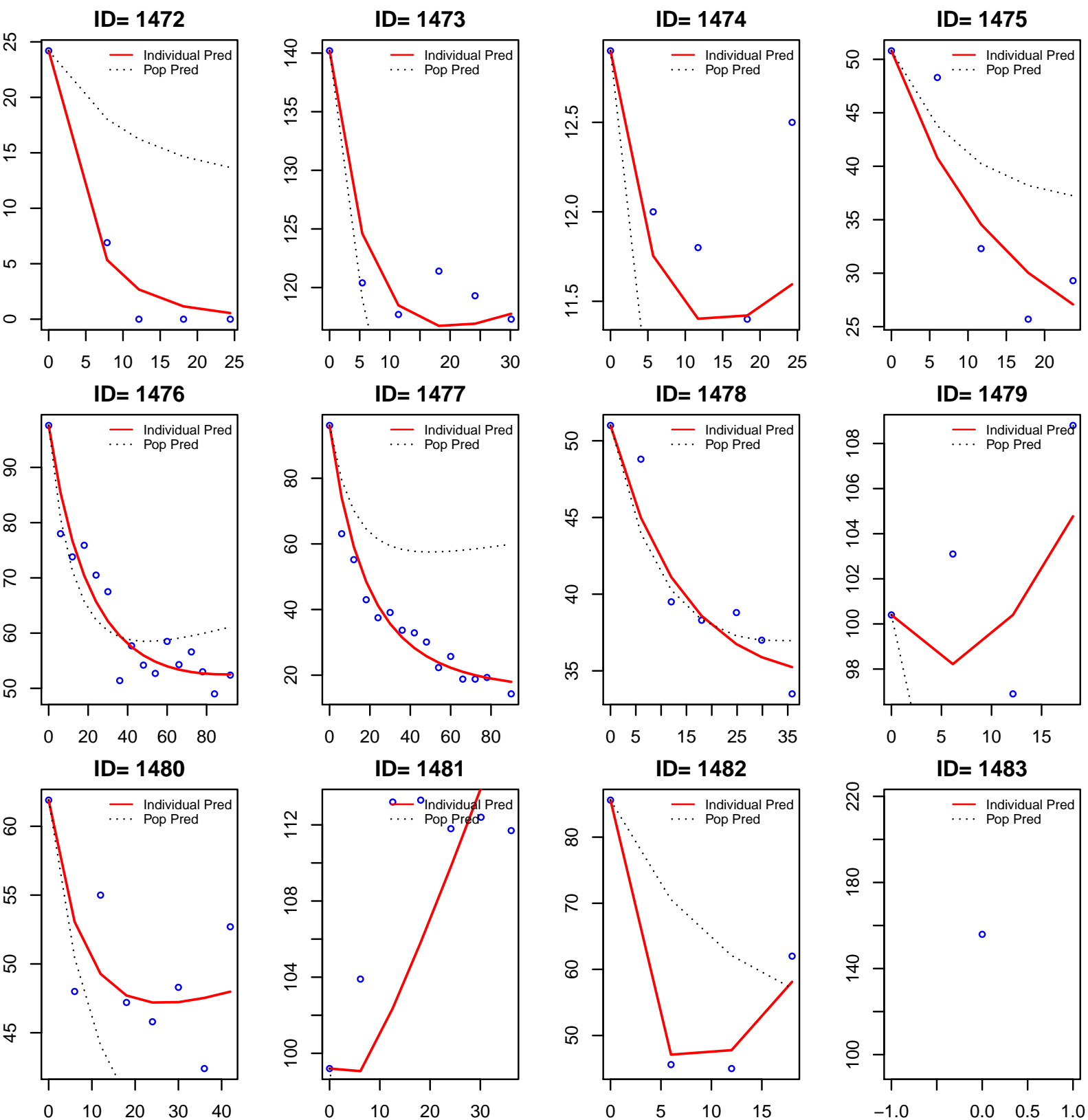


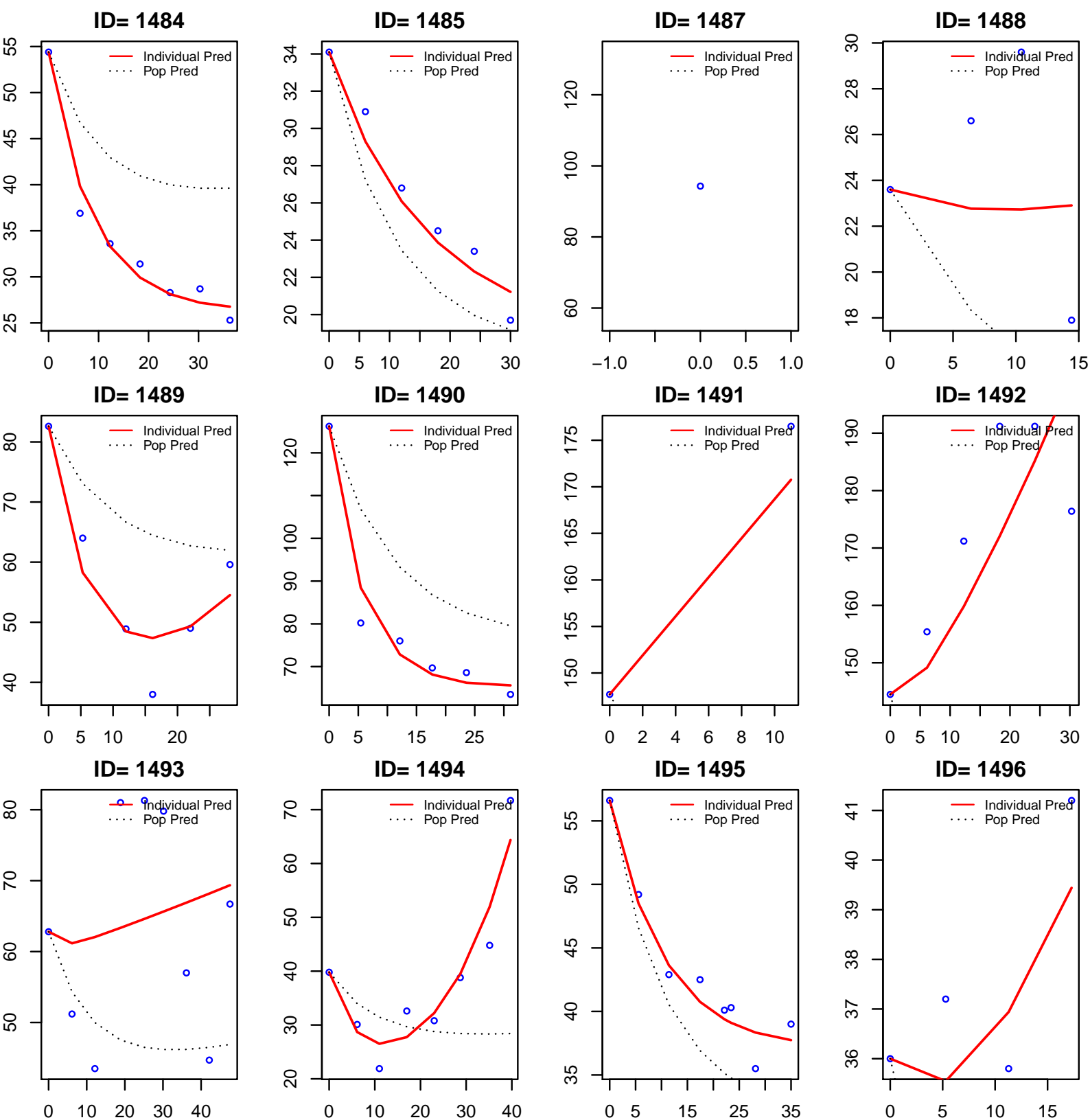


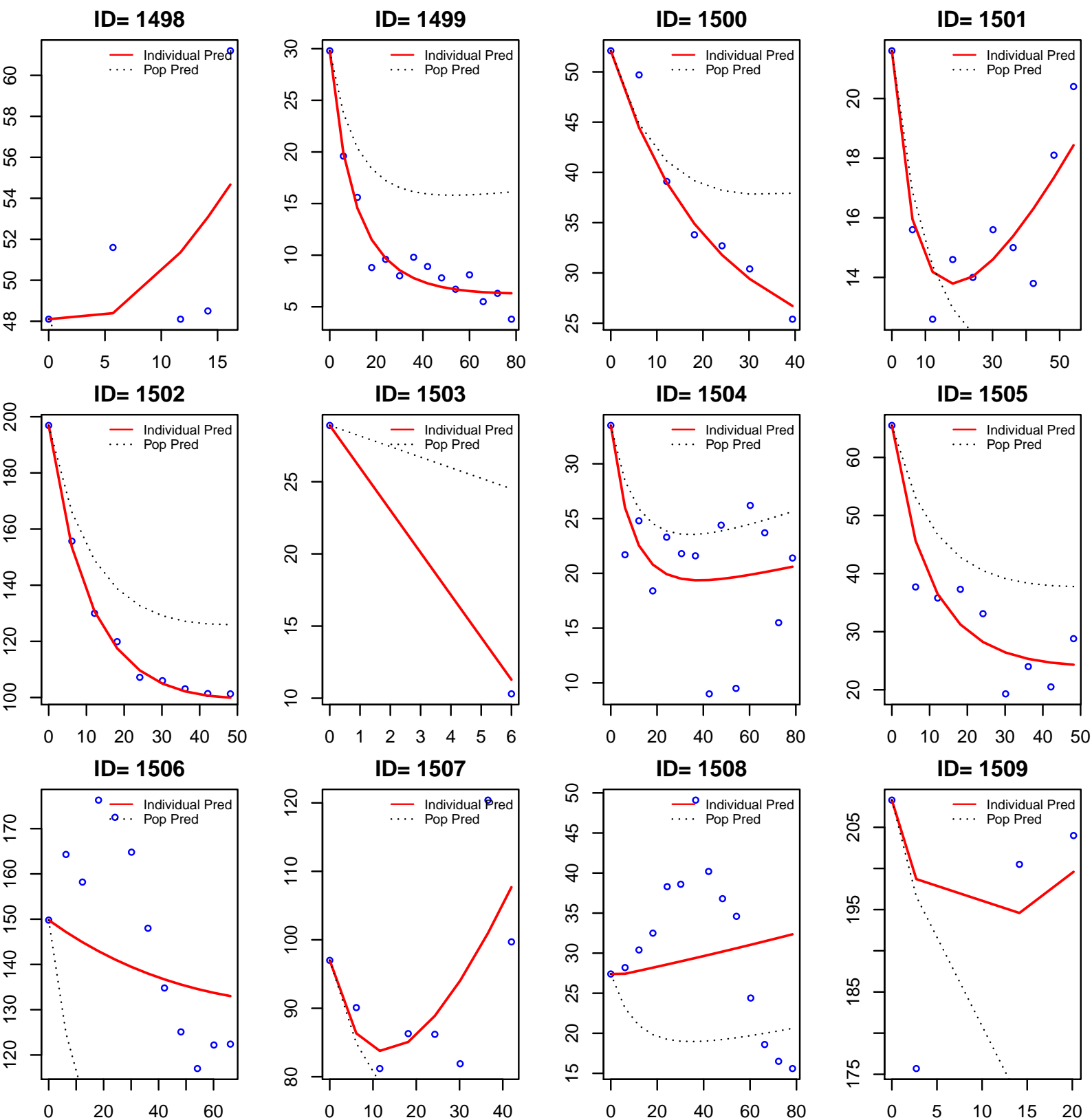


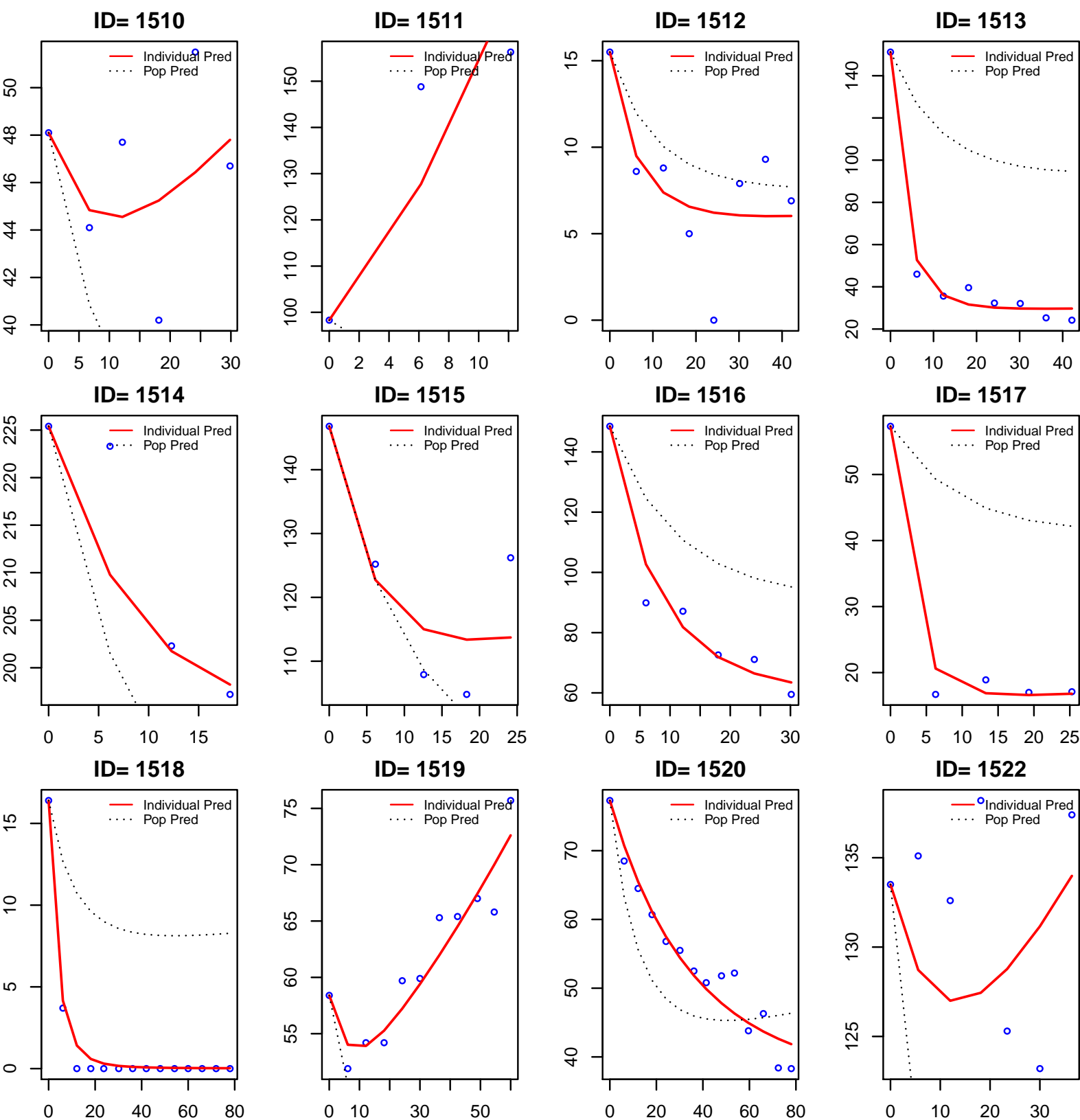


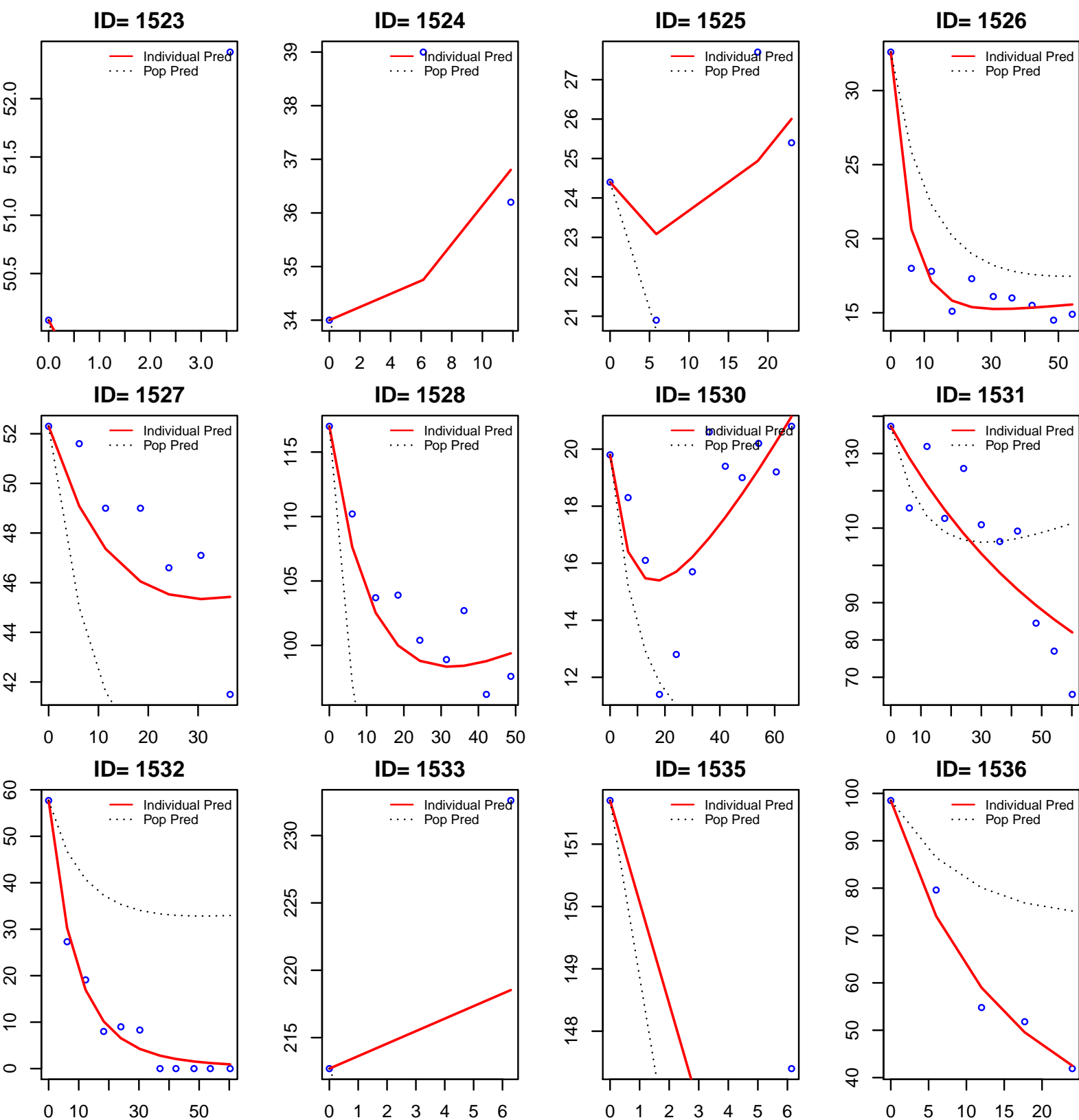


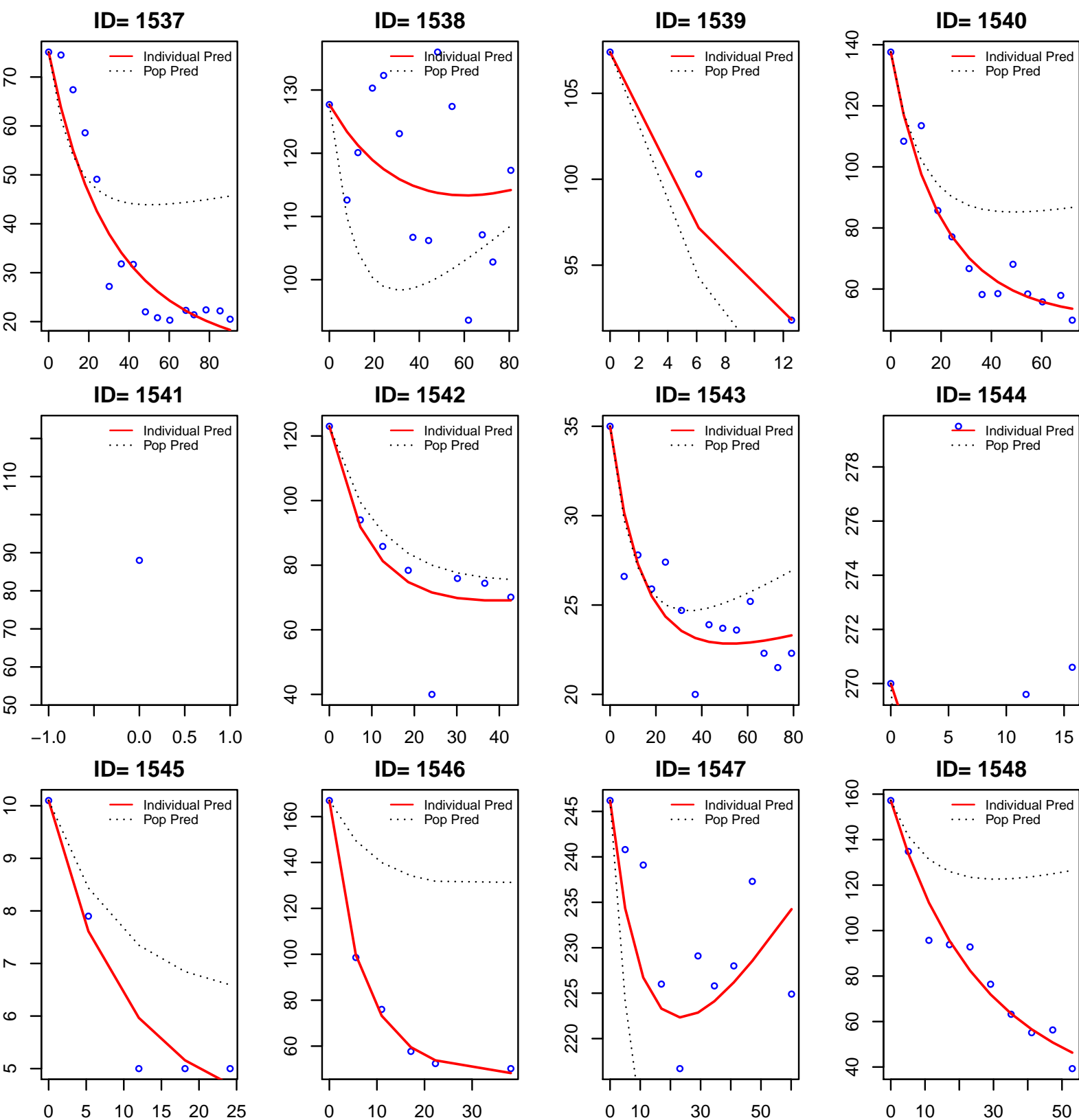


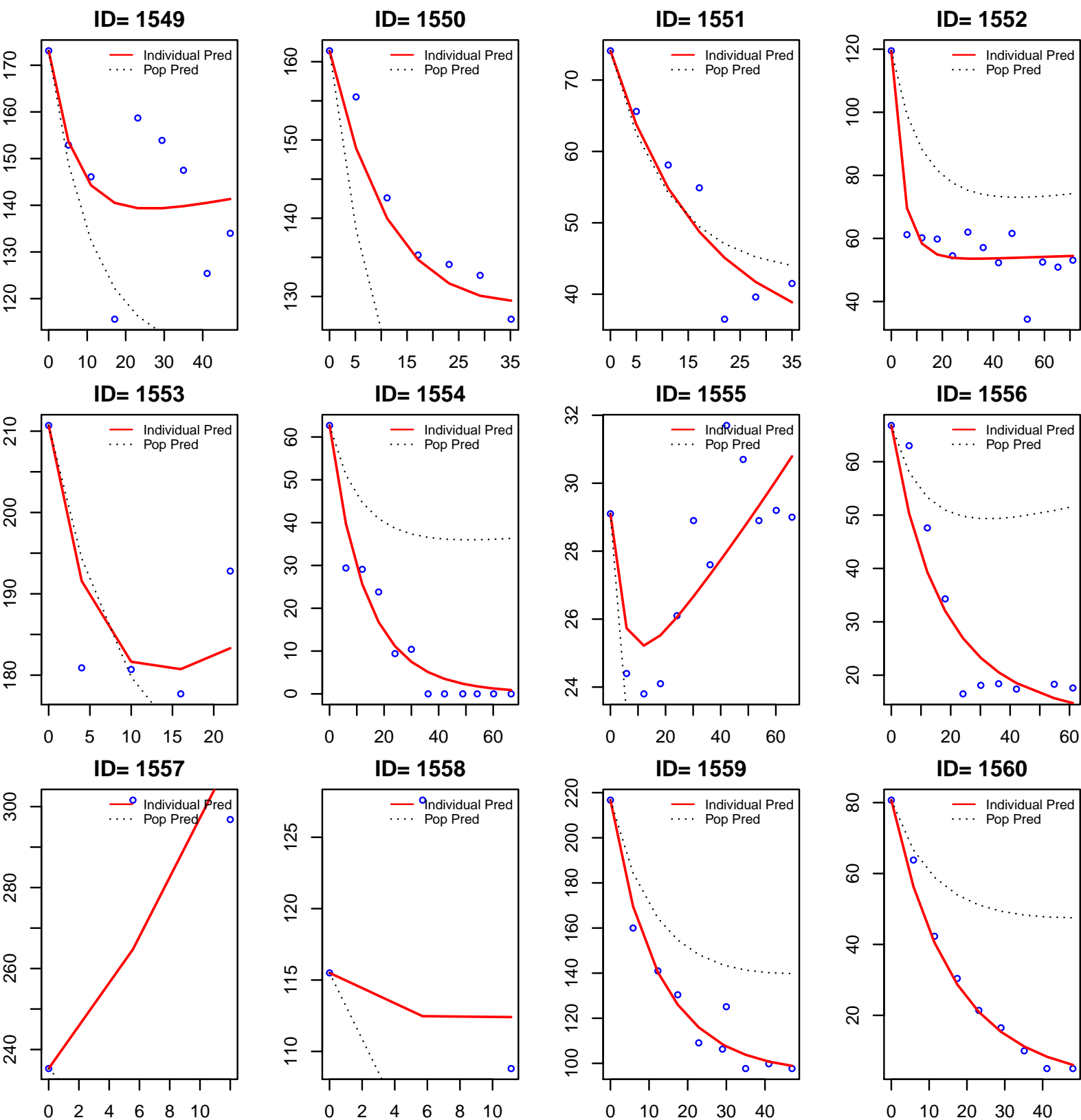


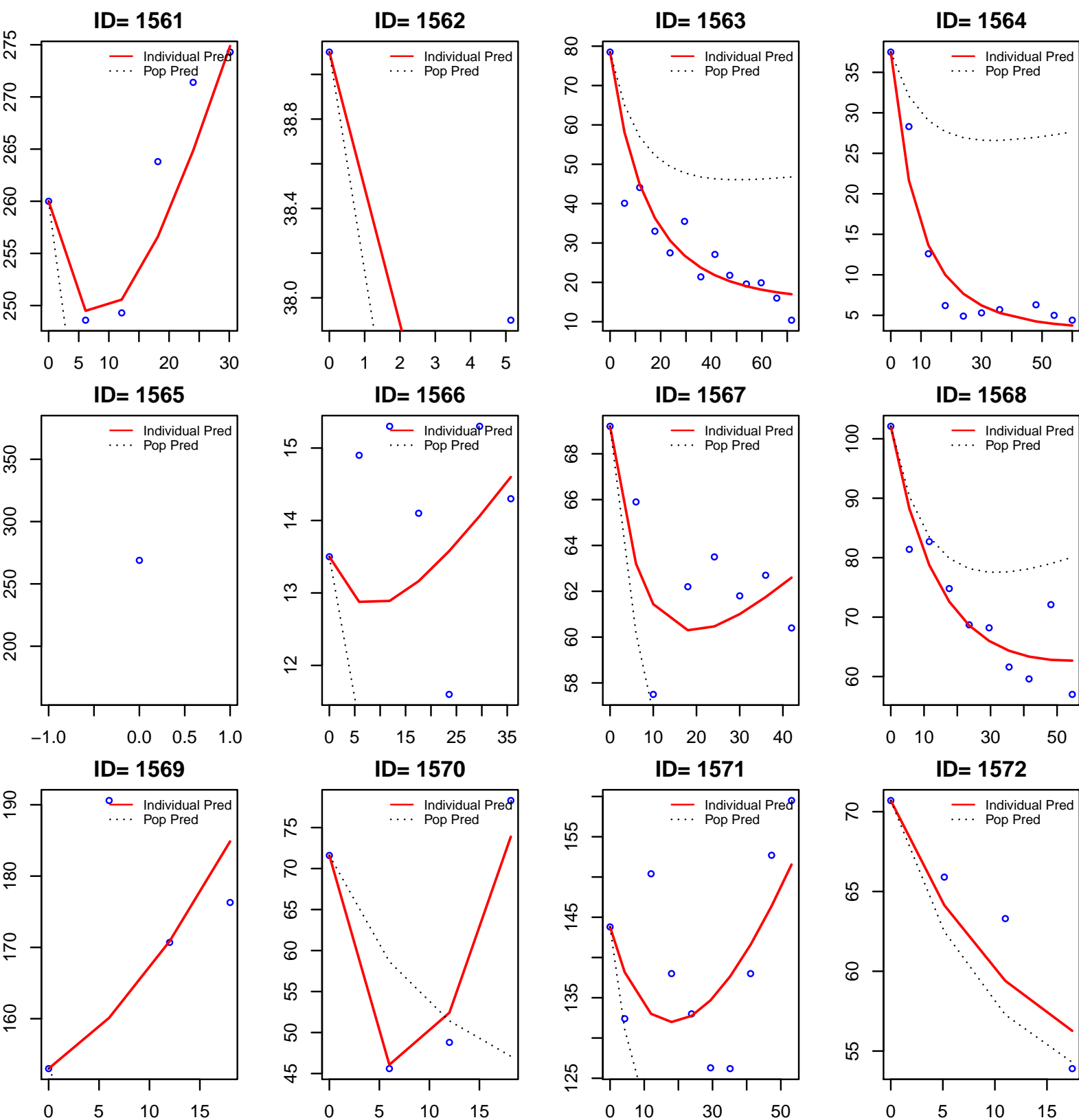


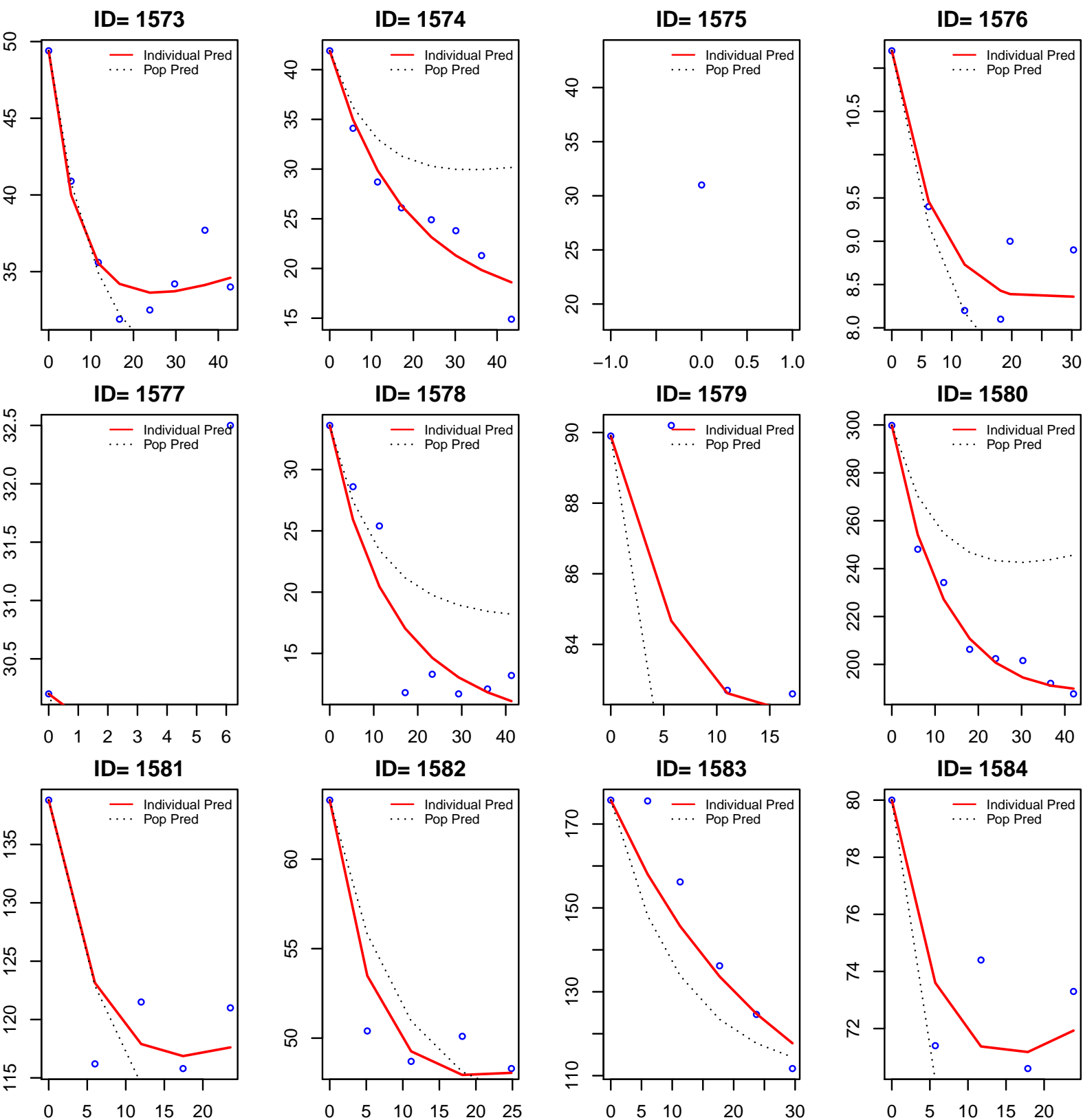


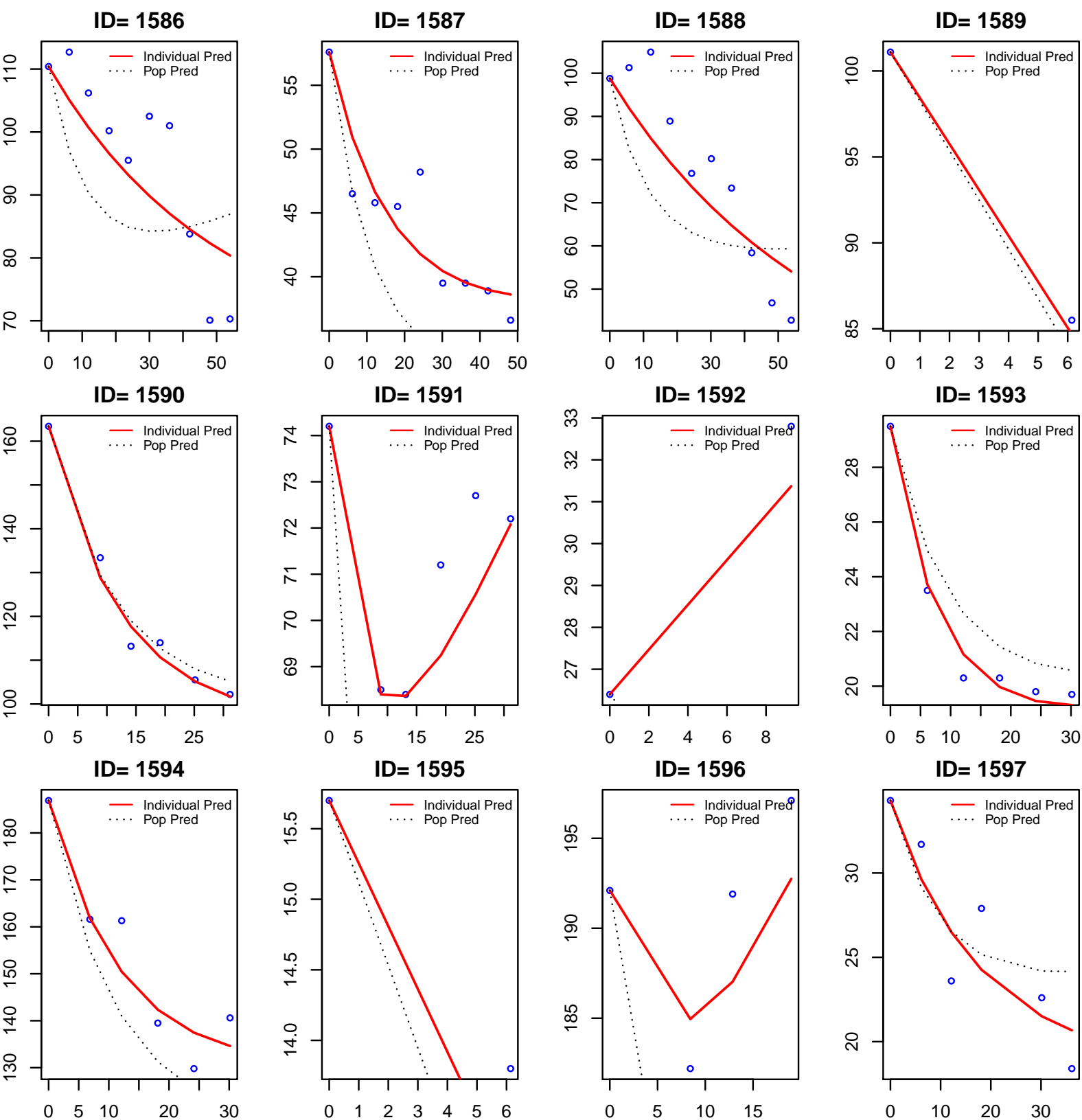


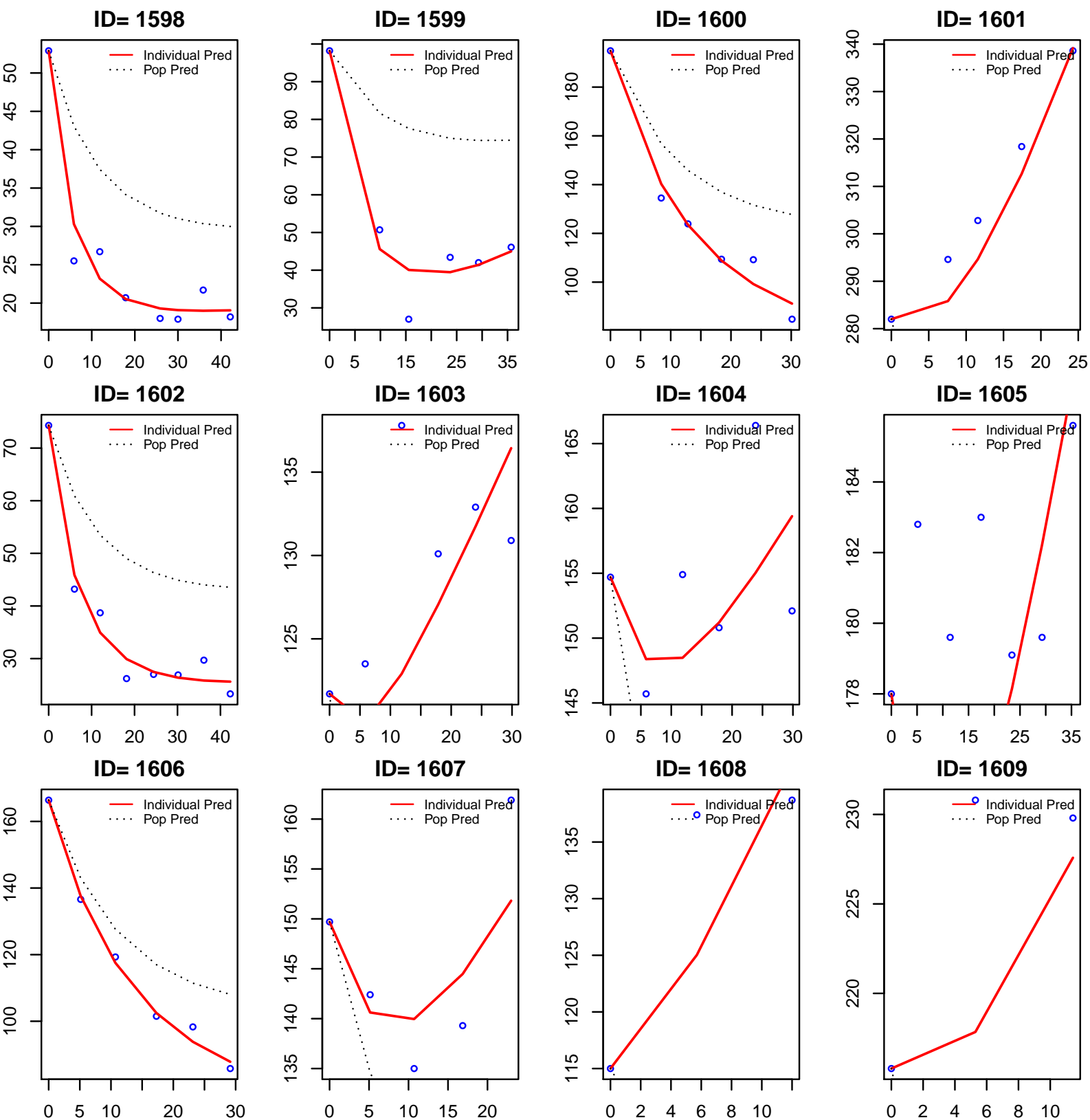


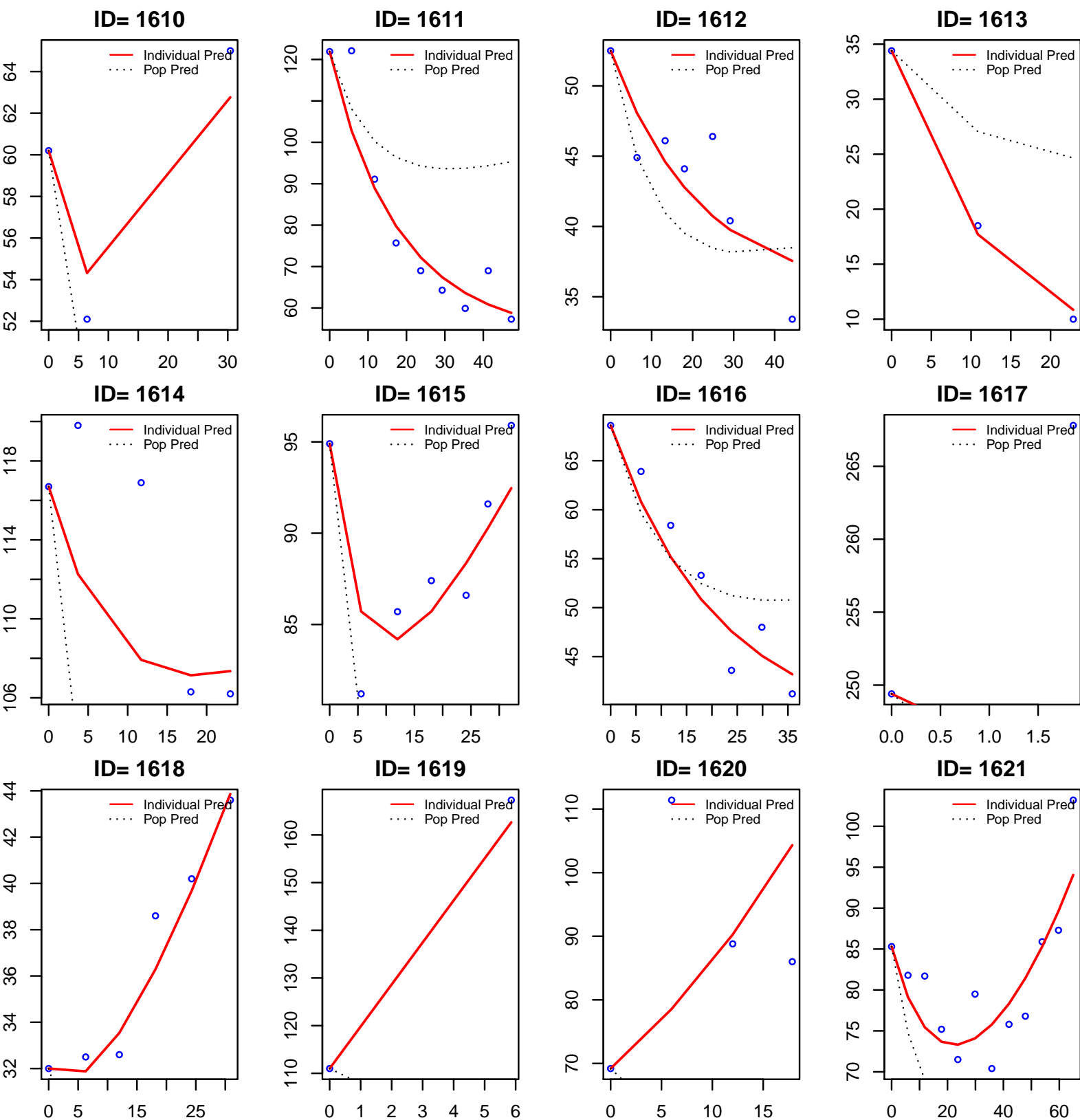


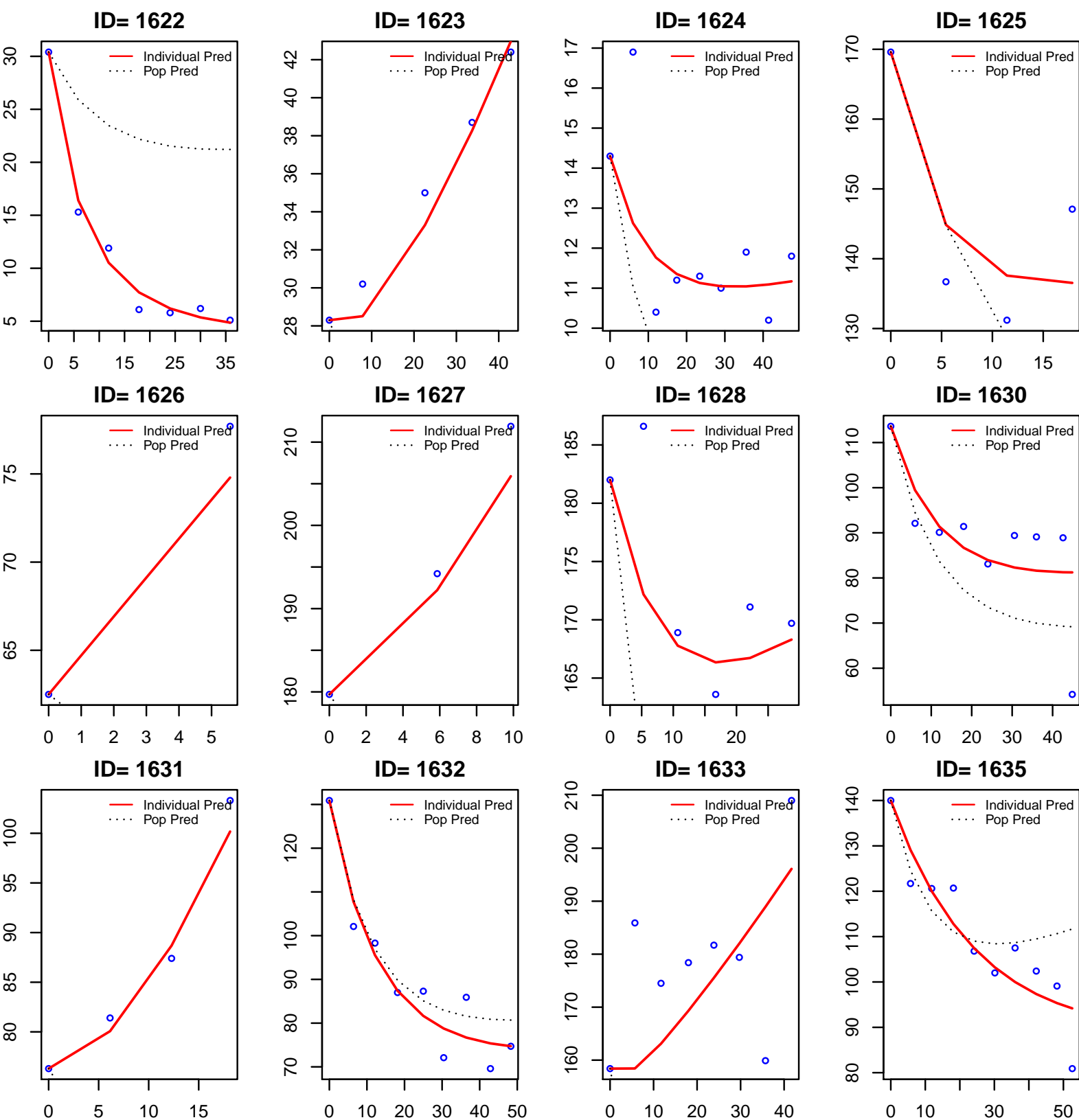


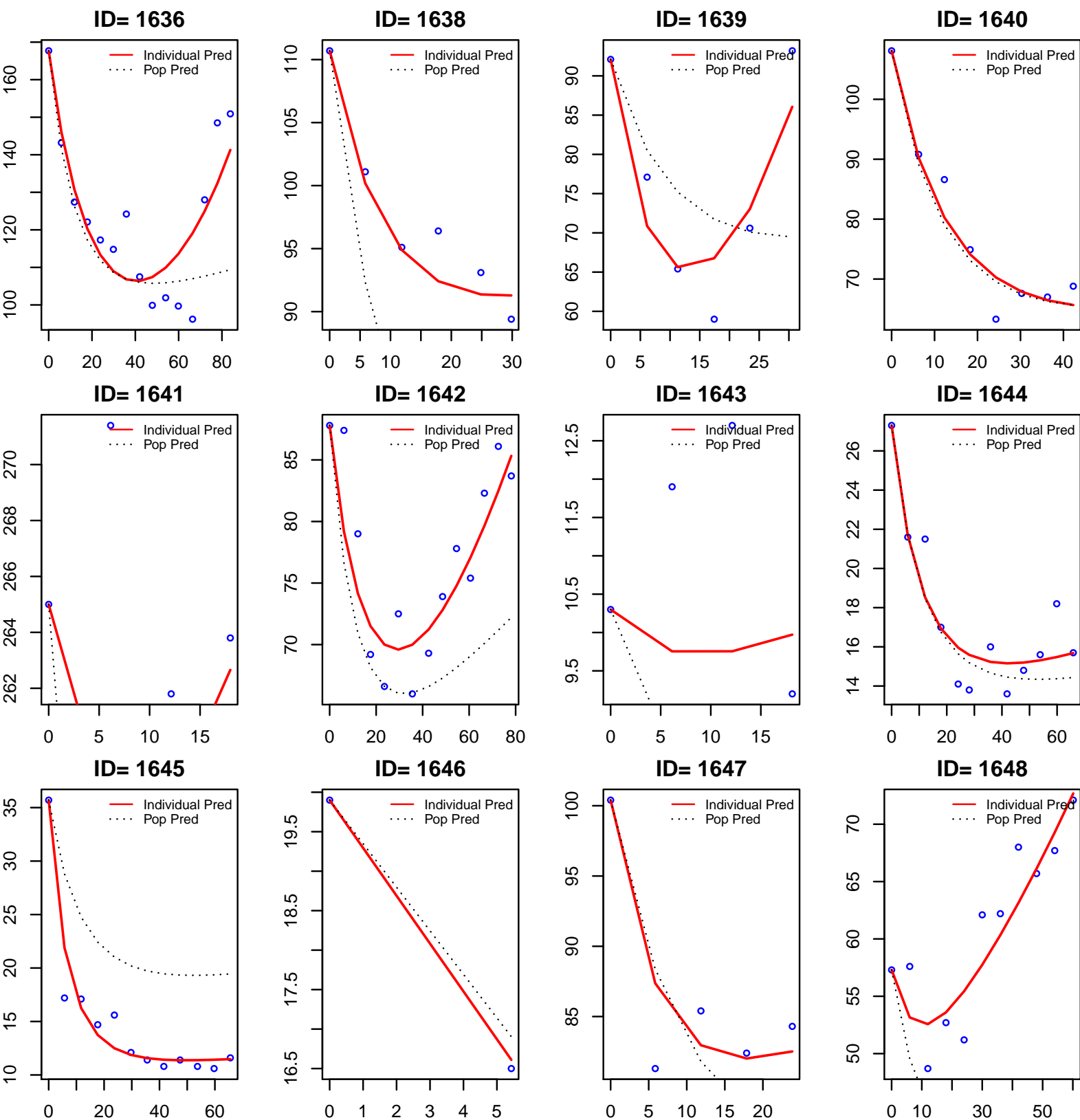


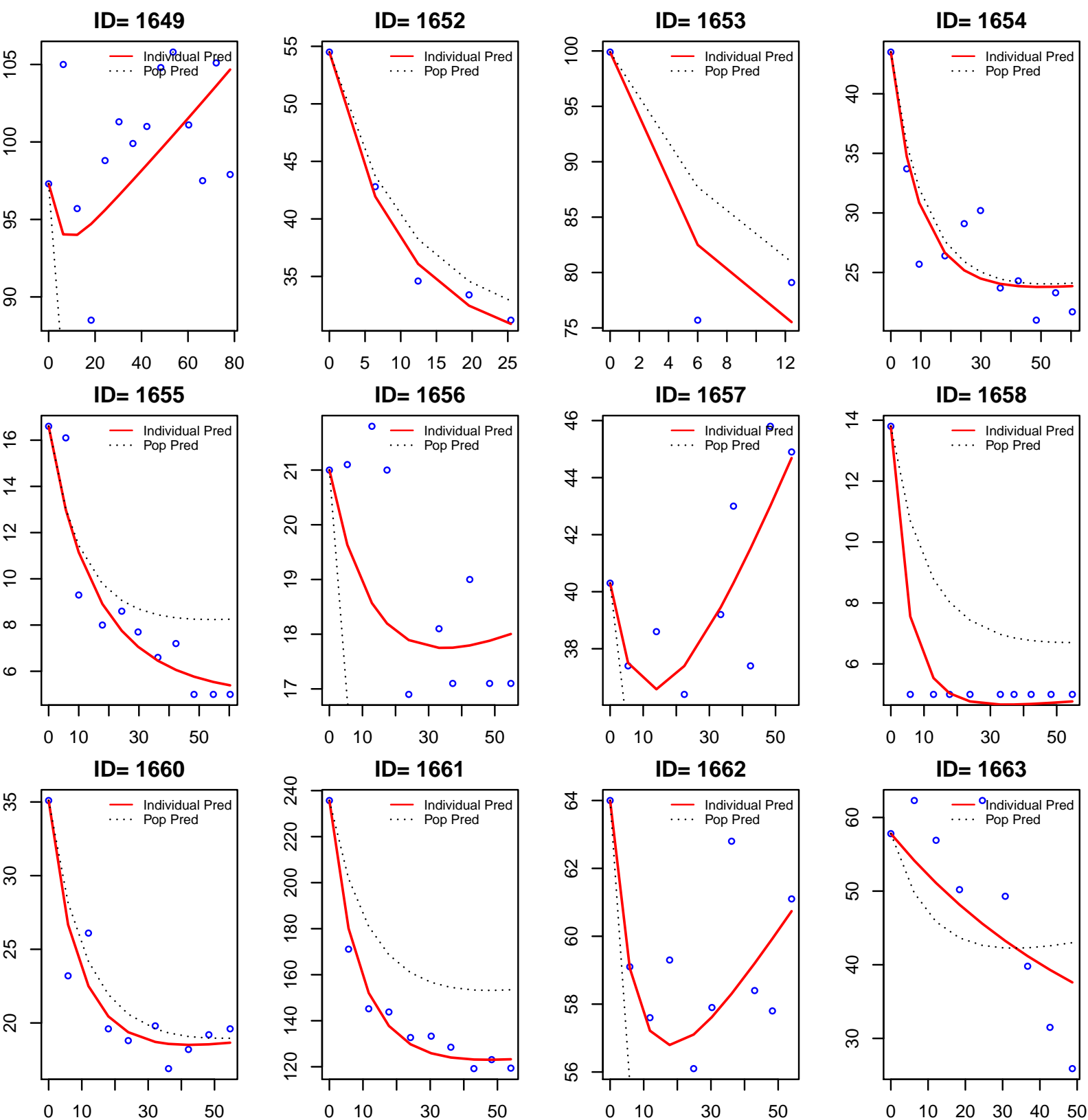


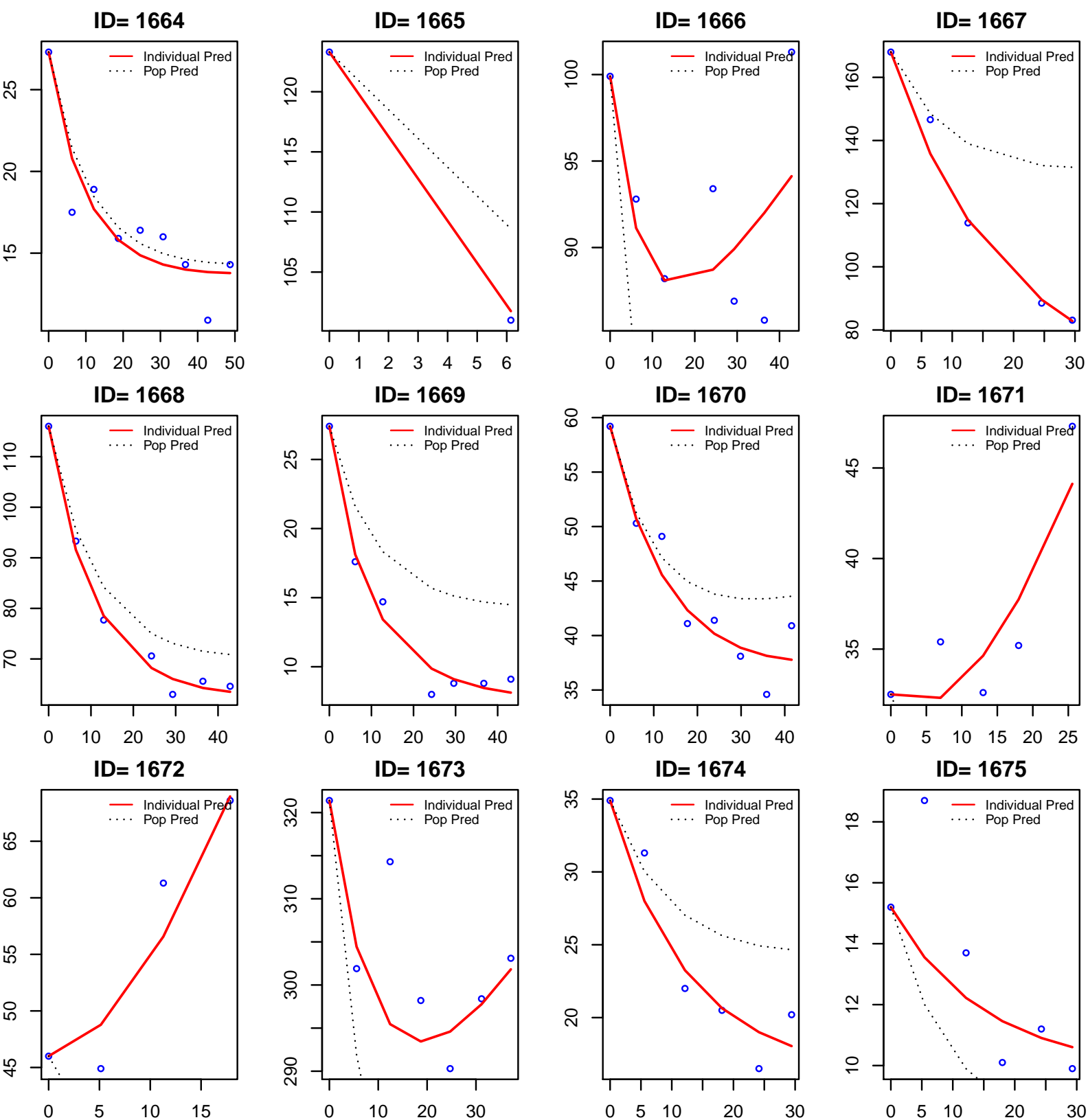


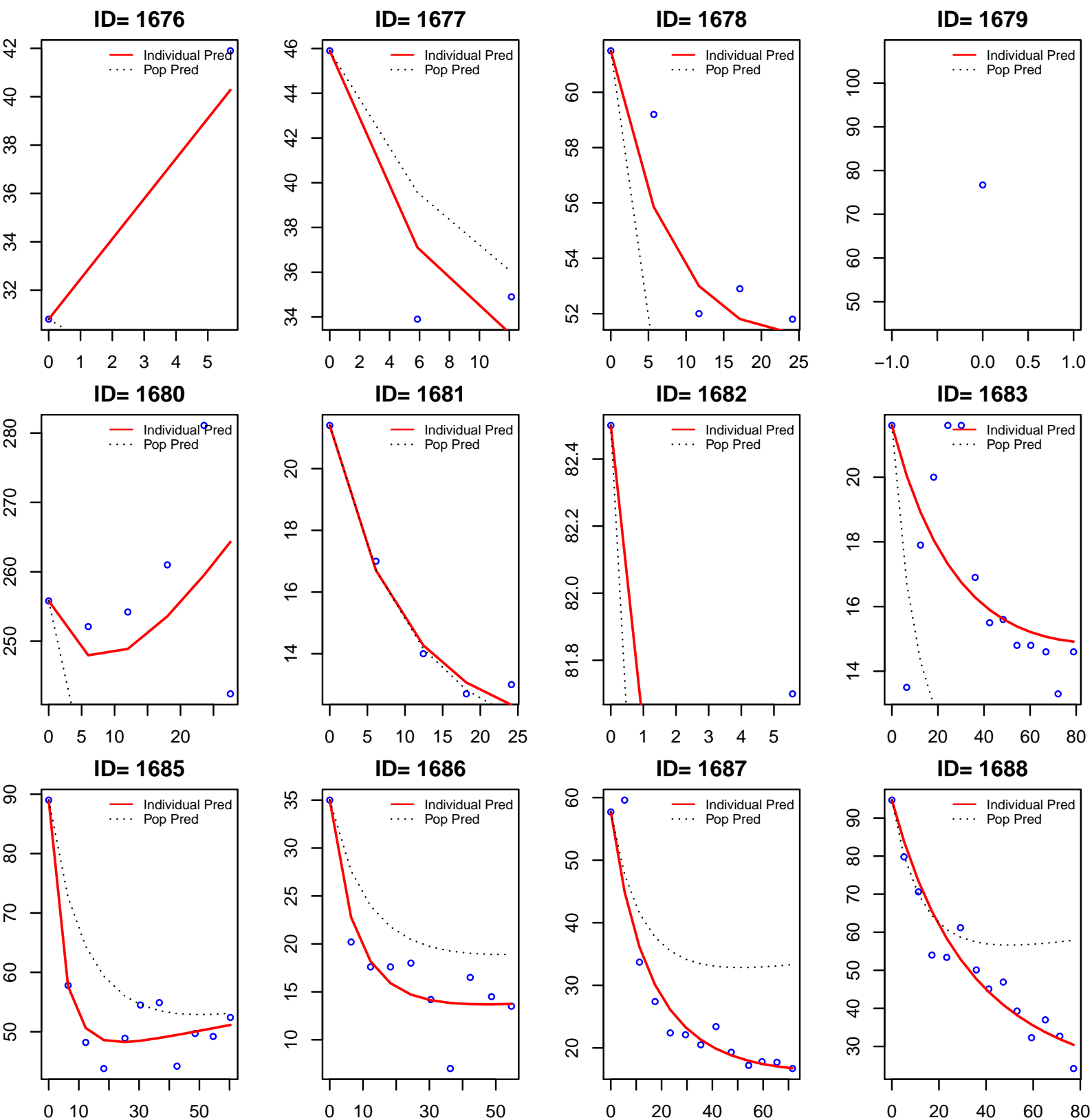


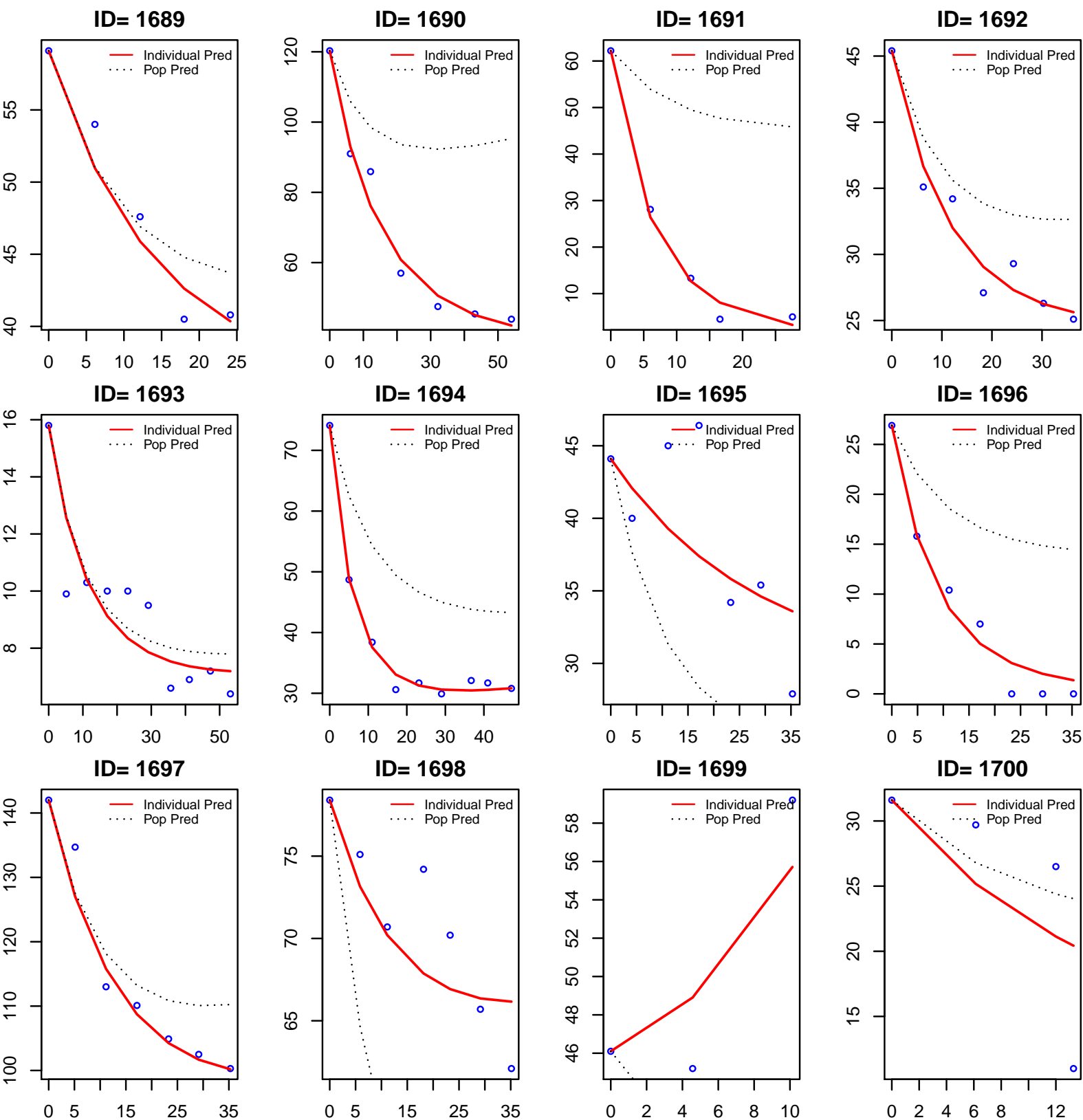


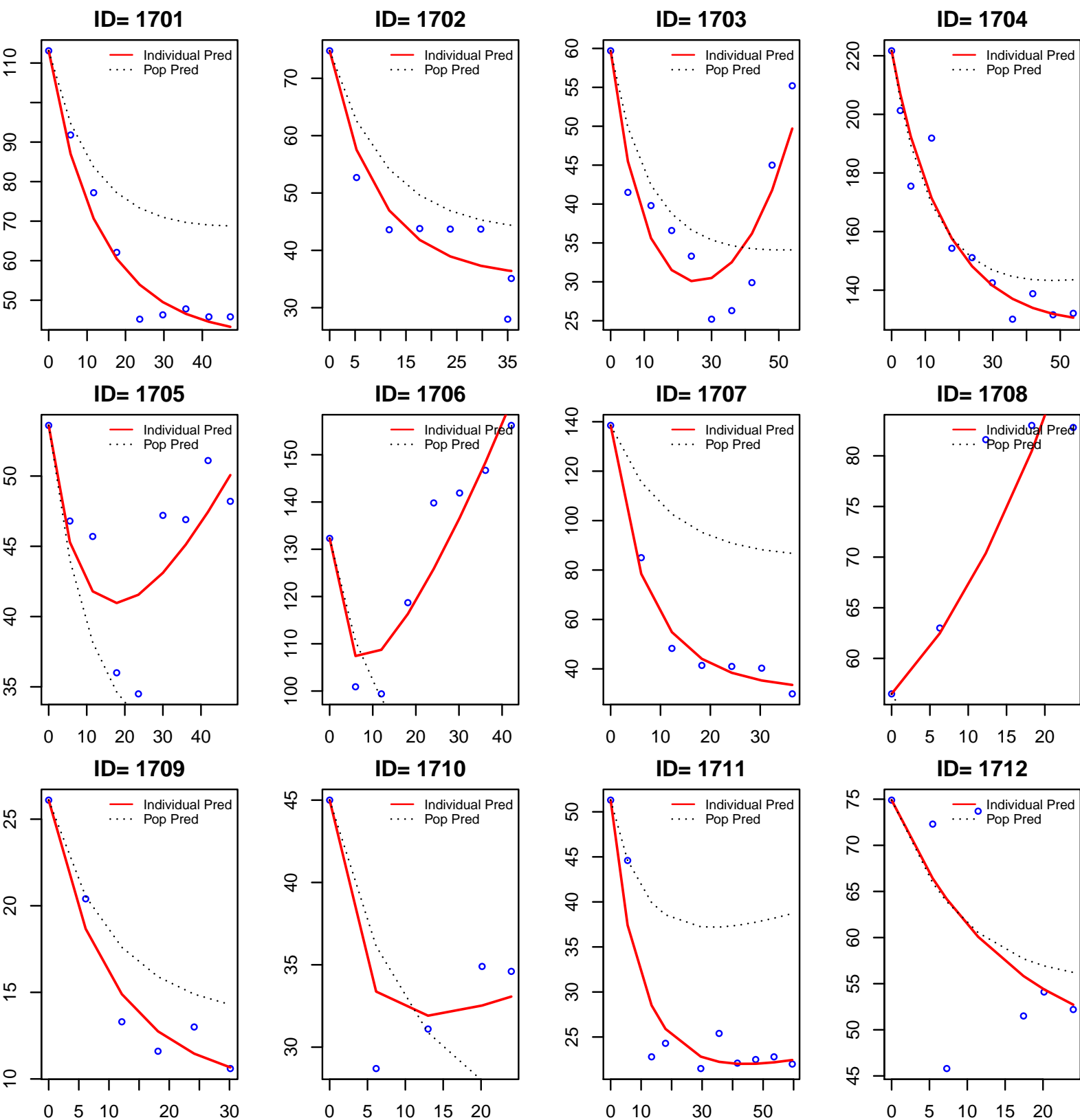


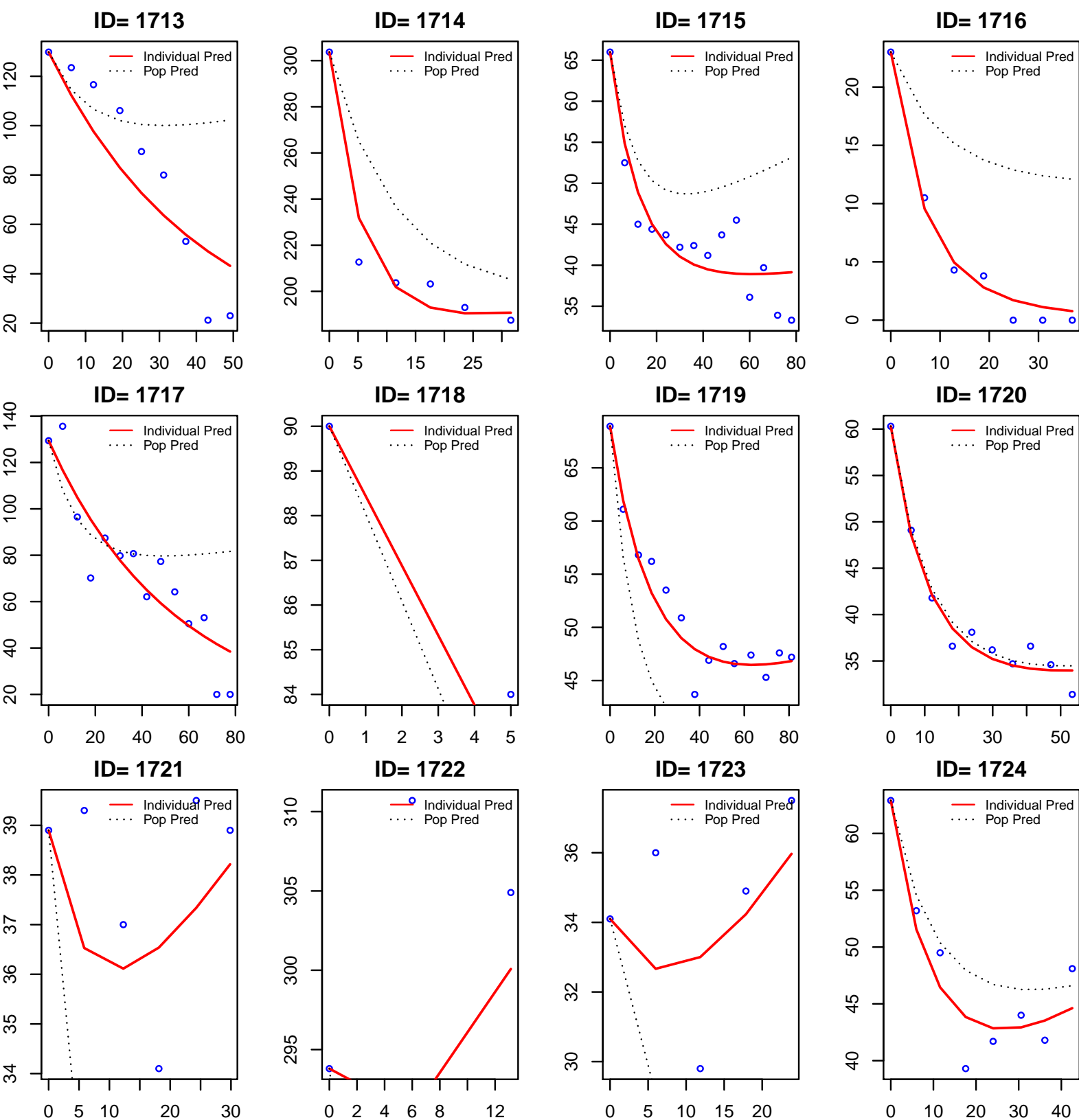


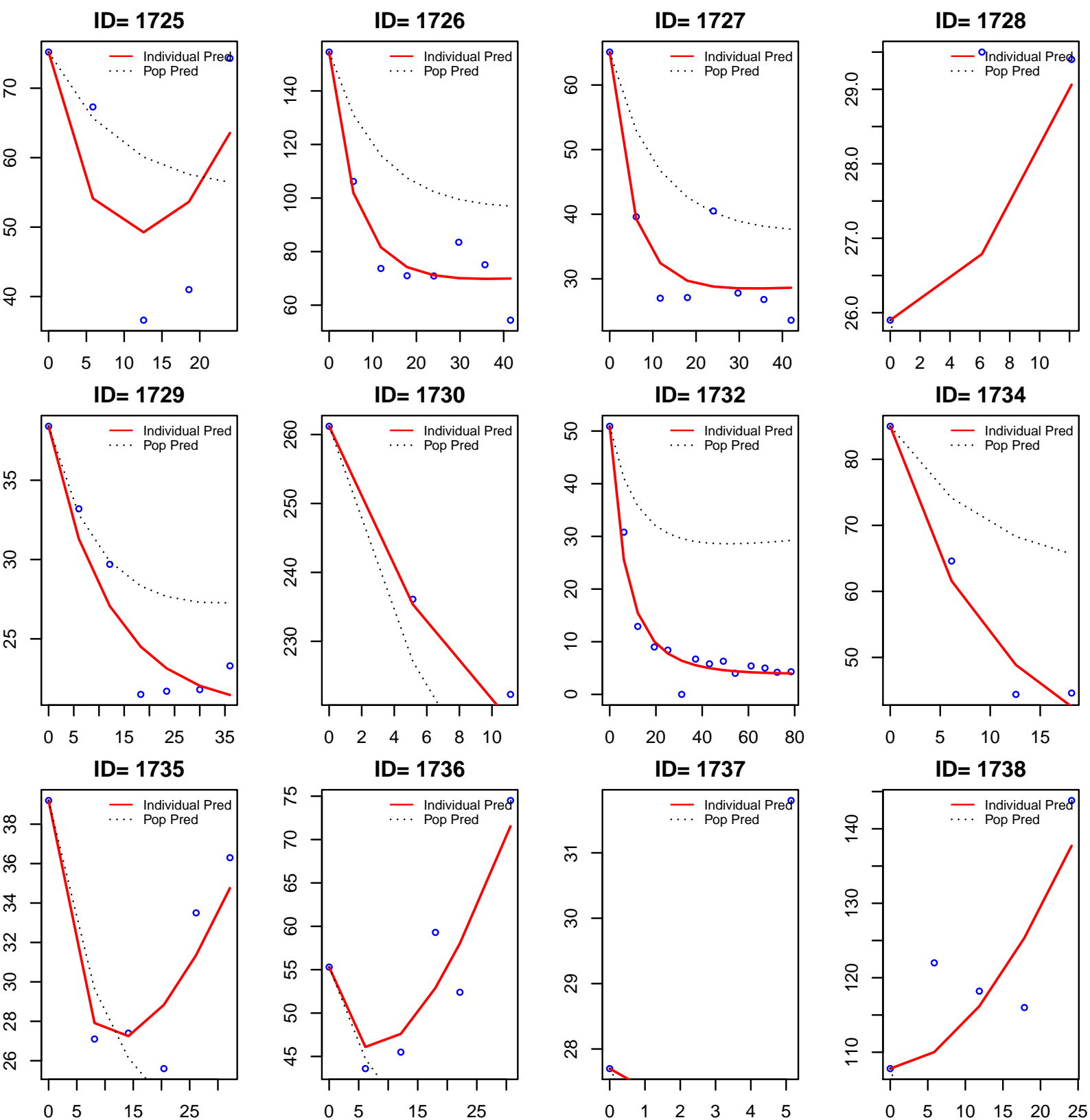


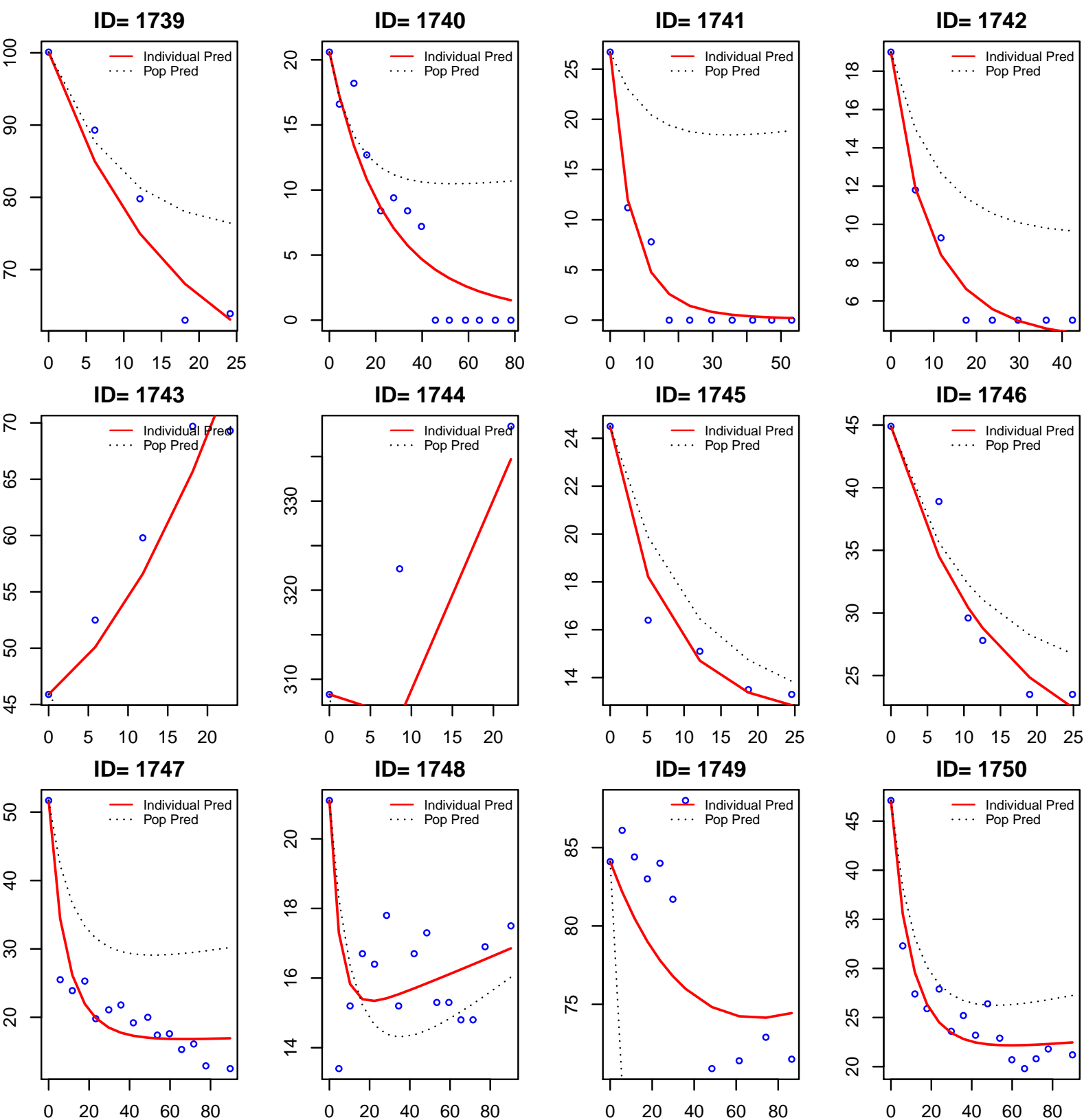


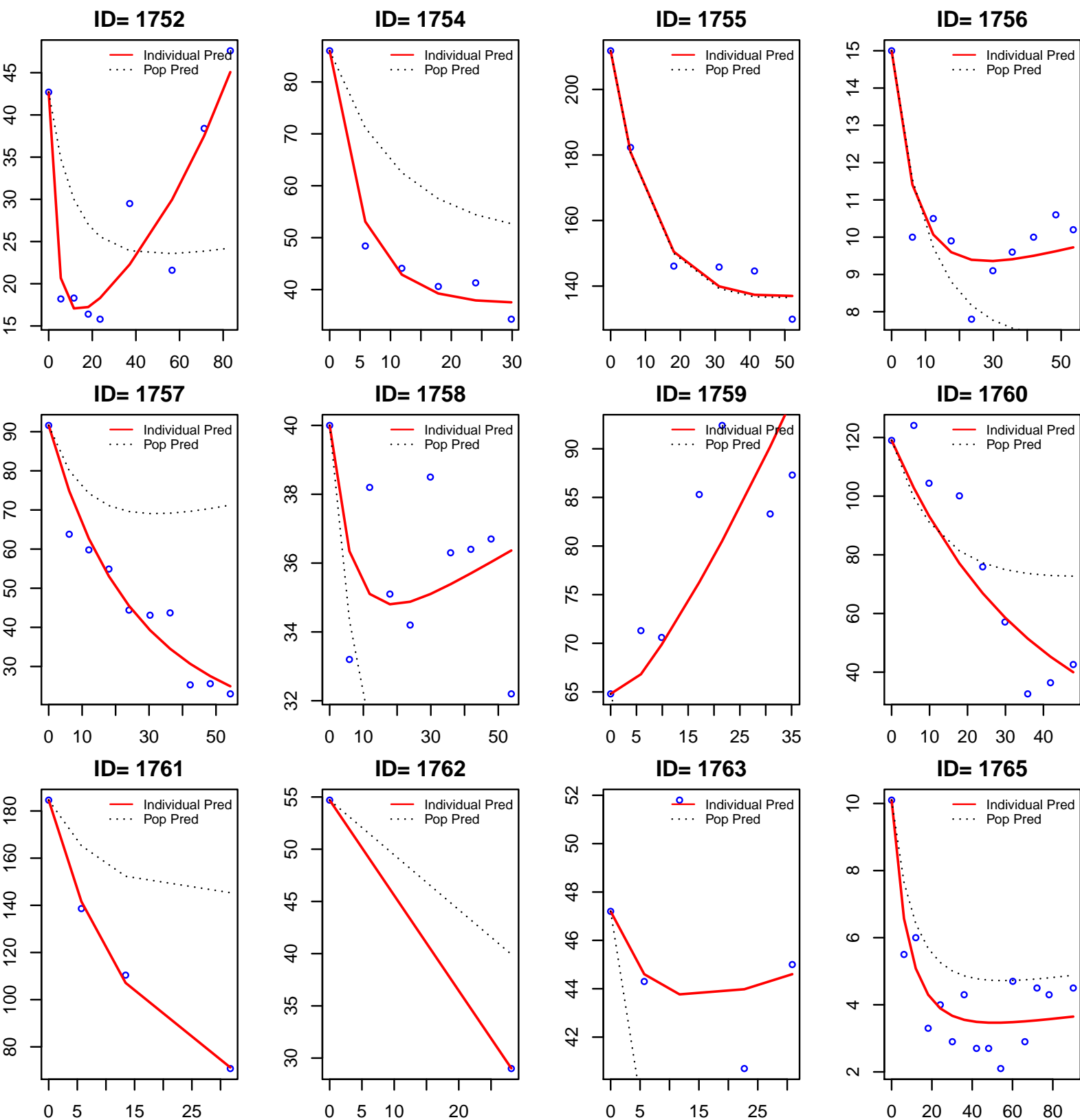


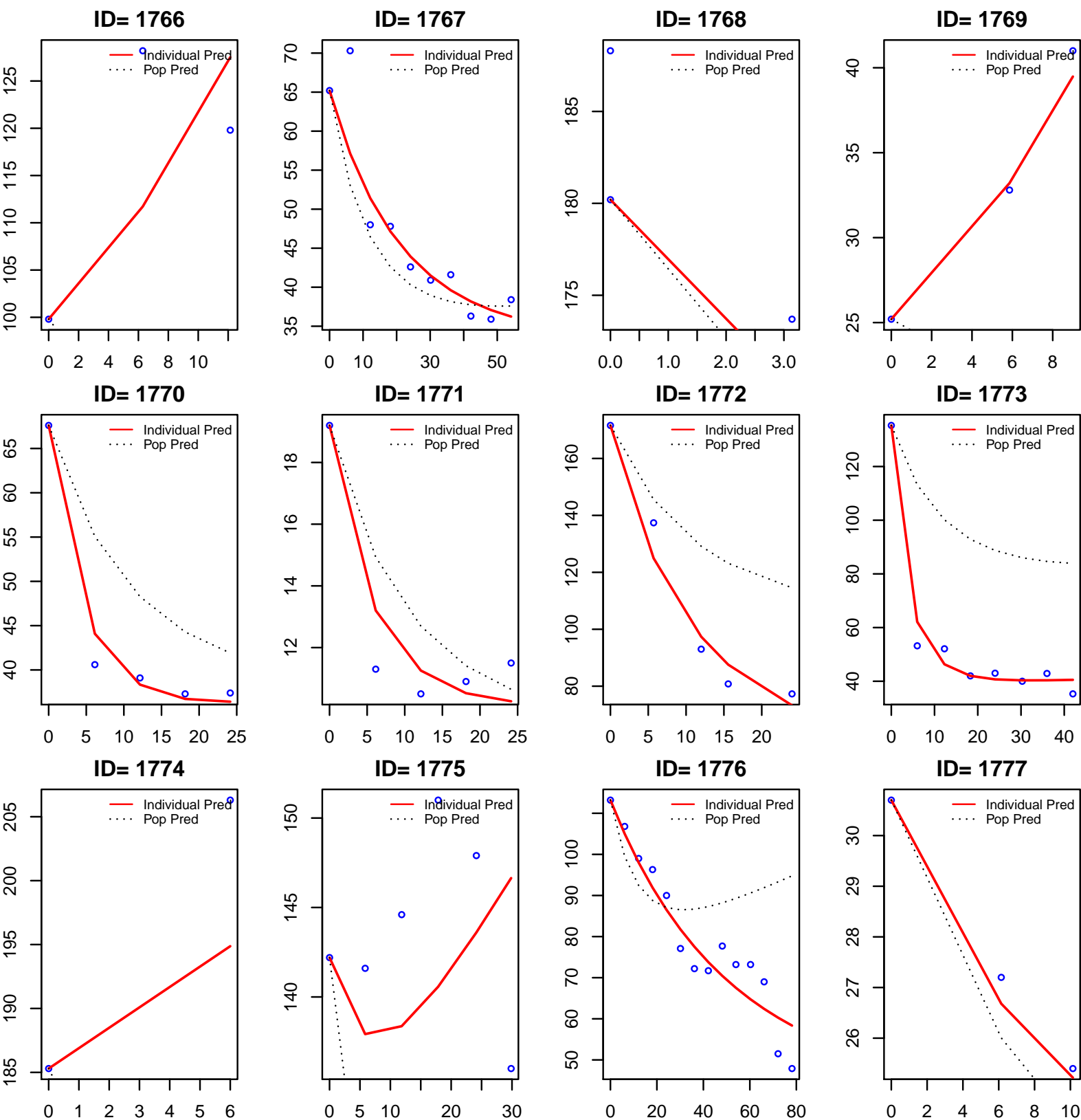


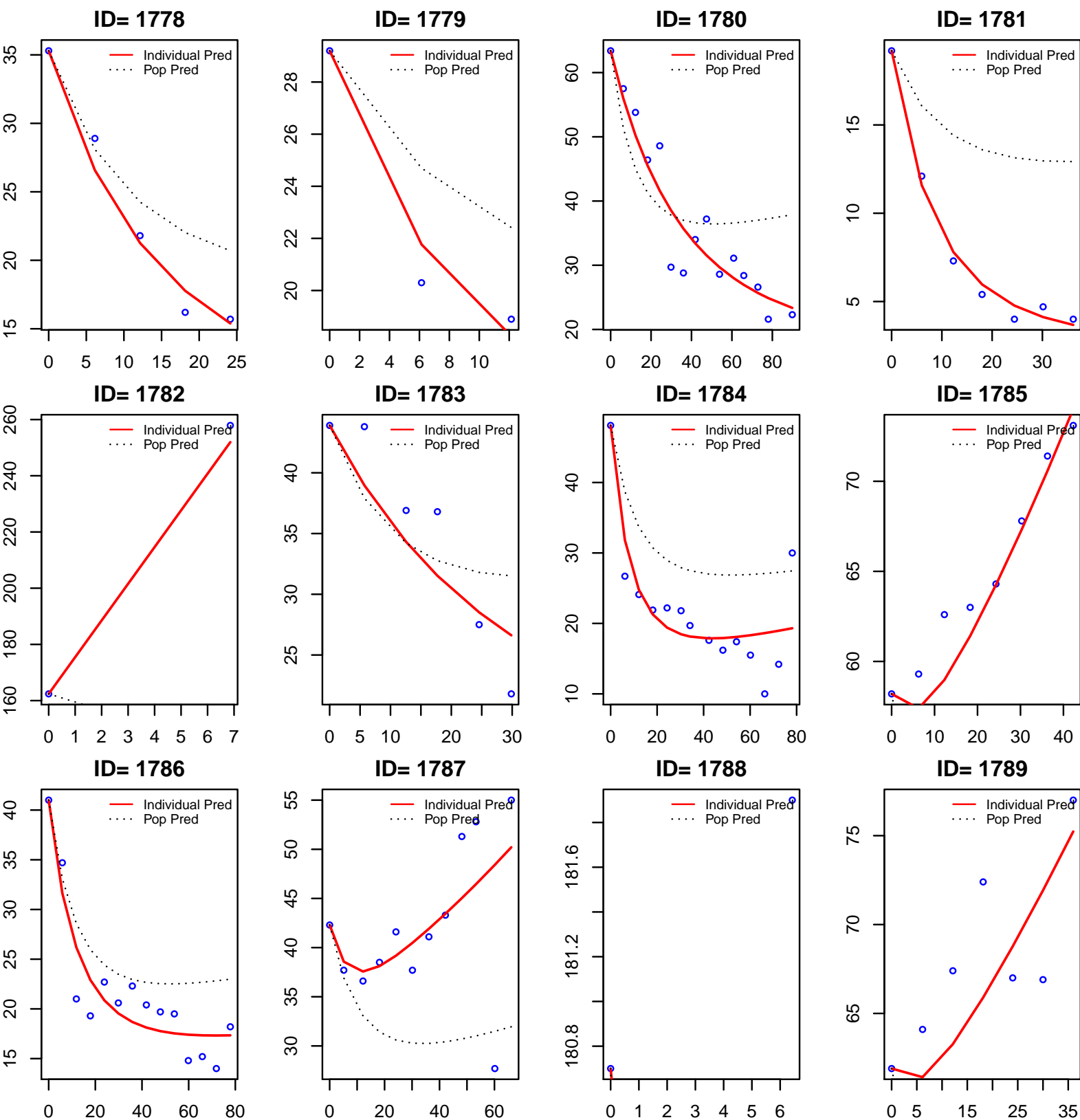


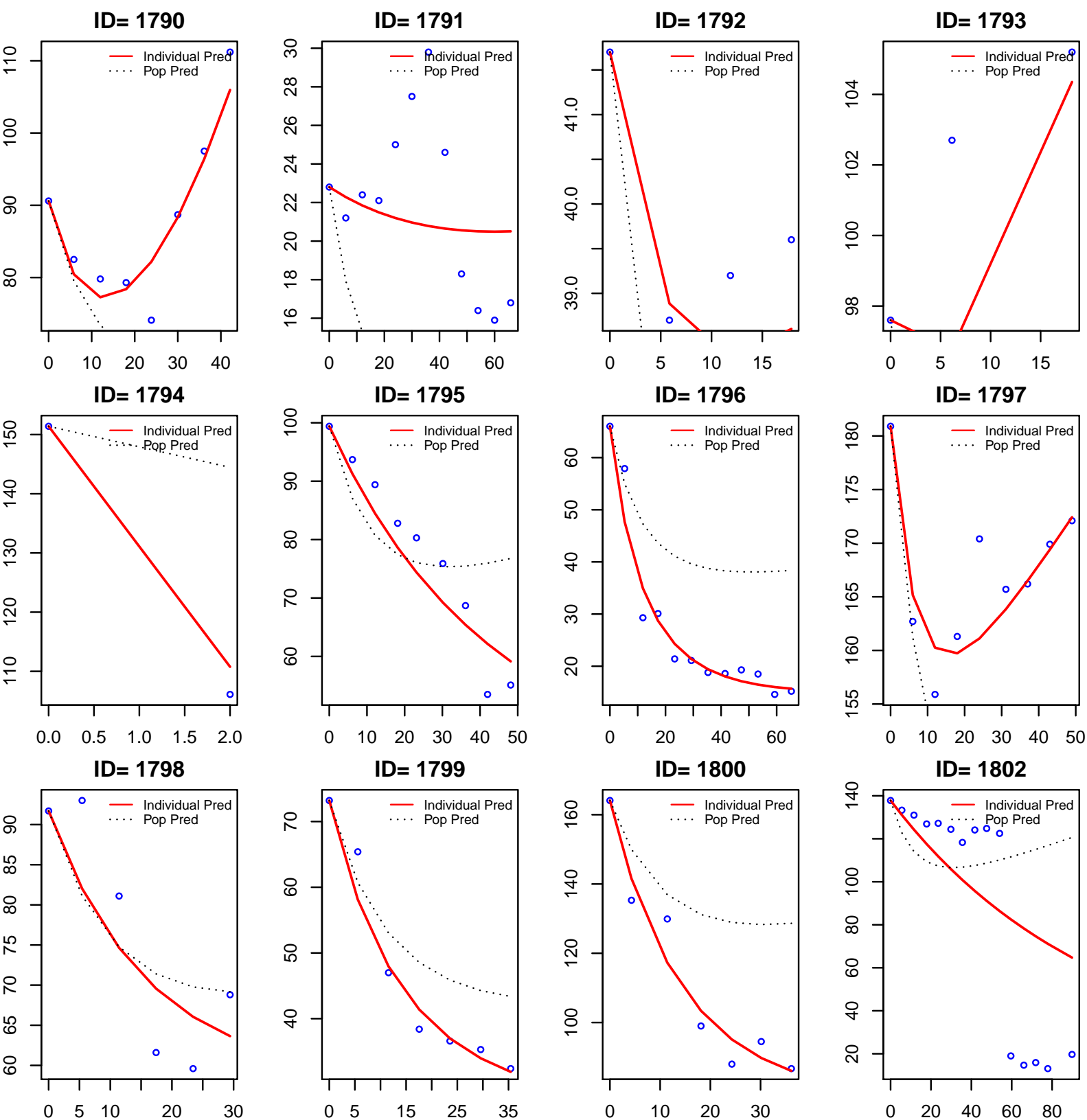


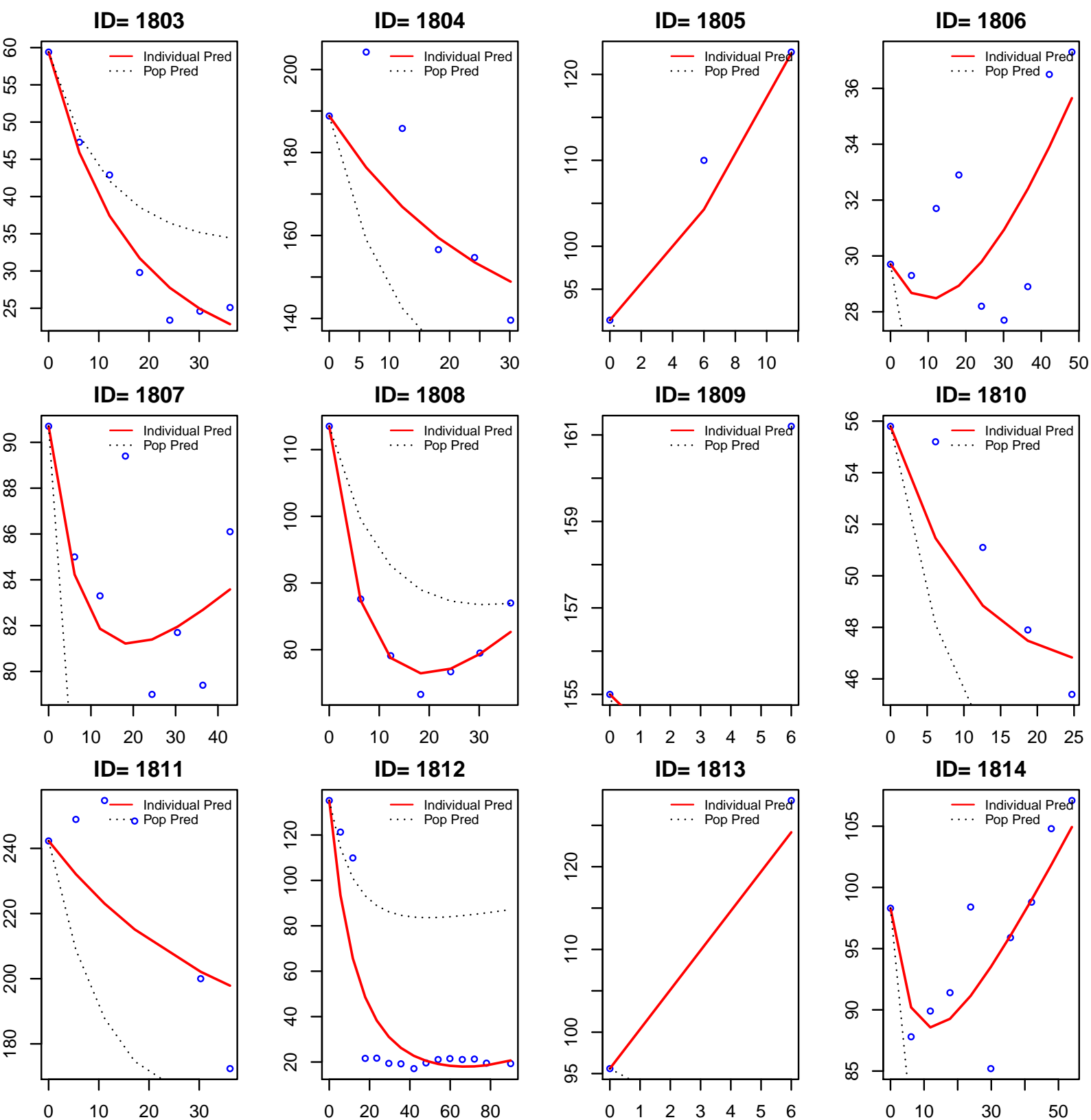


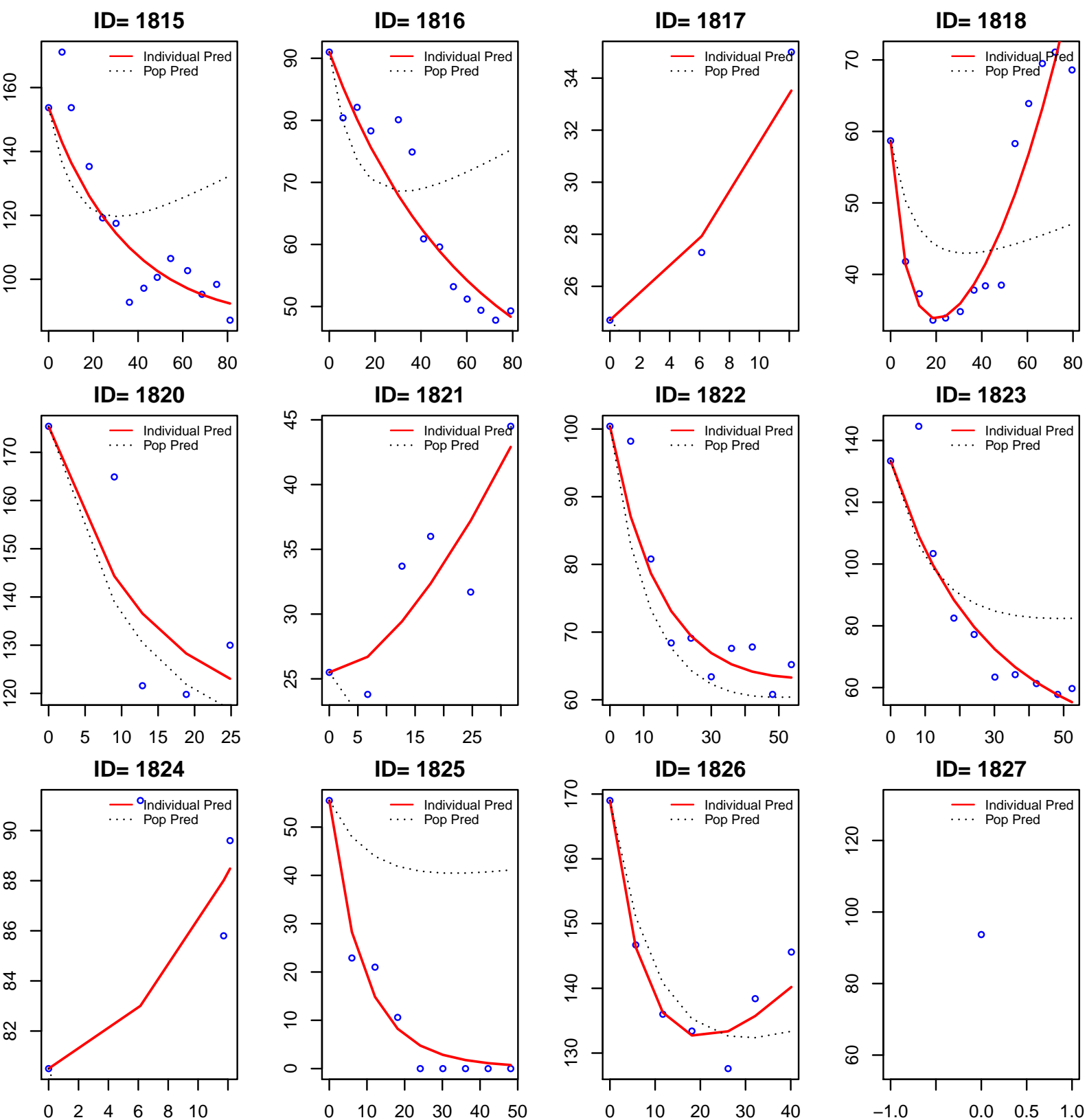


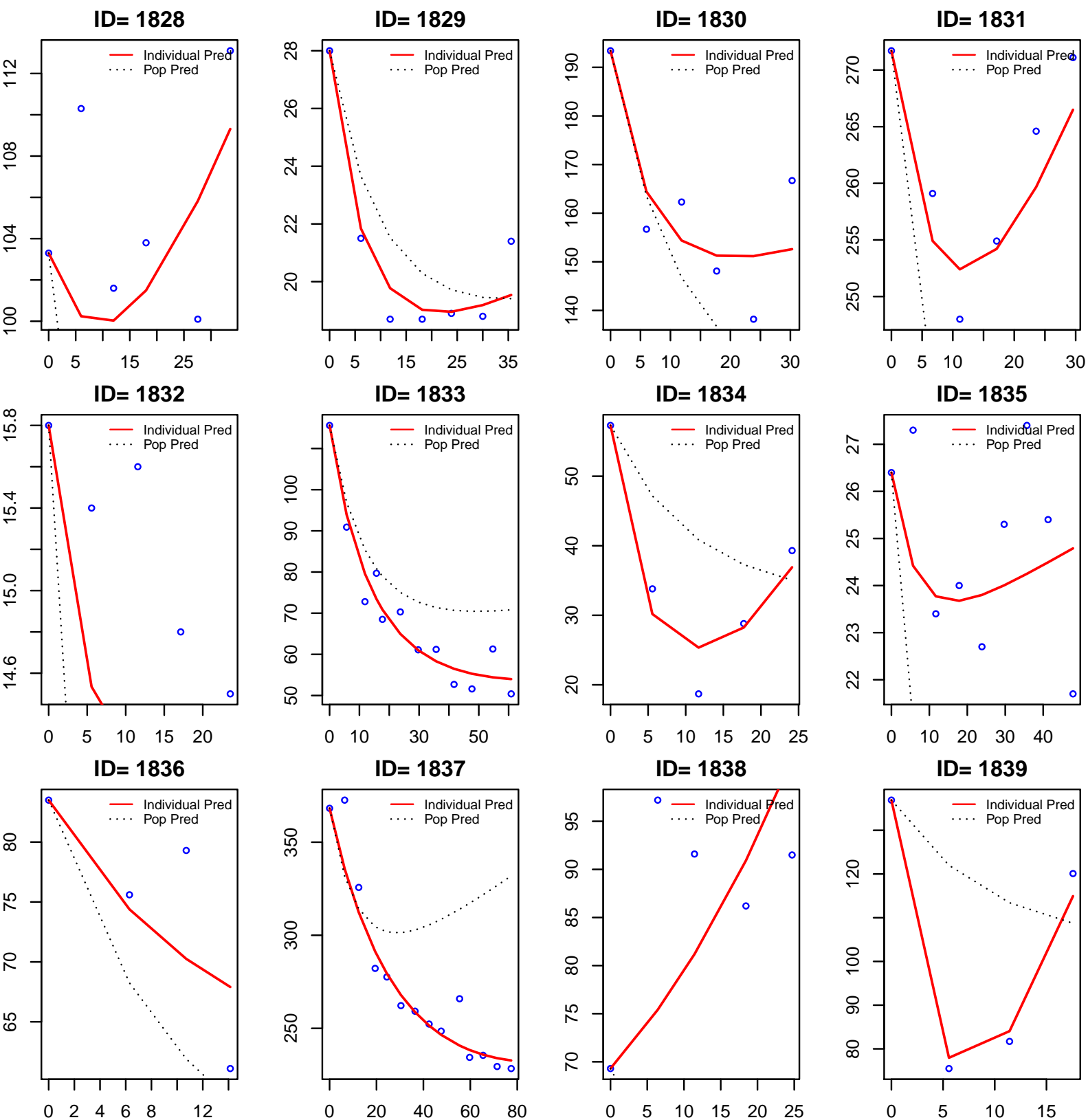


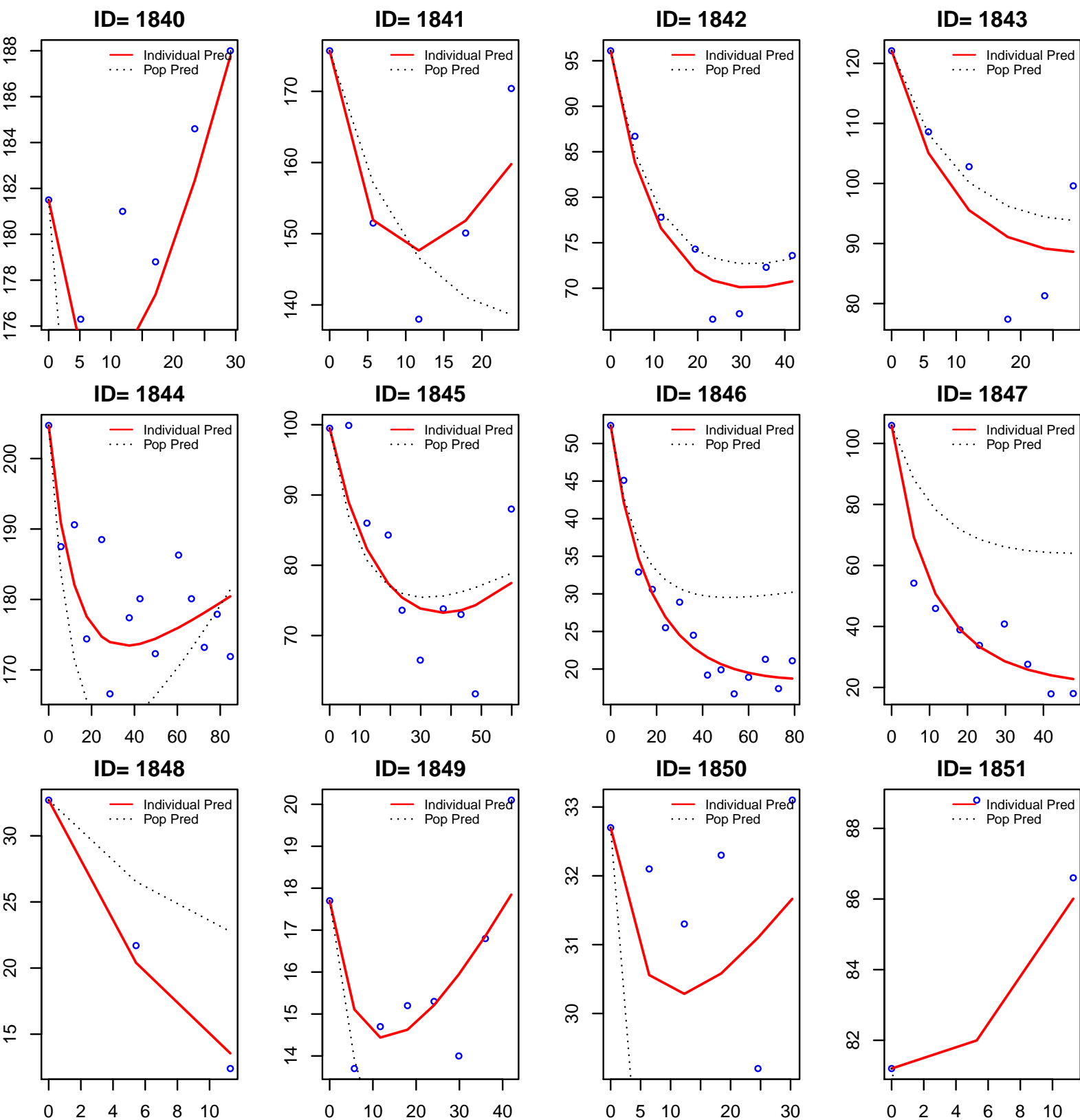


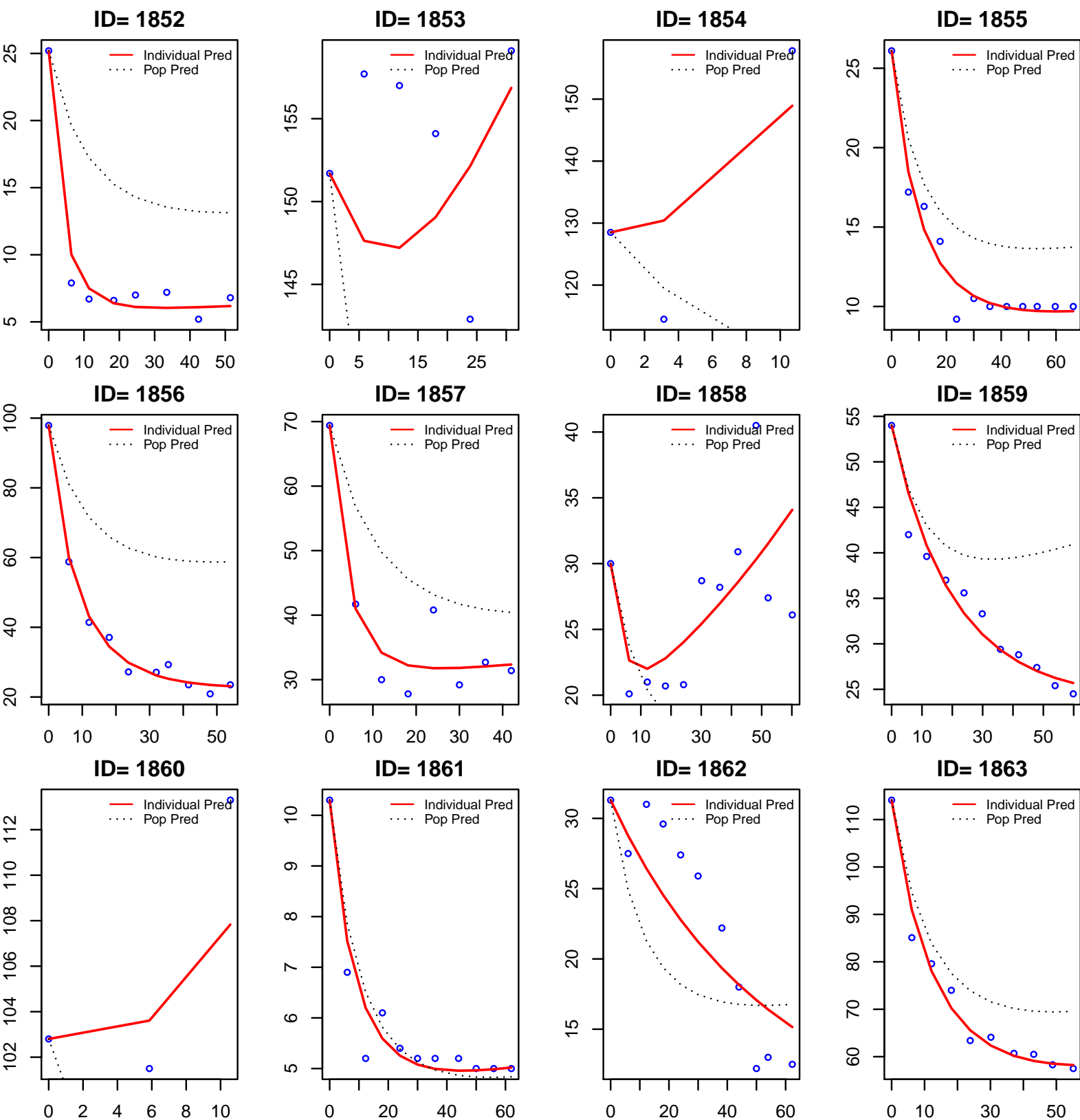


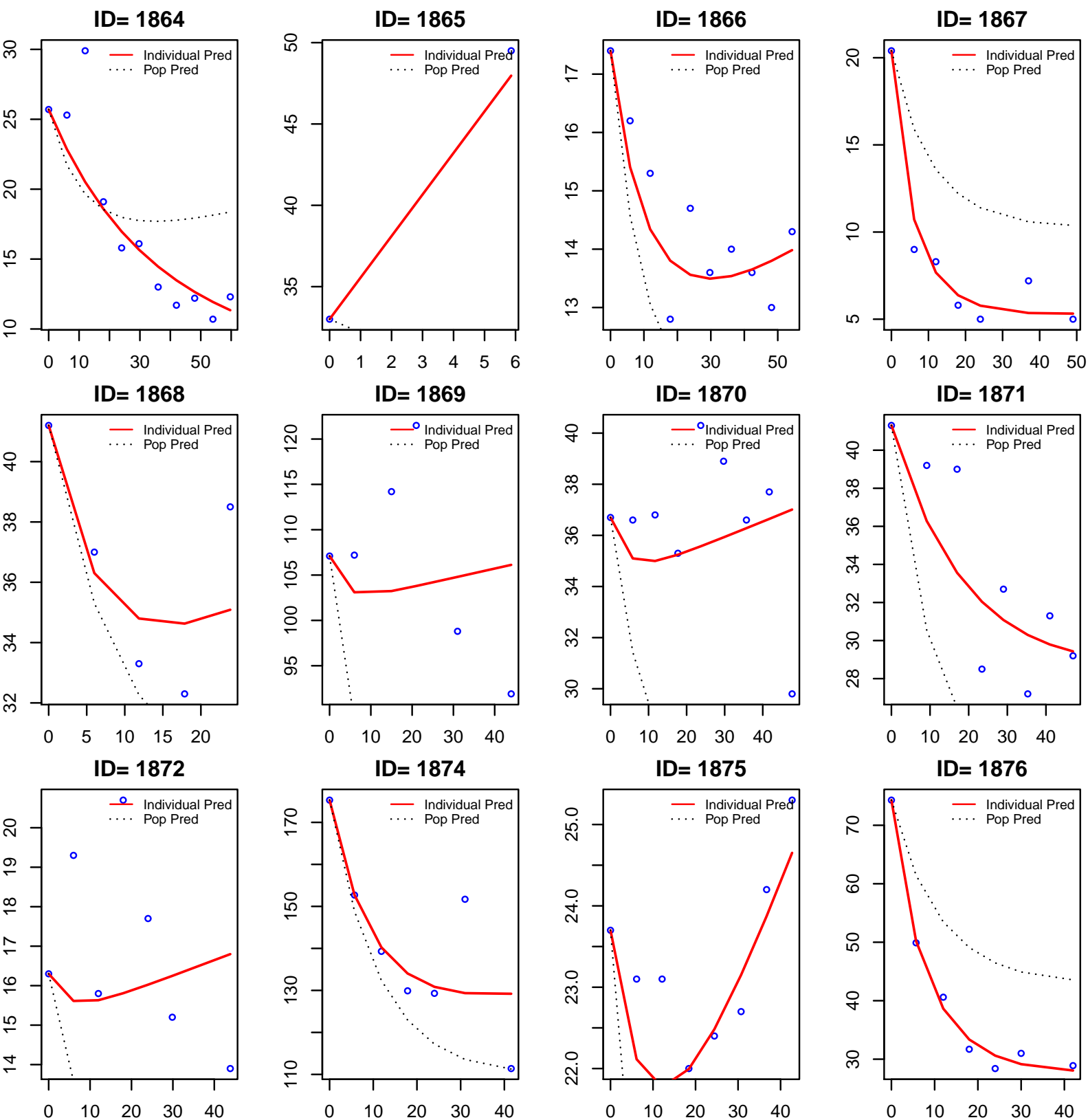


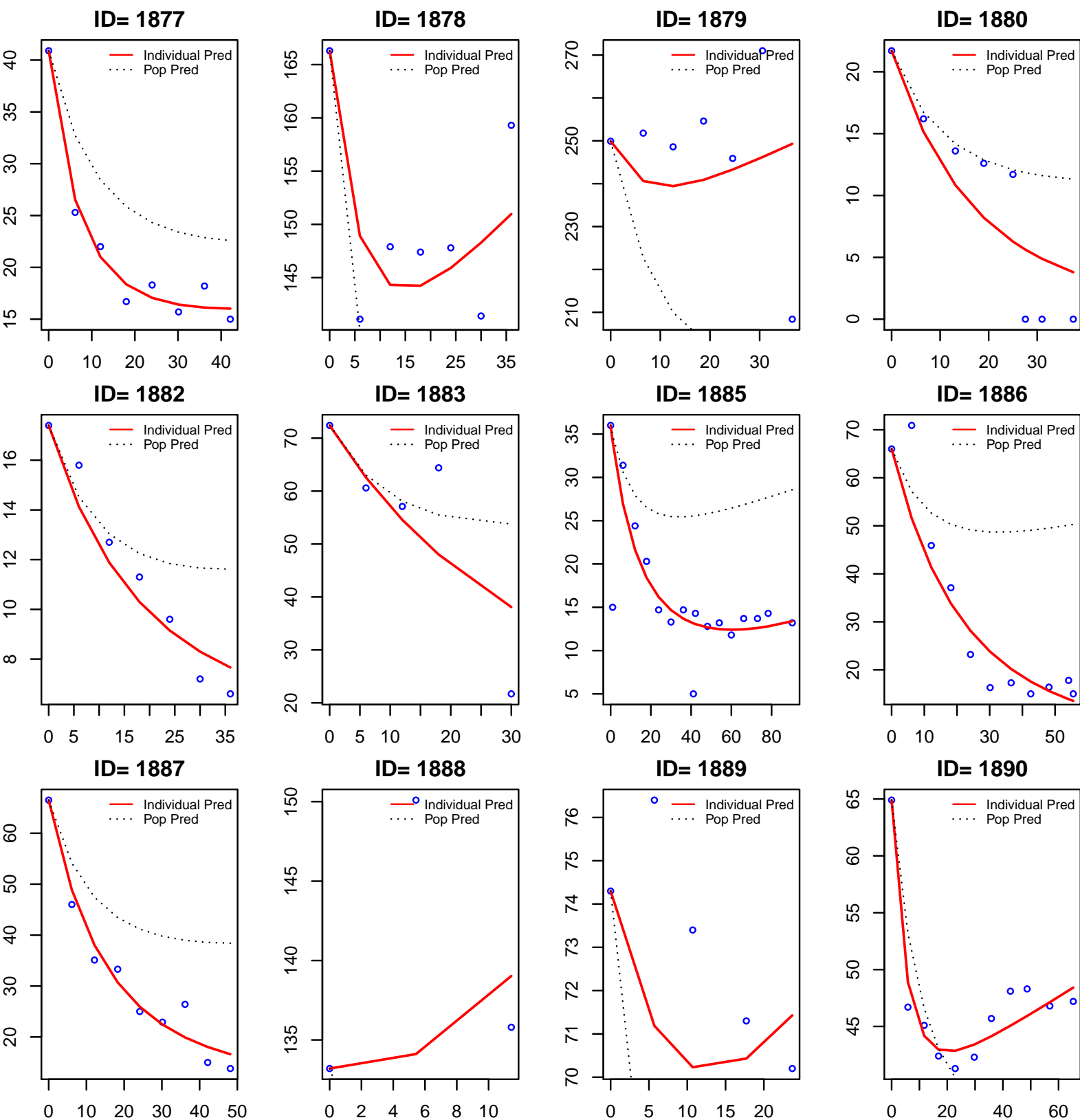


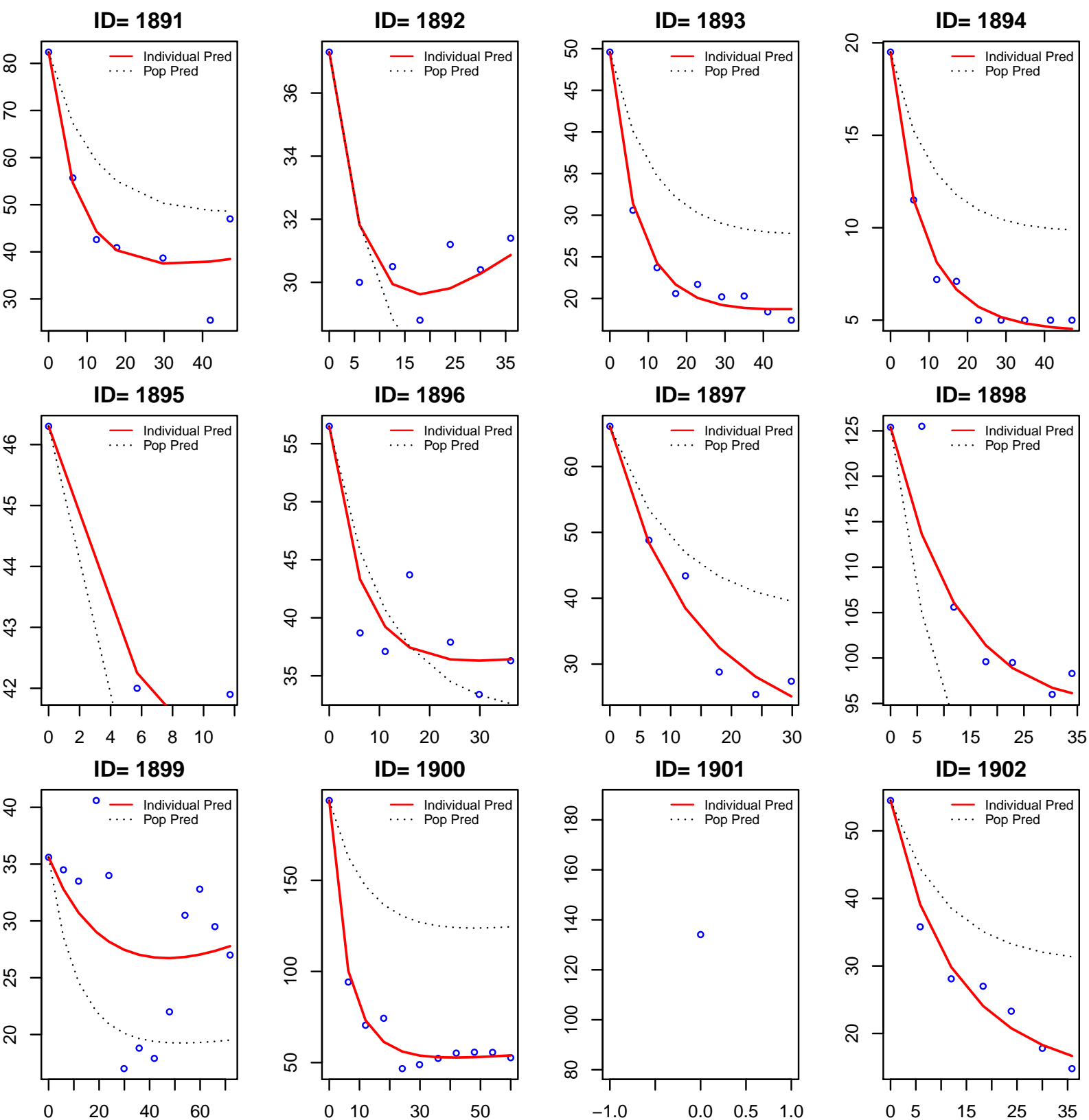


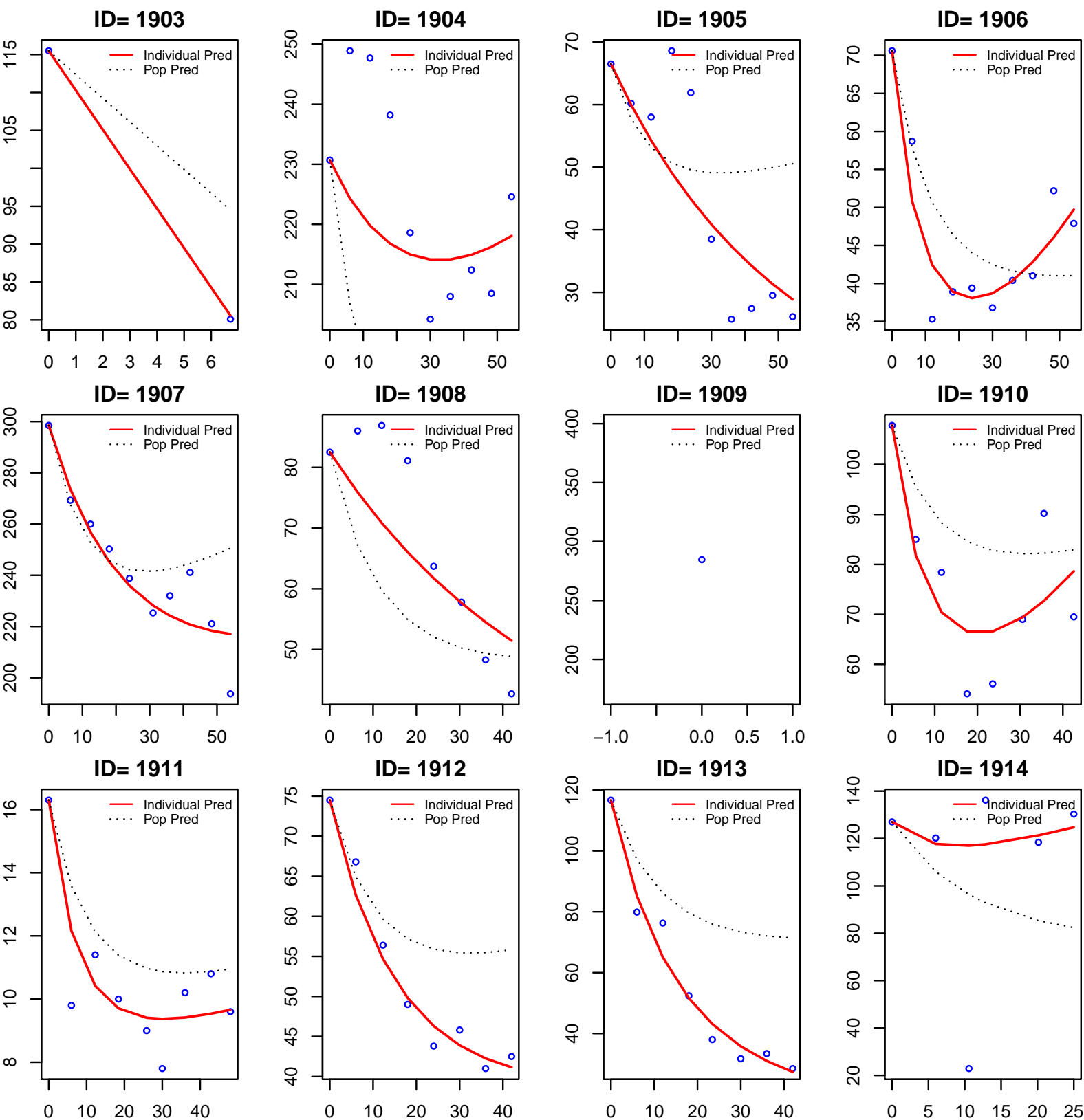


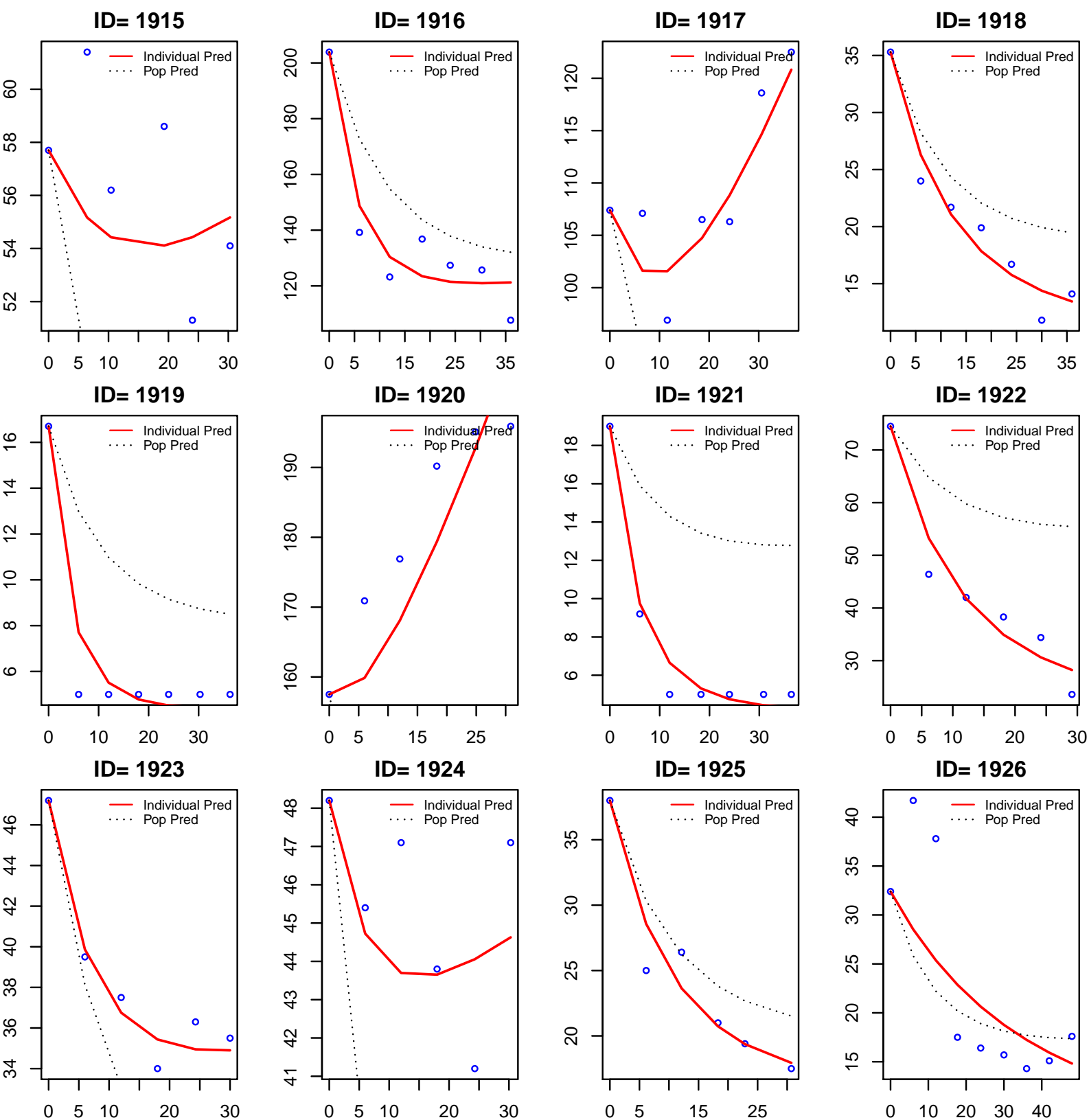


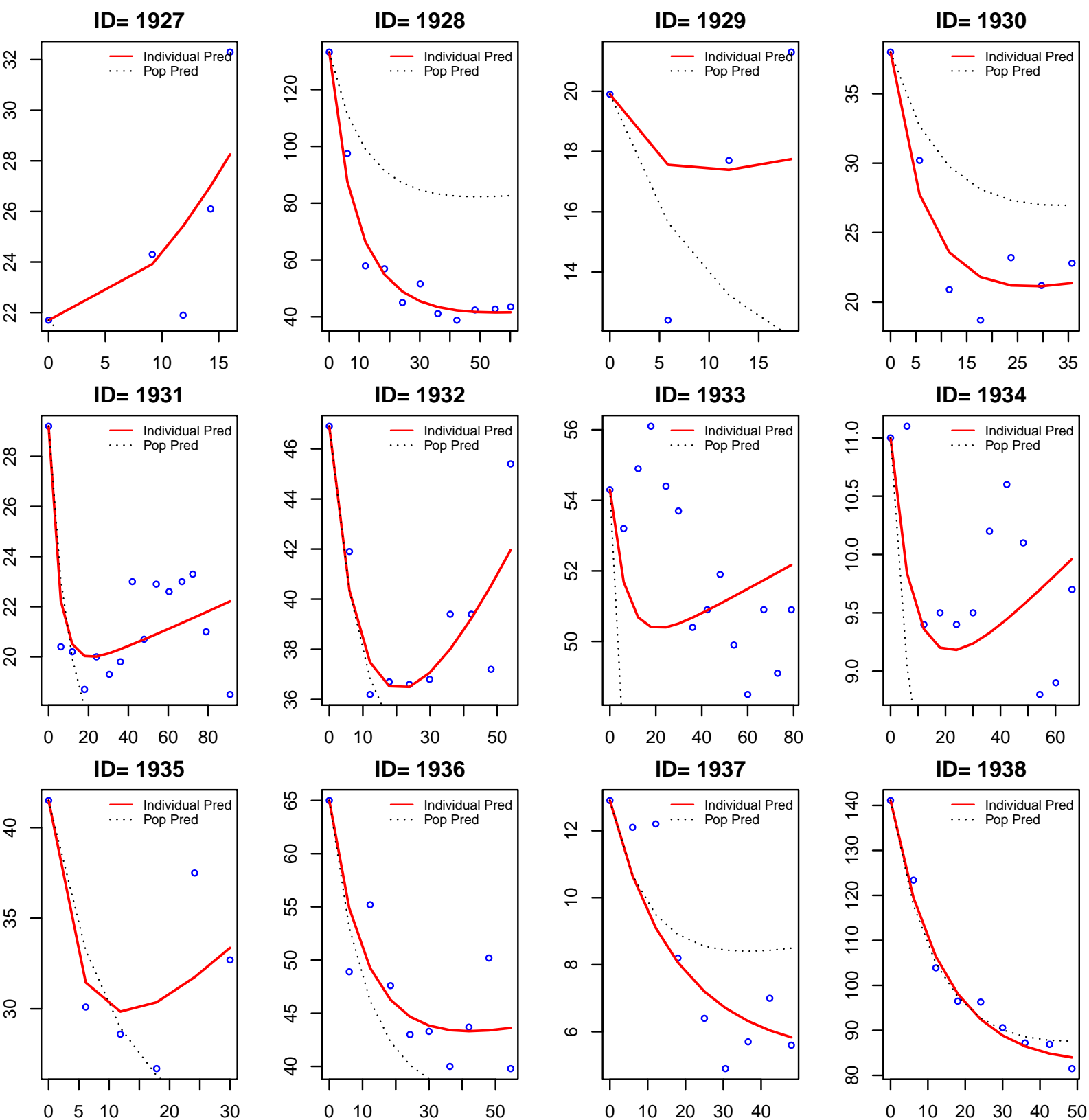


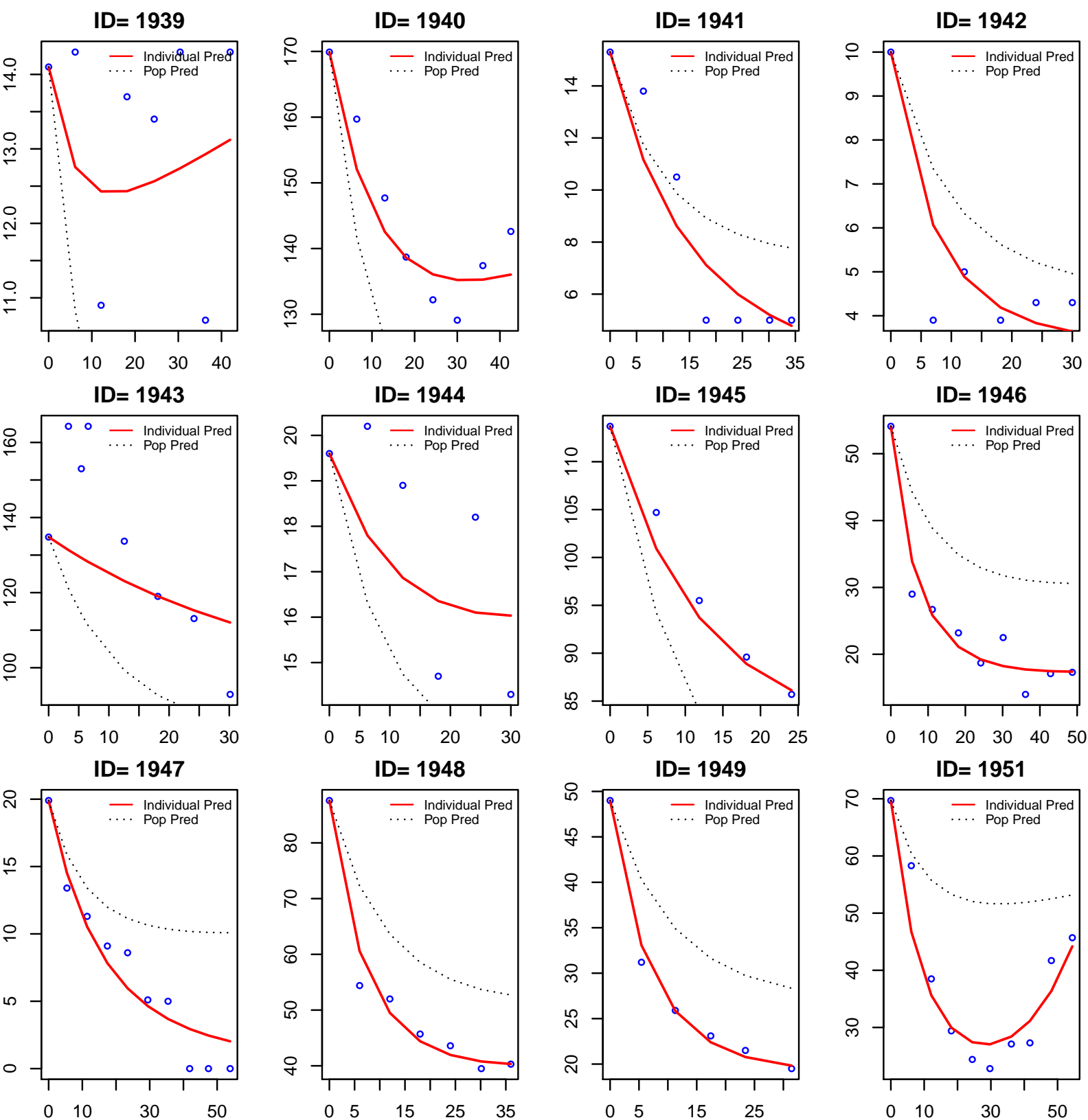


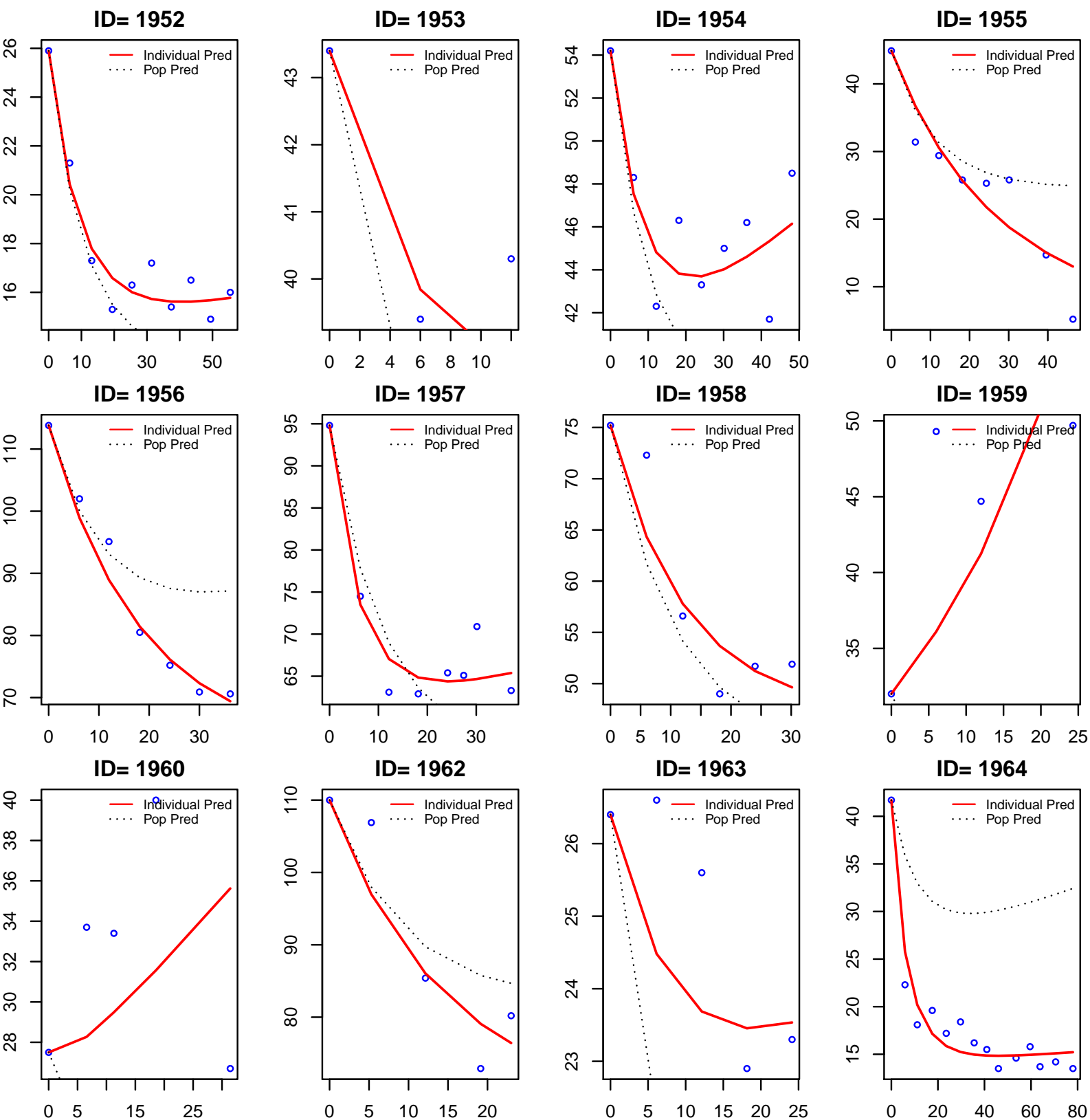


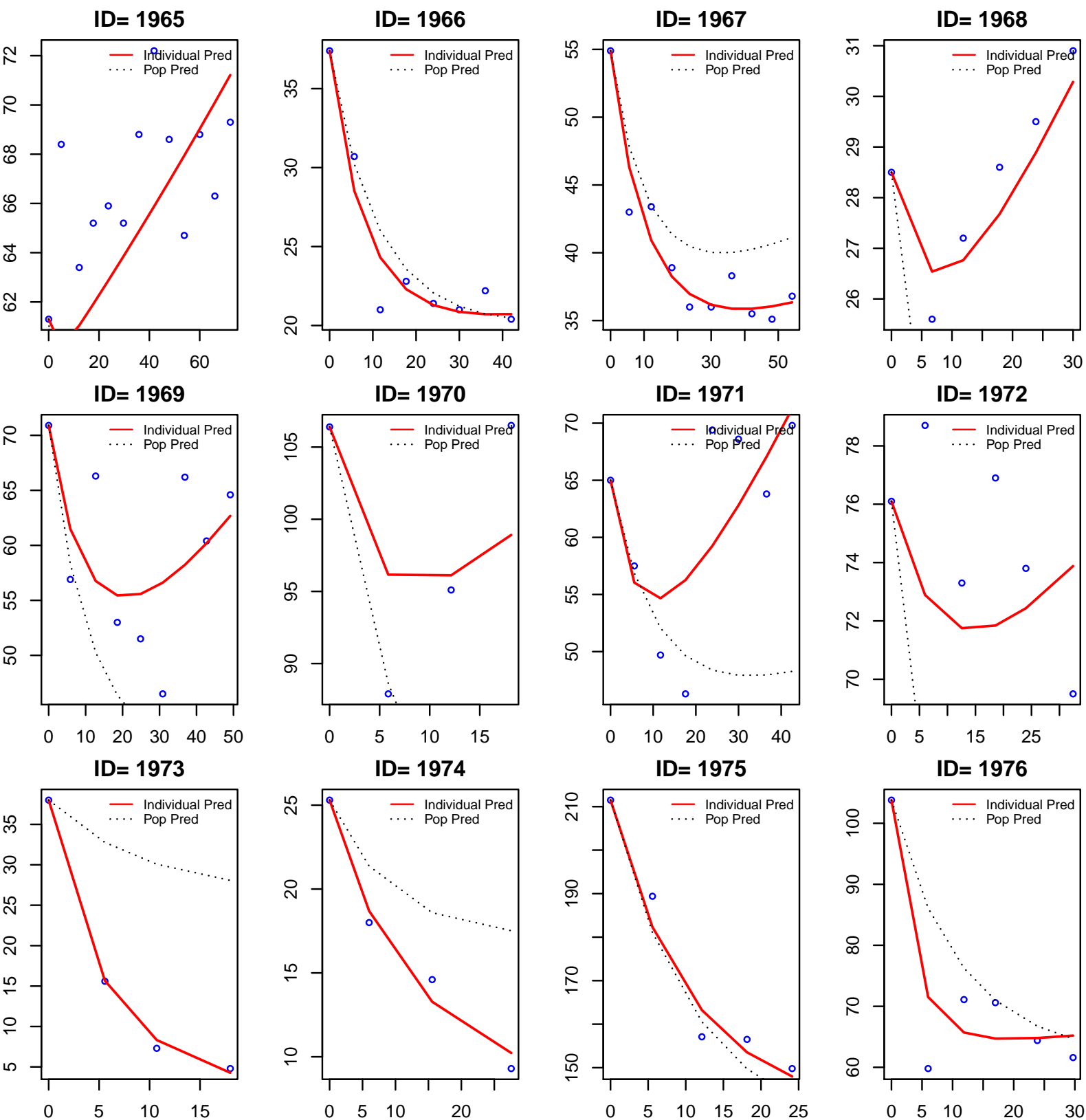


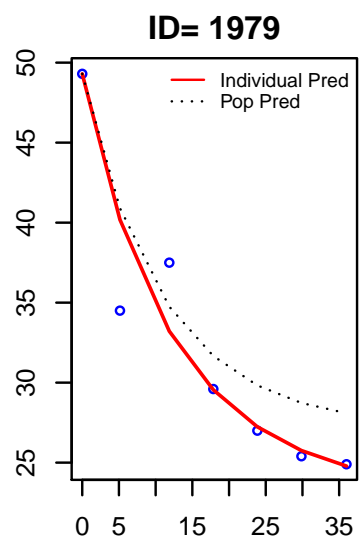
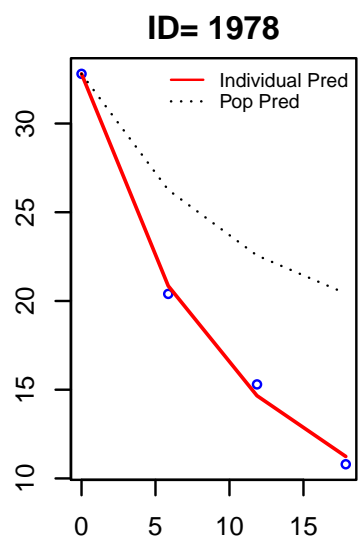
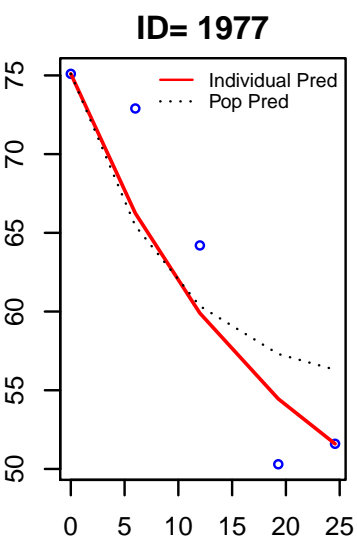












Appendix 6. NONMEM Control Stream and Output Files

Base Model output (1st) file is presented below:

```

1 Mon Feb 24 12:16:07 EST 2020
2 $SIZES PD=-150
3
4 $PROB run8.mod; Claret TGI model
5
6
7
8
9 $INPUT
10
11
12 C PROT NSID ID STID DOSE DOSEP DOSIV
13 DOSIVP DOS2 DOS2P TRT TRTG=DROP PERD NTPD DAY
14 TIME FLAGE AGE SEX RACE ETHN RACD BWT
15 SMOK BBMI BCCL BCAL BPLT BNEU BHGB BALB
16 BLDH BALT BAST BBIL BSLD DV SURT CENS
17 ECOG METS LIVMET LNGMET BONMET MSKCC HENG EGFR
18 EVID EVNT DOSRED DOSINT BLYM
19 DSLD TREAT=DROP TREAT2=DROP LBSLD LSLD
20
21
22 ;TAFD is time in weeks
23 ;DV is the SLD column in mm
24
25
26 $DATA RCC_COMBINED_PD2_SLD_31OCT2019.csv
27 IGNORE=@
28
29 $SUBROUTINE ADVAN 13 TOL=6
30
31 $MODEL
32 COMP=TUMOR
33
34 $PK
35
36 TVKL=LOG (THETA (1) /52) ; change to rate/year from /weeks
37 MU_1=TVKL
38 KL = EXP (MU_1+ETA (1) )
39
40 TVKD=LOG (THETA (2) /52)
41 MU_2=TVKD
42 KD = EXP (MU_2+ETA (2) )
43
44 TVLAM=LOG (THETA (3) /52)
45 MU_3=TVLAM
46 LAM = EXP (MU_3+ETA (3) )
47
48 A_0 (1) =BSLD
49
50
51
52 $DES
53
54 ;y(t) = y(0) exp[ kL t - (kD Treatment/lam)(1-exp(-lam t)) ].
55 ;dy/dt = [kL t - kD/lam Treatment (exp(-lam t))] y(t).
56
57
58 DADT (1) = (KL - KD*EXP (-LAM*T) ) *A (1)
59
60
61
62
63 $ERROR

```

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```

64
65 IPRED=A(1)
66 W = SQRT(THETA(4)**2*IPRED**2+THETA(5)**2)
67
68 Y=IPRED+W*ERR(1)
69
70 IWRES=(DV-IPRED)/W
71
72
73 XL=LOG(KL)
74 XD=LOG(LAM*KD)
75
76 IF(XL.GT.XD) THEN
77     TTG=0
78 ELSE
79     TTG=(LOG(LAM*KD)-LOG(KL))/LAM ; added lam for KD term to adjust
80 ENDIF
81
82
83 W6 = BSLD*EXP(KL*6-(KD/LAM)*(1-EXP(-LAM*6)))
84 W8 = BSLD*EXP(KL*8-(KD/LAM)*(1-EXP(-LAM*8)))
85 TR6= W6/BSLD
86 TR8= W8/BSLD
87
88
89 $THETA
90     (0, 0.1) ; KL
91     (0, 1) ; KD
92     (0, 3) ; LAM
93     (0.01,1) ; Proportional Error
94     (0.01,1) ; Additive Error
95
96
97 $OMEGA
98     0.4 ; ETA(KL)
99     0.4 ; ETA(KD)
100    0.4 ; ETA(LAM)
101
102
103 $SIGMA
104     1 FIX
105
106
107 ;$EST PRINT=10 MAXEVAL=9999 METHOD=1 INTER FILE=run4.ext
108
109 $EST METHOD=SAEM EONLY=0 INTER NBURN=3000 NITER=250 SEED=2019 PRINT=50 DF=0
110 GRD=DDDSS CTYPE=3 CITER=10 CALPHA=0.05 ISAMPLE=2 IACCEPT=0.4
111 $EST METHOD=IMP EONLY=1 NITER=5 ISAMPLE=4000 PRINT=1 DF=4 GRD=DDDSS IACCEPT=1.0 MAPITER=0 FILE
    =run8.ext
112 CTYPE=3 CITER=10 CALPHA=0.05 MSFO=MK8.msf
113
114 $COV PRINT=E
115
116 $TABLE PROT ID TIME IPRED WRES CWRES IWRES
117 KL KD LAM TTG TR6 TR8
118 BSLD DV DSLD LBSLD LSLD TRT
119 ETA1 ETA2 ETA3
120 FORMAT=sf12.6 ONEHEADER NOPRINT FILE=tgi8.fit
121
122
123 NM-TRAN MESSAGES
124
125 WARNINGS AND ERRORS (IF ANY) FOR PROBLEM 1
126
127 (WARNING 2) NM-TRAN INFERS THAT THE DATA ARE POPULATION.
128
129 License Registered to: Pfizer
130 Expiration Date: 14 JUN 2020

```

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```
131 Current Date:          24 FEB 2020
132 Days until program expires : 110
133 1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.4.3
134 ORIGINALLY DEVELOPED BY STUART BEAL, LEWIS SHEINER, AND ALISON BOECKMANN
135 CURRENT DEVELOPERS ARE ROBERT BAUER, ICON DEVELOPMENT SOLUTIONS,
136 AND ALISON BOECKMANN. IMPLEMENTATION, EFFICIENCY, AND STANDARDIZATION
137 PERFORMED BY NOUS INFOSYSTEMS.
138
139 PROBLEM NO.:          1
140 run8.mod; Claret TGI model
141 0DATA CHECKOUT RUN:          NO
142 DATA SET LOCATED ON UNIT NO.: 2
143 THIS UNIT TO BE REWOUND:          NO
144 NO. OF DATA RECS IN DATA SET: 12356
145 NO. OF DATA ITEMS IN DATA SET: 56
146 ID DATA ITEM IS DATA ITEM NO.: 4
147 DEP VARIABLE IS DATA ITEM NO.: 37
148 MDV DATA ITEM IS DATA ITEM NO.: 56
149 0INDICES PASSED TO SUBROUTINE PRED:
150 48 16 0 0 0 0 0 0 0 0 0
151 0LABELS FOR DATA ITEMS:
152 C PROT NSID ID STID DOSE DOSEP DOSIV DOSIVP DOS2 DOS2P TRT PERD NTPD DAY TIME FLAGE AGE SEX
    RACE ETHN RACD BWT SMOK BBMI
153 BCCL BCAL BPLT BNEU BHGB BALB BLDH BALT BAST BBIL BSLD DV SURT CENS ECOG METS LIVMET LNGMET
    BONMET MSKCC HENG EGFR EVID
154 EVNT DOSRED DOSINT BLYM DSLD LBSLD LSLD MDV
155 0(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:
156 KL KD LAM IPRED IWRES TTG TR6 TR8
157 0FORMAT FOR DATA:
158 (18(3E20.0/),1E20.0,1F2.0)
159
160 TOT. NO. OF OBS RECS: 12356
161 TOT. NO. OF INDIVIDUALS: 1839
162 0LENGTH OF THETA: 5
163 0DEFAULT THETA BOUNDARY TEST OMITTED: NO
164 0OMEGA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 3
165 0DEFAULT OMEGA BOUNDARY TEST OMITTED: NO
166 0SIGMA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 1
167 0DEFAULT SIGMA BOUNDARY TEST OMITTED: NO
168 0INITIAL ESTIMATE OF THETA:
169 LOWER BOUND INITIAL EST UPPER BOUND
170 0.0000E+00 0.1000E+00 0.1000E+07
171 0.0000E+00 0.1000E+01 0.1000E+07
172 0.0000E+00 0.3000E+01 0.1000E+07
173 0.1000E-01 0.1000E+01 0.1000E+07
174 0.1000E-01 0.1000E+01 0.1000E+07
175 0INITIAL ESTIMATE OF OMEGA:
176 0.4000E+00
177 0.0000E+00 0.4000E+00
178 0.0000E+00 0.0000E+00 0.4000E+00
179 0INITIAL ESTIMATE OF SIGMA:
180 0.1000E+01
181 0SIGMA CONSTRAINED TO BE THIS INITIAL ESTIMATE
182 0COVARIANCE STEP OMITTED: NO
183 EIGENVLS. PRINTED: YES
184 SPECIAL COMPUTATION: NO
185 COMPRESSED FORMAT: NO
186 GRADIENT METHOD USED: NOSLOW
187 SIGDIGITS ETAHAT (SIGLO): -1
188 SIGDIGITS GRADIENTS (SIGL): -1
189 EXCLUDE COV FOR FOCE (NOFCOV): NO
190 TURN OFF Cholesky Transposition of R Matrix (CHOLROFF): NO
191 KNUTHSUMOFF: -1
192 RESUME COV ANALYSIS (RESUME): NO
193 SIR SAMPLE SIZE (SIRSAMPLE): -1
194 NON-LINEARLY TRANSFORM THETAS DURING COV (THBND): 1
195 PRECONDITIONING CYCLES (PRECOND): 0
196 PRECONDITIONING TYPES (PRECONDS): TOS
```

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197  FORCED PRECONDITIONING CYCLES (PFCOND):0
198  PRECONDITIONING TYPE (PRETYPE):      0
199  FORCED POS. DEFINITE SETTING: (FPOSDEF):0
200  0TABLES STEP OMITTED:      NO
201  NO. OF TABLES:          1
202  SEED NUMBER (SEED):      11456
203  RANMETHOD:              3U
204  MC SAMPLES (ESAMPLE):    300
205  WRES SQUARE ROOT TYPE (WRESCHOL): EIGENVALUE
206  0-- TABLE 1 --
207  0RECORDS ONLY:      ALL
208  04 COLUMNS APPENDED:  YES
209  PRINTED:            NO
210  HEADERS:            ONE
211  FILE TO BE FORWARDED: NO
212  FORMAT:              sF12.6
213  LFORMAT:
214  RFORMAT:
215  FIXED_EFFECT_ETAS:
216  0USER-CHOSEN ITEMS:
217  PROT ID TIME IPRED CWRES IWRES KL KD LAM TTG TR6 TR8 BSLD DV DSLD LBSLD LSLD TRT ETA1 ETA2
      ETA3
218  1DOUBLE PRECISION PREDPP VERSION 7.4.3
219
220  GENERAL NONLINEAR KINETICS MODEL WITH STIFF/NONSTIFF EQUATIONS (LSODA, ADVAN13)
221  0MODEL SUBROUTINE USER-SUPPLIED - ID NO. 9999
222  0MAXIMUM NO. OF BASIC PK PARAMETERS: 3
223  0COMPARTMENT ATTRIBUTES
224  COMPT. NO.  FUNCTION  INITIAL  ON/OFF  DOSE  DEFAULT  DEFAULT
225              STATUS   ALLOWED  ALLOWED  FOR DOSE  FOR OBS.
226      1      TUMOR      ON      YES      YES      YES      YES
227      2      OUTPUT     OFF     YES     NO      NO      NO
228  INITIAL (BASE) TOLERANCE SETTINGS:
229  NRD (RELATIVE) VALUE(S) OF TOLERANCE: 6
230  ANRD (ABSOLUTE) VALUE(S) OF TOLERANCE: 12
231  1
232  ADDITIONAL PK PARAMETERS - ASSIGNMENT OF ROWS IN GG
233  COMPT. NO.  INDICES
234              SCALE  BIOAVAIL.  ZERO-ORDER  ZERO-ORDER  ABSORB
235              FRACTION  RATE      DURATION    LAG
236      1      *      *      *      *      *
237      2      *      -      -      -      -
238  - PARAMETER IS NOT ALLOWED FOR THIS MODEL
239  * PARAMETER IS NOT SUPPLIED BY PK SUBROUTINE;
240  WILL DEFAULT TO ONE IF APPLICABLE
241  0DATA ITEM INDICES USED BY PRED ARE:
242  EVENT ID DATA ITEM IS DATA ITEM NO.: 48
243  TIME DATA ITEM IS DATA ITEM NO.: 16
244
245  0PK SUBROUTINE CALLED WITH EVERY EVENT RECORD.
246  PK SUBROUTINE NOT CALLED AT NONEVENT (ADDITIONAL OR LAGGED) DOSE TIMES.
247  0PK SUBROUTINE INDICATES THAT COMPARTMENT AMOUNTS ARE INITIALIZED.
248  0ERROR SUBROUTINE CALLED WITH EVERY EVENT RECORD.
249  0ERROR SUBROUTINE INDICATES THAT DERIVATIVES OF COMPARTMENT AMOUNTS ARE USED.
250  0DES SUBROUTINE USES COMPACT STORAGE MODE.
251  1
252
253
254  #TBLN:      1
255  #METH: Stochastic Approximation Expectation-Maximization
256
257  ESTIMATION STEP OMITTED:      NO
258  ANALYSIS TYPE:      POPULATION
259  NUMBER OF SADDLE POINT RESET ITERATIONS: 0
260  GRADIENT METHOD USED:      NOSLOW
261  CONDITIONAL ESTIMATES USED:  YES
262  CENTERED ETA:      NO
263  EPS-ETA INTERACTION:  YES

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```

264 LAPLACIAN OBJ. FUNC.: NO
265 NO. OF FUNCT. EVALS. ALLOWED: 528
266 NO. OF SIG. FIGURES REQUIRED: 3
267 INTERMEDIATE PRINTOUT: YES
268 ESTIMATE OUTPUT TO MSF: YES
269 IND. OBJ. FUNC. VALUES SORTED: NO
270 NUMERICAL DERIVATIVE
271 FILE REQUEST (NUMBER): NONE
272 MAP (ETAHAT) ESTIMATION METHOD (OPTMAP): 0
273 ETA HESSIAN EVALUATION METHOD (ETADER): 0
274 INITIAL ETA FOR MAP ESTIMATION (MCETA): 0
275 SIGDIGITS FOR MAP ESTIMATION (SIGLO): 100
276 GRADIENT SIGDIGITS OF
277 FIXED EFFECTS PARAMETERS (SIGL): 100
278 NOPRIOR SETTING (NOPRIOR): OFF
279 NOCOV SETTING (NOCOV): OFF
280 DERCONT SETTING (DERCONT): OFF
281 FINAL ETA RE-EVALUATION (FNLETA): ON
282 EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS
283 IN SHRINKAGE (ETATYPE): NO
284 NON-INFL. ETA CORRECTION (NONINFETA): OFF
285 RAW OUTPUT FILE (FILE): run8.ext
286 EXCLUDE TITLE (NOTITLE): NO
287 EXCLUDE COLUMN LABELS (NOLABEL): NO
288 FORMAT FOR ADDITIONAL FILES (FORMAT): S1PE12.5
289 PARAMETER ORDER FOR OUTPUTS (ORDER): TSOL
290 WISHART PRIOR DF INTERPRETATION (WISHTYPE): 0
291 KNUTHSUMOFF: 0
292 INCLUDE LNTWOPI: NO
293 INCLUDE CONSTANT TERM TO PRIOR (PRIORC): NO
294 INCLUDE CONSTANT TERM TO OMEGA (ETA) (OLNTWOPI): NO
295 EM OR BAYESIAN METHOD USED: STOCHASTIC APPROXIMATION EXPECTATION MAXIMIZATION
    (SAEM)
296 MU MODELING PATTERN (MUM):
297 GRADIENT/GIBBS PATTERN (GRD): DDDSS
298 AUTOMATIC SETTING FEATURE (AUTO): OFF
299 CONVERGENCE TYPE (CTYPE): 3
300 CONVERGENCE INTERVAL (CINTERVAL): 50
301 CONVERGENCE ITERATIONS (CITER): 10
302 CONVERGENCE ALPHA ERROR (CALPHA): 5.000000000000000E-02
303 BURN-IN ITERATIONS (NBURN): 3000
304 ITERATIONS (NITER): 250
305 ANEAL SETTING (CONSTRAIN): 1
306 STARTING SEED FOR MC METHODS (SEED): 2019
307 MC SAMPLES PER SUBJECT (ISAMPLE): 2
308 RANDOM SAMPLING METHOD (RANMETHOD): 3U
309 EXPECTATION ONLY (EONLY): 0
310 PROPOSAL DENSITY SCALING RANGE
311 (ISCALE_MIN, ISCALE_MAX): 1.000000000000000E-06 , 1000000.00000000
312 SAMPLE ACCEPTANCE RATE (IACCEPT): 0.400000000000000
313 METROPOLIS HASTINGS SAMPLING FOR INDIVIDUAL ETAS:
314 SAMPLES FOR GLOBAL SEARCH KERNEL (ISAMPLE_M1): 2
315 SAMPLES FOR NEIGHBOR SEARCH KERNEL (ISAMPLE_M1A): 0
316 SAMPLES FOR MASS/IMP/POST. MATRIX SEARCH (ISAMPLE_M1B): 2
317 SAMPLES FOR LOCAL SEARCH KERNEL (ISAMPLE_M2): 2
318 SAMPLES FOR LOCAL UNIVARIATE KERNEL (ISAMPLE_M3): 2
319 PWR. WT. MASS/IMP/POST MATRIX ACCUM. FOR ETAS (IKAPPA): 1.00000000000000
320 MASS/IMP./POST. MATRIX REFRESH SETTING (MASSREST): -1
321
322 TOLERANCES FOR ESTIMATION/EVALUATION STEP:
323 NRD (RELATIVE) VALUE(S) OF TOLERANCE: 6
324 ANRD (ABSOLUTE) VALUE(S) OF TOLERANCE: 12
325 TOLERANCES FOR COVARIANCE STEP:
326 NRD (RELATIVE) VALUE(S) OF TOLERANCE: 6
327 ANRD (ABSOLUTE) VALUE(S) OF TOLERANCE: 12
328
329 THE FOLLOWING LABELS ARE EQUIVALENT
330 PRED=PREDI

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```

331 RES=RESI
332 WRES=WRESI
333 IWRS=IWRESI
334 IPRD=IPREDI
335 IRS=IRESI
336
337 EM/BAYES SETUP:
338 THETAS THAT ARE MU MODELED:
339     1     2     3
340 THETAS THAT ARE SIGMA-LIKE:
341     4     5
342
343 MONITORING OF SEARCH:
344
345 Stochastic/Burn-in Mode
346 iteration      -3000  SAEMOBJ=    101538.31731013289
347 iteration      -2950  SAEMOBJ=    63542.606788194171
348 iteration      -2900  SAEMOBJ=    63305.549822774658
349 iteration      -2850  SAEMOBJ=    63505.838501257043
350 iteration      -2800  SAEMOBJ=    63402.190213283175
351 iteration      -2750  SAEMOBJ=    63420.329182924193
352 iteration      -2700  SAEMOBJ=    63419.249064224387
353 iteration      -2650  SAEMOBJ=    63549.161982879559
354 iteration      -2600  SAEMOBJ=    63643.088157072321
355 iteration      -2550  SAEMOBJ=    63627.633822273667
356 iteration      -2500  SAEMOBJ=    63682.353481370534
357 iteration      -2450  SAEMOBJ=    63796.322263690956
358 iteration      -2400  SAEMOBJ=    63710.167632775636
359 iteration      -2350  SAEMOBJ=    63544.083291199175
360 iteration      -2300  SAEMOBJ=    63640.330816128073
361 Convergence achieved
362 Reduced Stochastic/Accumulation Mode
363 iteration         0  SAEMOBJ=    63688.521347919515
364 iteration         50  SAEMOBJ=    62860.019027896640
365 iteration        100  SAEMOBJ=    62849.405608434565
366 iteration        150  SAEMOBJ=    62848.851763648599
367 iteration        200  SAEMOBJ=    62844.342882204197
368 iteration        250  SAEMOBJ=    62842.059290484467
369
370 #TERM:
371 STOCHASTIC PORTION WAS COMPLETED
372 REDUCED STOCHASTIC PORTION WAS COMPLETED
373
374 ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,
375 AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.
376
377 ETABAR:          3.4892E-05   3.8496E-05   2.8335E-05
378 SE:             2.3679E-02   1.8052E-02   2.0383E-02
379 N:               1839         1839         1839
380
381 P VAL.:          9.9882E-01   9.9830E-01   9.9889E-01
382
383 ETASHRINKSD (%)  3.5107E+01   2.0412E+01   3.6215E+01
384 ETASHRINKVR (%)  5.7888E+01   3.6657E+01   5.9314E+01
385 EBVSHRINKSD (%)  3.5102E+01   2.0406E+01   3.6220E+01
386 EBVSHRINKVR (%)  5.7882E+01   3.6648E+01   5.9321E+01
387 EPSSHRINKSD (%)  1.0000E-10
388 EPSSHRINKVR (%)  1.0000E-10
389
390
391 TOTAL DATA POINTS NORMALLY DISTRIBUTED (N):          12356
392 N*LOG(2PI) CONSTANT TO OBJECTIVE FUNCTION:          22708.809032553872
393 OBJECTIVE FUNCTION VALUE WITHOUT CONSTANT:          62842.059290484467
394 OBJECTIVE FUNCTION VALUE WITH CONSTANT:          85550.868323038332
395 REPORTED OBJECTIVE FUNCTION DOES NOT CONTAIN CONSTANT
396
397 TOTAL EFFECTIVE ETAS (NIND*NETA):                      5517
398 NIND*NETA*LOG(2PI) CONSTANT TO OBJECTIVE FUNCTION:      10139.567775380357

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B999e
Avelumab, Axitinib, Sunitinib
ASR-EQDD-B999e-Other-994

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399 OBJECTIVE FUNCTION VALUE WITHOUT CONSTANT:      62842.059290484467
400 OBJECTIVE FUNCTION VALUE WITH CONSTANT:          72981.627065864828
401 REPORTED OBJECTIVE FUNCTION DOES NOT CONTAIN CONSTANT
402
403 #TERE:
404 Elapsed estimation time in seconds:  1483.90
405 Elapsed covariance time in seconds:    0.22
406 1
407
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427 *****
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438 *****
439 #OBJV: ***** 62842.059 *****
440 1
441 *****
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448 *****
449 *****
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450 THETA - VECTOR OF FIXED EFFECTS PARAMETERS *****
451
452
453 TH 1 TH 2 TH 3 TH 4 TH 5
454
455 1.38E-01 1.52E+00 3.87E+00 8.14E-02 2.27E+00
456
457
458
459 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS *****
460
461
462 ETA1 ETA2 ETA3
463
464 ETA1
465 + 2.45E+00
466
467 ETA2
468 + 0.00E+00 9.47E-01
469
470 ETA3
471 + 0.00E+00 0.00E+00 1.88E+00
472
473
474
475 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****
476
477
478 EPS1
479
480 EPS1
481 + 1.00E+00
482
483 1
484
485
486 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS *****
487
488
489 ETA1 ETA2 ETA3
490
491 ETA1
492 + 1.57E+00
493
494 ETA2
495 + 0.00E+00 9.73E-01
496
497 ETA3
498 + 0.00E+00 0.00E+00 1.37E+00
499
500
501
502 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS ***
503
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507 EPS1
508 + 1.00E+00
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B999e
Avelumab, Axitinib, Sunitinib
ASR-EQDD-B999e-Other-994

```
514 ***** STANDARD ERROR OF ESTIMATE (S)
515 *****
516 *****
517 *****
518 *****
519 *****
520 THETA - VECTOR OF FIXED EFFECTS PARAMETERS *****
521
522 TH 1 TH 2 TH 3 TH 4 TH 5
523 1.19E-02 6.42E-02 3.19E-01 1.96E-04 1.67E-02
524
525
526
527
528 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS *****
529
530 ETA1 ETA2 ETA3
531
532 ETA1
533 + 2.41E-01
534
535 ETA2
536 + 0.00E+00 6.87E-02
537
538 ETA3
539 + 0.00E+00 0.00E+00 1.79E-01
540
541
542
543
544 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****
545
546 EPS1
547
548 EPS1
549 + 0.00E+00
550
551 1
552
553
554 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS *****
555
556 ETA1 ETA2 ETA3
557
558 ETA1
559 + 7.68E-02
560
561 ETA2
562 + ..... 3.53E-02
563
564 ETA3
565 + ..... 6.51E-02
566
567
568
569
570 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS ***
571
572 EPS1
573
574 EPS1
```

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ASR-EQDD-B999e-Other-994

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578 +          .....
579
580 1
581 *****
582          *****
583          *****
584          *****
585          *****
586          *****
587          *****
588          *****
589          TH 1      TH 2      TH 3      TH 4      TH 5      OM11      OM12      OM13
                    OM22      OM23      OM33      SG11
590
591
592 TH 1
593 +          1.41E-04
594
595 TH 2
596 +          -6.83E-05  4.13E-03
597
598 TH 3
599 +          -1.73E-03  1.12E-02  1.01E-01
600
601 TH 4
602 +          4.55E-08 -7.20E-07  1.92E-06  3.85E-08
603
604 TH 5
605 +          7.47E-06 -2.26E-04 -5.52E-04 -1.42E-06  2.79E-04
606
607 OM11
608 +          -1.96E-03  2.63E-03  2.90E-02 -2.14E-06 -2.82E-04  5.79E-02
609
610 OM12
611 +          .....
612
613 OM13
614 +          .....
615
616 OM22
617 +          4.17E-05 -2.55E-03 -1.21E-02 -2.24E-07  1.68E-04 -2.82E-03  0.00E+00  0.00E+00  4.72E
-03
618
619 OM23
620 +          .....
621          .....
622 OM33
623 +          -6.27E-04  7.66E-03  3.68E-02 -4.24E-06 -1.06E-03  1.28E-02  0.00E+00  0.00E+00 -6.05E
-03  0.00E+00  3.19E-02
624
625 SG11
626 +          .....
627          .....
628 1
629 *****
630          *****
631          *****
632          *****
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B999e

Avelumab, Axitinib, Sunitinib

ASR-EQDD-B999e-Other-994

[illegible]

B999e
Avelumab, Axitinib, Sunitinib
ASR-EQDD-B999e-Other-994

```

682      *****
683      *****
684      *****
685      TH 1      TH 2      TH 3      TH 4      TH 5      OM11      OM12      OM13
686      OM22      OM23      OM33      SG11
687
688      TH 1
689      +      1.66E+04
690
691      TH 2
692      +      -4.64E+02      5.33E+02
693
694      TH 3
695      +      2.36E+02      -1.72E+01      2.65E+01
696
697      TH 4
698      +      6.86E+03      1.45E+03      -7.63E+03      3.89E+07
699
700      TH 5
701      +      1.67E+02      -1.01E+01      -1.02E+02      2.69E+05      6.10E+03
702
703      OM11
704      +      4.75E+02      -4.94E+00      7.86E-01      1.95E+03      1.91E+01      3.42E+01
705
706      OM12
707      +      .....
708
709      OM13
710      +      .....
711
712      OM22
713      +      6.13E+02      1.29E+02      3.49E+01      3.49E+03      -1.09E+01      1.44E+01      0.00E+00      0.00E+00      3.85E
714      +02
715      OM23
716      +      .....
717      .....
718      OM33
719      +      9.85E+01      -9.10E+01      -1.99E+01      2.25E+04      3.52E+02      -4.16E-01      0.00E+00      0.00E+00      8.23E
720      +00      0.00E+00      9.45E+01
721      SG11
722      +      .....
723      .....
724      1
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B999e
Avelumab, Axitinib, Sunitinib
ASR-EQDD-B999e-Other-994

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STOCHASTIC APPROXIMATION EXPECTATION-MAXIMIZATION

EIGENVALUES OF COR MATRIX OF ESTIMATE (S)

	1	2	3	4	5	6	7	8
1	1.96E-01	2.42E-01	3.70E-01	4.65E-01	6.94E-01	1.35E+00	1.53E+00	3.16E+00

#TBLN: 2

#METH: Objective Function Evaluation by Importance Sampling

ESTIMATION STEP OMITTED: NO

ANALYSIS TYPE: POPULATION

NUMBER OF SADDLE POINT RESET ITERATIONS: 0

GRADIENT METHOD USED: NOSLOW

CONDITIONAL ESTIMATES USED: YES

CENTERED ETA: NO

EPS-ETA INTERACTION: YES

LAPLACIAN OBJ. FUNC.: NO

NO. OF FUNCT. EVALS. ALLOWED: 528

NO. OF SIG. FIGURES REQUIRED: 3

INTERMEDIATE PRINTOUT: YES

ESTIMATE OUTPUT TO MSF: YES

IND. OBJ. FUNC. VALUES SORTED: NO

NUMERICAL DERIVATIVE

FILE REQUEST (NUMBER): NONE

MAP (ETAHAT) ESTIMATION METHOD (OPTMAP): 0

ETA HESSIAN EVALUATION METHOD (ETADER): 0

INITIAL ETA FOR MAP ESTIMATION (MCETA): 0

SIGDIGITS FOR MAP ESTIMATION (SIGLO): 100

GRADIENT SIGDIGITS OF

FIXED EFFECTS PARAMETERS (SIGL): 100

NOPRIOR SETTING (NOPRIOR): OFF

NOCOV SETTING (NOCOV): OFF

DERCONT SETTING (DERCONT): OFF

FINAL ETA RE-EVALUATION (FNLETA): ON

EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS

IN SHRINKAGE (ETATYPE): NO

NON-INFL. ETA CORRECTION (NONINFETA): OFF

RAW OUTPUT FILE (FILE): run8.ext

EXCLUDE TITLE (NOTITLE): NO

EXCLUDE COLUMN LABELS (NOLABEL): NO

FORMAT FOR ADDITIONAL FILES (FORMAT): S1PE12.5

PARAMETER ORDER FOR OUTPUTS (ORDER): TSOL

WISHART PRIOR DF INTERPRETATION (WISHTYPE): 0

KNUTHSUMOFF: 0

INCLUDE LNTWOPI: NO

INCLUDE CONSTANT TERM TO PRIOR (PRIORC): NO

INCLUDE CONSTANT TERM TO OMEGA (ETA) (OLNTWOPI): NO

EM OR BAYESIAN METHOD USED: IMPORTANCE SAMPLING (IMP)

MU MODELING PATTERN (MUM):

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ASR-EQDD-B999e-Other-994

```

803 GRADIENT/GIBBS PATTERN (GRD): DDDSS
804 AUTOMATIC SETTING FEATURE (AUTO): OFF
805 CONVERGENCE TYPE (CTYPE): 3
806 CONVERGENCE INTERVAL (CINTERVAL): 1
807 CONVERGENCE ITERATIONS (CITER): 10
808 CONVERGENCE ALPHA ERROR (CALPHA): 5.000000000000000E-02
809 ITERATIONS (NITER): 5
810 ANEAL SETTING (CONSTRAIN): 1
811 STARTING SEED FOR MC METHODS (SEED): 2019
812 MC SAMPLES PER SUBJECT (ISAMPLE): 4000
813 RANDOM SAMPLING METHOD (RANMETHOD): 3U
814 EXPECTATION ONLY (EONLY): 1
815 PROPOSAL DENSITY SCALING RANGE
816 (ISCALE_MIN, ISCALE_MAX): 0.1000000000000000 ,10.00000000000000
817 SAMPLE ACCEPTANCE RATE (IACCEPT): 1.000000000000000
818 LONG TAIL SAMPLE ACCEPT. RATE (IACCEPTL): 0.000000000000000
819 T-DIST. PROPOSAL DENSITY (DF): 4
820 NO. ITERATIONS FOR MAP (MAPITER): 0
821 INTERVAL ITER. FOR MAP (MAPINTER): 0
822 MAP COVARIANCE/MODE SETTING (MAPCOV): 1
823 Gradient Quick Value (GRDQ): 0.000000000000000
824
825 TOLERANCES FOR ESTIMATION/EVALUATION STEP:
826 NRD (RELATIVE) VALUE(S) OF TOLERANCE: 6
827 ANRD (ABSOLUTE) VALUE(S) OF TOLERANCE: 12
828 TOLERANCES FOR COVARIANCE STEP:
829 NRD (RELATIVE) VALUE(S) OF TOLERANCE: 6
830 ANRD (ABSOLUTE) VALUE(S) OF TOLERANCE: 12
831 TOLERANCES FOR TABLE/SCATTER STEP:
832 NRD (RELATIVE) VALUE(S) OF TOLERANCE: 6
833 ANRD (ABSOLUTE) VALUE(S) OF TOLERANCE: 12
834
835 THE FOLLOWING LABELS ARE EQUIVALENT
836 PRED=PREDI
837 RES=RESI
838 WRES=WRESI
839 IWRS=IWRESI
840 IPRD=IPREDI
841 IRS=IRESI
842
843 EM/BAYES SETUP:
844 THETAS THAT ARE MU MODELED:
845 1 2 3
846 THETAS THAT ARE SIGMA-LIKE:
847 4 5
848
849 MONITORING OF SEARCH:
850
851 iteration 0 OBJ= 66314.428289312316 eff.= 2060. Smpl.= 4000. Fit.=
852 0.91716
853 iteration 1 OBJ= 66311.845441183017 eff.= 2456. Smpl.= 4000. Fit.=
854 0.91926
855 iteration 2 OBJ= 66312.106612013900 eff.= 2513. Smpl.= 4000. Fit.=
856 0.91836
857 iteration 3 OBJ= 66316.455487397427 eff.= 2499. Smpl.= 4000. Fit.=
858 0.91884
859 iteration 4 OBJ= 66315.923028181875 eff.= 2492. Smpl.= 4000. Fit.=
860 0.91866
861 iteration 5 OBJ= 66317.839555514351 eff.= 2504. Smpl.= 4000. Fit.=
862 0.91897
863
864 #TERM:
865 EXPECTATION ONLY PROCESS COMPLETED
866
867 ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,
868 AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.
869

```

865	ETABAR:	-7.2565E-03	8.7512E-04	2.8971E-03
866	SE:	2.3746E-02	1.8050E-02	2.0403E-02
867	N:	1839	1839	1839
868				
869	P VAL.:	7.5992E-01	9.6133E-01	8.8708E-01
870				
871	ETASHRINKSD (%)	3.4923E+01	2.0418E+01	3.6151E+01
872	ETASHRINKVR (%)	5.7650E+01	3.6667E+01	5.9234E+01
873	EBVSHRINKSD (%)	3.5211E+01	2.0526E+01	3.6451E+01
874	EBVSHRINKVR (%)	5.8024E+01	3.6838E+01	5.9615E+01
875	EPSSHRINKSD (%)	1.2184E-02		
876	EPSSHRINKVR (%)	2.4366E-02		

```

885      TOTAL EFFECTIVE ETAS  (NIND*NETA) :                               5517

```

890 1

```
914 #OBJT:*****FINAL VALUE OF OBJECTIVE FUNCTION  

*****
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915 *****

917

918

919

920

921

922

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923  #OBJV:*****66317.840*****
      *****
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B999e
Avelumab, Axitinib, Sunitinib
ASR-EQDD-B999e-Other-994

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924 1
925 *****
926 *****
927 *****
928 *****
929 *****
930 *****
931 *****
932 *****
933 *****
934 THETA - VECTOR OF FIXED EFFECTS PARAMETERS *****
935
936 TH 1 TH 2 TH 3 TH 4 TH 5
937
938 1.38E-01 1.52E+00 3.87E+00 8.14E-02 2.27E+00
939
940
941
942
943 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS *****
944
945 ETA1 ETA2 ETA3
946
947 ETA1
948 + 2.45E+00
949
950 ETA2
951 + 0.00E+00 9.47E-01
952
953 ETA3
954 + 0.00E+00 0.00E+00 1.88E+00
955
956
957
958
959 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****
960
961 EPS1
962
963 EPS1
964 + 1.00E+00
965
966
967 1
968
969
970 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS *****
971
972 ETA1 ETA2 ETA3
973
974 ETA1
975 + 1.57E+00
976
977 ETA2
978 + 0.00E+00 9.73E-01
979
980 ETA3
981 + 0.00E+00 0.00E+00 1.37E+00
982
983
```

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```
984
985
986 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS ***
987
988
989 EPS1
990
991 EPS1
992 + 1.00E+00
993
994 1
995 *****
996 *****
997 *****
998 *****
999 *****
1000 *****
1001 *****
1002
1003
1004 THETA - VECTOR OF FIXED EFFECTS PARAMETERS *****
1005
1006
1007 TH 1 TH 2 TH 3 TH 4 TH 5
1008
1009 1.38E-02 6.82E-02 2.77E-01 5.38E-03 1.97E-01
1010
1011
1012
1013 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS *****
1014
1015
1016 ETA1 ETA2 ETA3
1017
1018 ETA1
1019 + 1.94E-01
1020
1021 ETA2
1022 + 0.00E+00 6.68E-02
1023
1024 ETA3
1025 + 0.00E+00 0.00E+00 2.91E-01
1026
1027
1028
1029 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ***
1030
1031
1032 EPS1
1033
1034 EPS1
1035 + 0.00E+00
1036
1037 1
1038
1039
1040 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS *****
1041
1042
1043 ETA1 ETA2 ETA3
```

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```
1044
1045  ETA1
1046  +      6.19E-02
1047
1048  ETA2
1049  +      ..... 3.43E-02
1050
1051  ETA3
1052  +      ..... 1.06E-01
1053
1054
1055
1056  SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS  ***
1057
1058
1059      EPS1
1060
1061  EPS1
1062  +      .....
1063
1064  1
1065  *****
1066  *****
1067  *****
1068  *****
1069  *****
1070  *****
1071
1072
1073      TH 1      TH 2      TH 3      TH 4      TH 5      OM11      OM12      OM13
           OM22      OM23      OM33      SG11
1074
1075
1076  TH 1
1077  +      1.91E-04
1078
1079  TH 2
1080  +      -1.07E-04  4.65E-03
1081
1082  TH 3
1083  +      -1.44E-03  1.23E-02  7.70E-02
1084
1085  TH 4
1086  +      -1.65E-05  3.36E-05  1.39E-04  2.89E-05
1087
1088  TH 5
1089  +      3.56E-04  2.38E-04 -3.14E-03 -6.71E-04  3.87E-02
1090
1091  OM11
1092  +      -1.99E-03  6.22E-04  1.11E-02 -1.11E-04  3.13E-04  3.76E-02
1093
1094  OM12
1095  +      .....
1096
1097  OM13
1098  +      .....
1099
1100  OM22
1101  +      -3.16E-06 -2.72E-03 -4.79E-03 -1.16E-04  3.83E-04  2.11E-03  0.00E+00  0.00E+00  4.46E
           -03
```


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```
1155 +      -1.64E-01  4.79E-01  5.45E-01  3.37E-03  1.62E-01 -5.72E-03  0.00E+00  0.00E+00 -2.79E
      -01  0.00E+00  2.91E-01
1156
1157 SG11
1158 +      .....
      .....
1159
1160 1
1161 *****
      *****
1162 *****
                                     *****
      *****
1163 *****                                OBJECTIVE FUNCTION EVALUATION BY IMPORTANCE SAMPLING
      *****
1164 *****                                INVERSE COVARIANCE MATRIX OF ESTIMATE (RSR)
      *****
1165 *****
                                     *****
      *****
1166 *****
      *****
1167
1168
1169          TH 1      TH 2      TH 3      TH 4      TH 5      OM11      OM12      OM13
              OM22      OM23      OM33      SG11
1170
1171
1172 TH 1
1173 +      1.78E+04
1174
1175 TH 2
1176 +      -6.55E+02  6.19E+02
1177
1178 TH 3
1179 +      2.27E+02 -7.93E+01  3.24E+01
1180
1181 TH 4
1182 +      1.53E+04  4.86E+02  1.13E+02  8.42E+04
1183
1184 TH 5
1185 +      9.86E+01  4.97E+00  5.16E+00  1.30E+03  4.90E+01
1186
1187 OM11
1188 +      9.40E+02 -3.74E+01  5.33E+00  8.93E+02  5.41E+00  7.95E+01
1189
1190 OM12
1191 +      .....
1192
1193 OM13
1194 +      .....
1195
1196 OM22
1197 +      -9.85E+01  3.04E+02 -2.34E+01  2.08E+03  2.83E+01 -2.26E+01  0.00E+00  0.00E+00  4.50E
      +02
1198
1199 OM23
1200 +      .....
      .....
1201
1202 OM33
1203 +      8.02E+01 -1.46E+01 -8.24E+00 -3.85E+00 -6.06E+00  6.98E+00  0.00E+00  0.00E+00  2.78E
      +00  0.00E+00  1.92E+01
1204
1205 SG11
1206 +      .....
      .....
1207
```

```

1208 1
1209
1210
1211
1212
1213
1214
1215
1216
1217
1218
1219
1220
1221
1222
1223
1224
1225
1226
1227
1228
1229 *****
      *****
1230 *****
                                     *****
      *****
1231 *****                                OBJECTIVE FUNCTION EVALUATION BY IMPORTANCE SAMPLING
      *****
1232 *****                                EIGENVALUES OF COR MATRIX OF ESTIMATE (RSR)
      *****
1233 *****
                                     *****
      *****
1234 ***** *****
      *****
1235
1236
1237           1           2           3           4           5           6           7           8
1238
1239           1.45E-01   2.08E-01   3.10E-01   5.40E-01   7.23E-01   1.70E+00   1.77E+00   2.60E+00
1240
1241 Elapsed postprocess time in seconds:      3.41
1242 Elapsed finaloutput time in seconds:      0.46
1243 #CPUT: Total CPU Time in Seconds,      3470.736
1244 Stop Time:
1245 Mon Feb 24 13:14:12 EST 2020

```

```
1 ;$PROBLEM scm.conf
2
3 ;---This is a command line example:
4 ;scm-4.8.0 -config=scm.conf -min_retries=0
5 ;Additional options on command line will override any options specified below
6
7 ;---This option can NOT be specified on command line. Change run number in inventory and/or
   here:
8 model=run9.mod
9
10
11 search_direction=both
12 p_forward=0.05
13 p_backward=0.001
14 seed=8
15
16 ;THESE OPTIONS CAN BE ACTIVATED AND CHANGED, UNLESS YOU PREFER TO STAY WITH DEFAULT AS BELOW
```

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```
17
18     ;If only covariate models with successful covstep should pass:
19 ;picky=0
20
21     ;Unless acceptable model fit; each covariate model may be tried again with perturbed
        estimates (retries number of times):
22 ;retries=0
23
24 ;Try with perturbed initial estimates AT least this many times:
25 ;PsN bug. This option can only be set on command line: min_retries=0
26
27 ;Other options that can be set here:
28 ;threads=30
29 nm_version=nonmem-7.4.3
30 ;If missing covariates are coded by other value in your dataset it is VERY IMPORTANT to set
        this:
31 missing_data_token=-999
32 ;Also; if you use other value than -99; check that it is working. It did not for PsN-3.2.12
33 ;abort_on_fail=0
34 ;gof=pvalue
35
36     ;Switch on to 1 to run covariate models in parallel, rather than testing conditioned on
        previous state passing:
37 ;parallel_states=0
38
39     ;XXX is list of parameters that are estimated on logit scale:
40 ;logit=XXX
41
42 directory=scml
43
44 ;---Any covariates that manually put in the model may have to be included here:
45 do_not_drop=PROT,TRT,BSLD
46
47 ;---Replace XXX with a value, if you start with included relations:
48 ;base_criteria_values={ ofv => XXX }
49
50 ;-----
51 ;---Vector and complex-structure options follow below:---
52 continuous_covariates=BSLD
53 categorical_covariates=TRT
54 ;time_varying=DOSE
55
56 [test_relations]
57 KL=BSLD,TRT
58 KD=BSLD,TRT
59 LAM=BSLD,TRT
60
61 ;---Continuous will be tested in the order below. 1 none, 2 linear, 3 piece-wise linear, 4
        exponential, 5 power.
62 [valid_states]
63 continuous = 1,5,4,2
64 categorical = 1,2
65
66 ;---The starting model will include these relations, but they are subject to any backward
        elimination
67 ;[included_relations]
68
69
70
71
72
73 ;[inits]
74 ;CL:*-2 = 0.0001
75 ; V:*-2 = 0.0001
76 ;KA:*-2 = 0.0001
77
78 [code]
79
```

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```

80 ;; PARTRT-DEFINITION
81 *:TRT-2=      IF (TRT.EQ.2)    PARTRT = 1 \
82             IF (TRT.EQ.1)    PARTRT = (1+THETA(1)) \
83             IF (TRT.EQ.3)    PARTRT = (1+THETA(2)) \
84             IF (TRT.EQ.4)    PARTRT = (1+THETA(3)) \
85             IF (TRT.EQ.5)    PARTRT = (1+THETA(4))
86
87
88
89 ;[upper_bounds]
90 ;*:WT-2 = 0.0128
91 ;*:WT-3 = 0.0128,10000000
92
93 ;[lower_bounds]
94 ;*:WT-2 = -10000000
95 ;*:WT-3 = -10000000,-0.012
96
97

```

Repository artifact ID FI-482257.

SCM log output file is presented below:

```

1 Model directory /data/impprd/runserver/improve/5B2AC15F885C435F96BA9DBE8C4AA68E/scml/ml
2
3 MODEL          TEST          BASE OFV      NEW OFV          TEST OFV (DROP)  GOAL      dDF
4 KDBSLD-5       PVAL        66309.13076   66260.44053      48.69023 >    3.84150    1
5 YES!          3.00e-12
6 KDBSLD-5       PVAL        66309.13076   66025.22559      283.90517 >    9.48770    4
7 YES!          3.21e-60
8 KLBSLD-5       PVAL        66309.13076   66296.52382      12.60695 >    3.84150    1
9 YES!          0.000384
10 KLTRT-2       PVAL        66309.13076   66205.30396      103.82681 >    9.48770    4
11 YES!          1.51e-21
12 LAMBSLD-5     PVAL        66309.13076   66282.93065      26.20011 >    3.84150    1
13 YES!          3.08e-07
14 LAMTRT-2     PVAL        66309.13076   66133.87462      175.25614 >    9.48770    4
15 YES!          7.78e-37
16
17 Parameter-covariate relation chosen in this forward step: KD-TRT-2
18 CRITERION          PVAL < 0.05
19 BASE_MODEL_OFV      66309.13076
20 CHOSEN_MODEL_OFV    66025.22559
21 Relations included after this step:
22 KD          TRT-2
23 KL
24 LAM
25 -----
26 Model directory /data/impprd/runserver/improve/5B2AC15F885C435F96BA9DBE8C4AA68E/scml/forward_
27 scm_dir1/ml
28
29 MODEL          TEST          BASE OFV      NEW OFV          TEST OFV (DROP)  GOAL      dDF
30 KDBSLD-5       PVAL        66025.22559   65998.74220      26.48339 >    3.84150    1
31 YES!          2.66e-07
32 KLBSLD-5       PVAL        66025.22559   66013.39958      11.82601 >    3.84150    1
33 YES!          0.000584
34 KLTRT-2       PVAL        66025.22559   65973.76003      51.46556 >    9.48770    4
35 YES!          1.78e-10
36 LAMBSLD-5     PVAL        66025.22559   66000.17645      25.04914 >    3.84150    1
37 YES!          0.000001
38 LAMTRT-2     PVAL        66025.22559   65992.97348      32.25211 >    9.48770    4
39 YES!          0.000002
40
41 Parameter-covariate relation chosen in this forward step: KL-TRT-2
42 CRITERION          PVAL < 0.05

```


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```

32 BASE_MODEL_OFV          66025.22559
33 CHOSEN_MODEL_OFV        65973.76003
34 Relations included after this step:
35 KD          TRT-2
36 KL          TRT-2
37 LAM
38 -----
39
40 Model directory /data/impprd/runserver/improve/5B2AC15F885C435F96BA9DBE8C4AA68E/scml/forward_
   scm_dir1/scm_dir1/ml
41
42 MODEL          TEST      BASE OFV      NEW OFV          TEST OFV (DROP)      GOAL      dDF
   SIGNIFICANT PVAL
43 KDBSLD-5      PVAL      65973.76003    65955.59161      18.16842 >      3.84150    1
   YES! 0.000020
44 KLBSLD-5      PVAL      65973.76003    65977.72867      -3.96864 >      3.84150    1
   9999
45 LAMBSLD-5     PVAL      65973.76003    65964.62416      9.13588 >      3.84150    1
   YES! 0.002507
46 LAMTRT-2     PVAL      65973.76003    65954.08896      19.67107 >      9.48770    4
   YES! 0.000580
47
48 Parameter-covariate relation chosen in this forward step: KD-BSLD-5
49 CRITERION          PVAL < 0.05
50 BASE_MODEL_OFV      65973.76003
51 CHOSEN_MODEL_OFV    65955.59161
52 Relations included after this step:
53 KD          BSLD-5          TRT-2
54 KL          TRT-2
55 LAM
56 -----
57
58 Model directory /data/impprd/runserver/improve/5B2AC15F885C435F96BA9DBE8C4AA68E/scml/forward_
   scm_dir1/scm_dir1/scm_dir1/ml
59
60 MODEL          TEST      BASE OFV      NEW OFV          TEST OFV (DROP)      GOAL      dDF
   SIGNIFICANT PVAL
61 KDBSLD-4      PVAL      65955.59161    65962.64503      -7.05341 >      0.00000    0
   999
62 KLBSLD-5      PVAL      65955.59161    65952.86604      2.72558 >      3.84150    1
   0.098752
63 LAMBSLD-5     PVAL      65955.59161    65946.58085      9.01076 >      3.84150    1
   YES! 0.002684
64 LAMTRT-2     PVAL      65955.59161    65929.13262      26.45899 >      9.48770    4
   YES! 0.000026
65
66 Parameter-covariate relation chosen in this forward step: LAM-TRT-2
67 CRITERION          PVAL < 0.05
68 BASE_MODEL_OFV      65955.59161
69 CHOSEN_MODEL_OFV    65929.13262
70 Relations included after this step:
71 KD          BSLD-5          TRT-2
72 KL          TRT-2
73 LAM          TRT-2
74 -----
75
76 Model directory /data/impprd/runserver/improve/5B2AC15F885C435F96BA9DBE8C4AA68E/scml/forward_
   scm_dir1/scm_dir1/scm_dir1/scm_dir1/ml
77
78 MODEL          TEST      BASE OFV      NEW OFV          TEST OFV (DROP)      GOAL      dDF
   SIGNIFICANT PVAL
79 KDBSLD-4      PVAL      65929.13262    65936.28895      -7.15633 >      0.00000    0
   999
80 KLBSLD-5      PVAL      65929.13262    65926.78418      2.34844 >      3.84150    1
   0.125410
81 LAMBSLD-5     PVAL      65929.13262    65928.56510      0.56752 >      3.84150    1
   0.451250
82

```

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```

83 -----
84
85 -----
86
87 Forward search done. Starting backward search inside forward top level directory
88 Model directory /data/imprpd/runserver/improve/5B2AC15F885C435F96BA9DBE8C4AA68E/scml/backward_
    scm_dir1/ml
89
90 MODEL          TEST          BASE OFV          NEW OFV          TEST OFV (DROP)    GOAL          dDF
91      INSIGNIFICANT PVAL
92 KDBSLD-1        PVAL  65929.13262  65953.98414          -24.85152 > -10.82800    -1
93                PVAL  65929.13262  66065.04984          -135.91722 > -18.46700    -4
94                PVAL  65929.13262  65972.40280          -43.27018 > -18.46700    -4
95                PVAL  65929.13262  65954.25372          -25.12110 > -18.46700    -4
96                PVAL  65929.13262  65954.25372          -25.12110 > -18.46700    -4
97 -----

```

Repository artifact ID FI-482270.

Final Model output (lst) file is presented below:

```

1 Mon Feb 24 12:17:19 EST 2020
2 $SIZES      PD=-150
3
4 $PROB run13.mod; Claret TGI model
5
6
7
8
9 $INPUT
10
11
12 C  PROT      NSID      ID  STID      DOSE      DOSEP      DOSIV
13 DOSIVP  DOS2      DOS2P  TRT TRTG=DROP  PERD      NTPD      DAY
14 TIME    FLAGE     AGE SEX  RACE      ETHN      RACD      BWT
15 SMOK    BBMI      BCCL      BCAL      BPLT      BNEU      BHGB      BALB
16 BLDH    BALT      BAST      BBIL      BSLD      DV      SURT      CENS
17 ECOG    METS      LIVMET    LNGMET    BONMET    MSKCC      HENG      EGFR
18 EVID    EVNT      DOSRED    DOSINT    BLYM
19 DSLD    TREAT=DROP  TREAT2=DROP  LBSLD      LSLD
20
21
22 ;TAFD is time in weeks
23 ;DV is the SLD column in mm
24
25
26 $DATA RCC_COMBINED_PD2_SLD_31OCT2019.csv
27 IGNORE=@
28
29 $SUBROUTINE ADVAN 13 TOL=6
30
31 $MODEL
32 COMP=TUMOR
33
34 $PK
35 ;; LAMTRT-DEFINITION START
36 IF (TRT.EQ.2) LAMTRT = 1
37 IF (TRT.EQ.1) LAMTRT = (1+THETA(15))
38 IF (TRT.EQ.3) LAMTRT = (1+THETA(16))
39 IF (TRT.EQ.4) LAMTRT = (1+THETA(17))
40 IF (TRT.EQ.5) LAMTRT = (1+THETA(18))
41 ;; LAMTRT-DEFINITION END
42

```

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```

43   ;;; LAM-RELATION START
44   LAMCOV=LAMTRT
45   ;;; LAM-RELATION END
46
47
48   ;;; KLTRT-DEFINITION START
49   IF (TRT.EQ.2)    KLTRT = 1
50   IF (TRT.EQ.1)    KLTRT = (1+THETA(11))
51   IF (TRT.EQ.3)    KLTRT = (1+THETA(12))
52   IF (TRT.EQ.4)    KLTRT = (1+THETA(13))
53   IF (TRT.EQ.5)    KLTRT = (1+THETA(14))
54   ;;; KLTRT-DEFINITION END
55
56   ;;; KL-RELATION START
57   KLCOV=KLTRT
58   ;;; KL-RELATION END
59
60
61   ;;; KDTRT-DEFINITION START
62   IF (TRT.EQ.2)    KDTRT = 1
63   IF (TRT.EQ.1)    KDTRT = (1+THETA(7))
64   IF (TRT.EQ.3)    KDTRT = (1+THETA(8))
65   IF (TRT.EQ.4)    KDTRT = (1+THETA(9))
66   IF (TRT.EQ.5)    KDTRT = (1+THETA(10))
67   ;;; KDTRT-DEFINITION END
68
69
70   ;;; KDBSLD-DEFINITION START
71       KDBSLD = ((BSLD/91)**THETA(6))
72   ;;; KDBSLD-DEFINITION END
73
74   ;;; KD-RELATION START
75   KDCOV=KDBSLD*KDTRT
76   ;;; KD-RELATION END
77
78
79
80   TVKL=LOG(THETA(1)/52)           ; change to rate/year from /weeks
81
82   TVKL = KLCOV*TVKL
83   MU_1=TVKL
84   KL = EXP(MU_1+ETA(1))
85
86   TVKD=LOG(THETA(2)/52)
87
88   TVKD = KDCOV*TVKD
89   MU_2=TVKD
90   KD = EXP(MU_2+ETA(2))
91
92   TVLAM=LOG(THETA(3)/52)
93
94   TVLAM = LAMCOV*TVLAM
95   MU_3=TVLAM
96   LAM = EXP(MU_3+ETA(3))
97
98   A_0(1)=BSLD
99
100
101
102   $DES
103
104       ;y(t) = y(0) exp[ kL t - (kD Treatment/lam)(1-exp(-lam t)) ].
105       ;dy/dt = [kL t - kD/lam Treatment (exp(-lam t))] y(t).
106
107
108   DADT(1) = (KL - KD*EXP(-LAM*T))*A(1)
109
110

```

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```

111
112
113 $ERROR
114
115 IPRED=A(1)
116 W = SQRT(THETA(4)**2*IPRED**2+THETA(5)**2)
117
118 Y=IPRED+W*ERR(1)
119
120 IWRES=(DV-IPRED)/W
121
122
123 XL=LOG(KL)
124 XD=LOG(LAM*KD)
125
126 IF (XL.GT.XD) THEN
127     TTG=0
128 ELSE
129     TTG=(LOG(LAM*KD)-LOG(KL))/LAM ; added lam for KD term to adjust
130 ENDIF
131
132
133 W6 = BSLD*EXP(KL*6-(KD/LAM)*(1-EXP(-LAM*6)))
134 W8 = BSLD*EXP(KL*8-(KD/LAM)*(1-EXP(-LAM*8)))
135 TR6= W6/BSLD
136 TR8= W8/BSLD
137
138
139 $THETA (0,0.143663) ; KL
140 (0,1.60217) ; KD
141 (0,3.939) ; LAM
142 (0.01,0.0811432) ; Proportional Error
143 (0.01,2.26872) ; Additive Error
144
145 $THETA (-100,0.0506293,100000) ; KDBSLD1
146
147 $THETA (-100000,0.352134,100000) ; KDTRT1
148 (-100000,-0.0745063,100000) ; KDTRT2
149 (-100000,0.0073258,100000) ; KDTRT3
150 (-100000,-0.0769689,100000) ; KDTRT4
151
152 $THETA (-100000,-0.0946182,100000) ; KLTRT1
153 (-100000,-0.036812,100000) ; KLTRT2
154 (-100000,0.0612846,100000) ; KLTRT3
155 (-100000,0.0898521,100000) ; KLTRT4
156
157 $THETA (-100000,0.212748,100000) ; LAMTRT1
158 (-100000,-0.397089,100000) ; LAMTRT2
159 (-100000,0.0522,100000) ; LAMTRT3
160 (-100000,0.0611664,100000) ; LAMTRT4
161
162 $OMEGA 2.26315 ; ETA(KL)
163 0.839075 ; ETA(KD)
164 1.66932 ; ETA(LAM)
165
166 $SIGMA 1 FIX
167
168 ;$EST PRINT=10 MAXEVAL=9999 METHOD=1 INTER FILE=run4.ext
169
170 $EST METHOD=SAEM EONLY=0 INTER NBURN=3000 NITER=250 SEED=2019 PRINT=50 DF=0
171 GRD=DDDSS CTYPE=3 CITER=10 CALPHA=0.05 ISAMPLE=2 IACCEPT=0.4
172 $EST METHOD=IMP EONLY=1 NITER=5 ISAMPLE=4000 PRINT=1 DF=4 GRD=DDDSS IACCEPT=1.0 MAPITER=0 FILE
    =run13.ext
173 CTYPE=3 CITER=10 CALPHA=0.05 MSFO=MK13.msf
174
175 $COV PRINT=E
176
177 $TABLE PROT ID TIME IPRED WRES CWRES IWRES

```

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```
178 KL KD LAM TTG TR6 TR8
179 BSLD DV DSLD LBSLD LSLD TRT
180 ETA1 ETA2 ETA3
181 FORMAT=sF12.6 ONEHEADER NOPRINT FILE=tgi13.fit
182
183
184 NM-TRAN MESSAGES
185
186 WARNINGS AND ERRORS (IF ANY) FOR PROBLEM      1
187
188 (WARNING  2) NM-TRAN INFERS THAT THE DATA ARE POPULATION.
189
190 (MU_WARNING 26) DATA ITEM(S) USED IN DEFINITION OF MU_(S) SHOULD BE CONSTANT FOR INDIV. REC.:
191   BSLD
192
193 License Registered to: Pfizer
194 Expiration Date:      14 JUN 2020
195 Current Date:         24 FEB 2020
196 Days until program expires : 110
197 1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.4.3
198   ORIGINALLY DEVELOPED BY STUART BEAL, LEWIS SHEINER, AND ALISON BOECKMANN
199   CURRENT DEVELOPERS ARE ROBERT BAUER, ICON DEVELOPMENT SOLUTIONS,
200   AND ALISON BOECKMANN. IMPLEMENTATION, EFFICIENCY, AND STANDARDIZATION
201   PERFORMED BY NOUS INFOSYSTEMS.
202
203 PROBLEM NO.:          1
204 run13.mod; Claret TGI model
205 0DATA CHECKOUT RUN:           NO
206 DATA SET LOCATED ON UNIT NO.: 2
207 THIS UNIT TO BE REWOUND:      NO
208 NO. OF DATA RECS IN DATA SET: 12356
209 NO. OF DATA ITEMS IN DATA SET: 56
210 ID DATA ITEM IS DATA ITEM NO.: 4
211 DEP VARIABLE IS DATA ITEM NO.: 37
212 MDV DATA ITEM IS DATA ITEM NO.: 56
213 0INDICES PASSED TO SUBROUTINE PRED:
214   48 16  0  0  0  0  0  0  0  0  0  0
215 0LABELS FOR DATA ITEMS:
216   C PROT NSID ID STID DOSE DOSEP DOSIV DOSIVP DOS2 DOS2P TRT PERD NTPD DAY TIME FLAG AGE SEX
    RACE ETHN RACD BWT SMOK BBMI
217   BCCL BCAL BPLT BNEU BHGB BALB BLDH BALT BAST BBIL BSLD DV SURT CENS ECOG METS LIVMET LNGMET
    BONMET MSKCC HENG EGFR EVID
218   EVNT DOSRED DOSINT BLYM DSLD LBSLD LSLD MDV
219 0(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:
220   KL KD LAM IPRED IWRES TTG TR6 TR8
221 0FORMAT FOR DATA:
222   (18(3E20.0/),1E20.0,1F2.0)
223
224 TOT. NO. OF OBS RECS:      12356
225 TOT. NO. OF INDIVIDUALS:    1839
226 0LENGTH OF THETA: 18
227 0DEFAULT THETA BOUNDARY TEST OMITTED: NO
228 0OMEGA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 3
229 0DEFAULT OMEGA BOUNDARY TEST OMITTED: NO
230 0SIGMA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 1
231 0DEFAULT SIGMA BOUNDARY TEST OMITTED: NO
232 0INITIAL ESTIMATE OF THETA:
233   LOWER BOUND      INITIAL EST      UPPER BOUND
234   0.0000E+00      0.1437E+00      0.1000E+07
235   0.0000E+00      0.1602E+01      0.1000E+07
236   0.0000E+00      0.3939E+01      0.1000E+07
237   0.1000E-01      0.8114E-01      0.1000E+07
238   0.1000E-01      0.2269E+01      0.1000E+07
239  -0.1000E+03      0.5063E-01      0.1000E+06
240  -0.1000E+06      0.3521E+00      0.1000E+06
241  -0.1000E+06     -0.7451E-01      0.1000E+06
242  -0.1000E+06      0.7326E-02      0.1000E+06
243  -0.1000E+06     -0.7697E-01      0.1000E+06
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244 -0.1000E+06 -0.9462E-01 0.1000E+06
245 -0.1000E+06 -0.3681E-01 0.1000E+06
246 -0.1000E+06 0.6128E-01 0.1000E+06
247 -0.1000E+06 0.8985E-01 0.1000E+06
248 -0.1000E+06 0.2127E+00 0.1000E+06
249 -0.1000E+06 -0.3971E+00 0.1000E+06
250 -0.1000E+06 0.5220E-01 0.1000E+06
251 -0.1000E+06 0.6117E-01 0.1000E+06
252 0INITIAL ESTIMATE OF OMEGA:
253 0.2263E+01
254 0.0000E+00 0.8391E+00
255 0.0000E+00 0.0000E+00 0.1669E+01
256 0INITIAL ESTIMATE OF SIGMA:
257 0.1000E+01
258 0SIGMA CONSTRAINED TO BE THIS INITIAL ESTIMATE
259 0COVARIANCE STEP OMITTED: NO
260 EIGENVLS. PRINTED: YES
261 SPECIAL COMPUTATION: NO
262 COMPRESSED FORMAT: NO
263 GRADIENT METHOD USED: NOSLOW
264 SIGDIGITS ETAHAT (SIGLO): -1
265 SIGDIGITS GRADIENTS (SIGL): -1
266 EXCLUDE COV FOR FOCE (NOFCOV): NO
267 TURN OFF Cholesky Transposition of R Matrix (CHOLROFF): NO
268 KNUTHSUMOFF: -1
269 RESUME COV ANALYSIS (RESUME): NO
270 SIR SAMPLE SIZE (SIRSAMPLE): -1
271 NON-LINEARLY TRANSFORM THETAS DURING COV (THBND): 1
272 PRECONDITIONING CYCLES (PRECOND): 0
273 PRECONDITIONING TYPES (PRECONDS): TOS
274 FORCED PRECONDITIONING CYCLES (PFCOND): 0
275 PRECONDITIONING TYPE (PRETYPE): 0
276 FORCED POS. DEFINITE SETTING: (FPOSDEF): 0
277 0TABLES STEP OMITTED: NO
278 NO. OF TABLES: 1
279 SEED NUMBER (SEED): 11456
280 RANMETHOD: 3U
281 MC SAMPLES (ESAMPLE): 300
282 WRES SQUARE ROOT TYPE (WRESCHOL): EIGENVALUE
283 0-- TABLE 1 --
284 0RECORDS ONLY: ALL
285 04 COLUMNS APPENDED: YES
286 PRINTED: NO
287 HEADERS: ONE
288 FILE TO BE FORWARDED: NO
289 FORMAT: sF12.6
290 LFORMAT:
291 RFORMAT:
292 FIXED_EFFECT_ETAS:
293 0USER-CHOSEN ITEMS:
294 PROT ID TIME IPRED CWRES IWRES KL KD LAM TTG TR6 TR8 BSLD DV DSLD LBSLD LSLD TRT ETA1 ETA2
    ETA3
295 1DOUBLE PRECISION PREDPP VERSION 7.4.3
296
297 GENERAL NONLINEAR KINETICS MODEL WITH STIFF/NONSTIFF EQUATIONS (LSODA, ADVAN13)
298 0MODEL SUBROUTINE USER-SUPPLIED - ID NO. 9999
299 0MAXIMUM NO. OF BASIC PK PARAMETERS: 3
300 0COMPARTMENT ATTRIBUTES
301 COMPT. NO. FUNCTION INITIAL ON/OFF DOSE DEFAULT DEFAULT
302 STATUS ALLOWED ALLOWED FOR DOSE FOR OBS.
303 1 TUMOR ON YES YES YES YES
304 2 OUTPUT OFF YES NO NO NO
305 INITIAL (BASE) TOLERANCE SETTINGS:
306 NRD (RELATIVE) VALUE(S) OF TOLERANCE: 6
307 ANRD (ABSOLUTE) VALUE(S) OF TOLERANCE: 12
308 1
309 ADDITIONAL PK PARAMETERS - ASSIGNMENT OF ROWS IN GG
310 COMPT. NO. INDICES

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	SCALE	BIOAVAIL. FRACTION	ZERO-ORDER RATE	ZERO-ORDER DURATION	ABSORB LAG
1	*	*	*	*	*
2	*	-	-	-	-
- PARAMETER IS NOT ALLOWED FOR THIS MODEL					
* PARAMETER IS NOT SUPPLIED BY PK SUBROUTINE;					
WILL DEFAULT TO ONE IF APPLICABLE					
ODATA ITEM INDICES USED BY PRED ARE:					
EVENT ID DATA ITEM IS DATA ITEM NO.:			48		
TIME DATA ITEM IS DATA ITEM NO.:			16		
OPK SUBROUTINE CALLED WITH EVERY EVENT RECORD.					
PK SUBROUTINE NOT CALLED AT NONEVENT (ADDITIONAL OR LAGGED) DOSE TIMES.					
OPK SUBROUTINE INDICATES THAT COMPARTMENT AMOUNTS ARE INITIALIZED.					
OERROR SUBROUTINE CALLED WITH EVERY EVENT RECORD.					
OERROR SUBROUTINE INDICATES THAT DERIVATIVES OF COMPARTMENT AMOUNTS ARE USED.					
ODES SUBROUTINE USES COMPACT STORAGE MODE.					
1					
#TBLN: 1					
#METH: Stochastic Approximation Expectation-Maximization					
ESTIMATION STEP OMITTED: NO					
ANALYSIS TYPE: POPULATION					
NUMBER OF SADDLE POINT RESET ITERATIONS: 0					
GRADIENT METHOD USED: NOSLOW					
CONDITIONAL ESTIMATES USED: YES					
CENTERED ETA: NO					
EPS-ETA INTERACTION: YES					
LAPLACIAN OBJ. FUNC.: NO					
NO. OF FUNCT. EVALS. ALLOWED: 2400					
NO. OF SIG. FIGURES REQUIRED: 3					
INTERMEDIATE PRINTOUT: YES					
ESTIMATE OUTPUT TO MSF: YES					
IND. OBJ. FUNC. VALUES SORTED: NO					
NUMERICAL DERIVATIVE					
FILE REQUEST (NUMBER): NONE					
MAP (ETAHAT) ESTIMATION METHOD (OPTMAP): 0					
ETA HESSIAN EVALUATION METHOD (ETADER): 0					
INITIAL ETA FOR MAP ESTIMATION (MCETA): 0					
SIGDIGITS FOR MAP ESTIMATION (SIGLO): 100					
GRADIENT SIGDIGITS OF					
FIXED EFFECTS PARAMETERS (SIGL): 100					
NOPRIOR SETTING (NOPRIOR): OFF					
NOCOV SETTING (NOCOV): OFF					
DERCONT SETTING (DERCONT): OFF					
FINAL ETA RE-EVALUATION (FNLETA): ON					
EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS					
IN SHRINKAGE (ETATYPE): NO					
NON-INFL. ETA CORRECTION (NONINFETA): OFF					
RAW OUTPUT FILE (FILE): run13.ext					
EXCLUDE TITLE (NOTITLE): NO					
EXCLUDE COLUMN LABELS (NOLABEL): NO					
FORMAT FOR ADDITIONAL FILES (FORMAT): S1PE12.5					
PARAMETER ORDER FOR OUTPUTS (ORDER): TSOL					
WISHART PRIOR DF INTERPRETATION (WISHTYPE): 0					
KNUTHSUMOFF: 0					
INCLUDE LNTWOPI: NO					
INCLUDE CONSTANT TERM TO PRIOR (PRIORC): NO					
INCLUDE CONSTANT TERM TO OMEGA (ETA) (OLNTWOPI): NO					
EM OR BAYESIAN METHOD USED: STOCHASTIC APPROXIMATION EXPECTATION MAXIMIZATION (SAEM)					
MU MODELING PATTERN (MUM):					
GRADIENT/GIBBS PATTERN (GRD): DDDSS					
AUTOMATIC SETTING FEATURE (AUTO): OFF					
CONVERGENCE TYPE (CTYPE): 3					
CONVERGENCE INTERVAL (CINTERVAL): 50					

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378 CONVERGENCE ITERATIONS (CITER): 10
379 CONVERGENCE ALPHA ERROR (CALPHA): 5.000000000000000E-02
380 BURN-IN ITERATIONS (NBURN): 3000
381 ITERATIONS (NITER): 250
382 ANEAL SETTING (CONSTRAIN): 1
383 STARTING SEED FOR MC METHODS (SEED): 2019
384 MC SAMPLES PER SUBJECT (ISAMPLE): 2
385 RANDOM SAMPLING METHOD (RANMETHOD): 3U
386 EXPECTATION ONLY (EONLY): 0
387 PROPOSAL DENSITY SCALING RANGE
388 (ISCALE_MIN, ISCALE_MAX): 1.000000000000000E-06 ,1000000.00000000
389 SAMPLE ACCEPTANCE RATE (IACCEPT): 0.400000000000000
390 METROPOLIS HASTINGS SAMPLING FOR INDIVIDUAL ETAS:
391 SAMPLES FOR GLOBAL SEARCH KERNEL (ISAMPLE_M1): 2
392 SAMPLES FOR NEIGHBOR SEARCH KERNEL (ISAMPLE_M1A): 0
393 SAMPLES FOR MASS/IMP/POST. MATRIX SEARCH (ISAMPLE_M1B): 2
394 SAMPLES FOR LOCAL SEARCH KERNEL (ISAMPLE_M2): 2
395 SAMPLES FOR LOCAL UNIVARIATE KERNEL (ISAMPLE_M3): 2
396 PWR. WT. MASS/IMP/POST MATRIX ACCUM. FOR ETAS (IKAPPA): 1.000000000000000
397 MASS/IMP./POST. MATRIX REFRESH SETTING (MASSREST): -1
398
399 TOLERANCES FOR ESTIMATION/EVALUATION STEP:
400 NRD (RELATIVE) VALUE(S) OF TOLERANCE: 6
401 ANRD (ABSOLUTE) VALUE(S) OF TOLERANCE: 12
402 TOLERANCES FOR COVARIANCE STEP:
403 NRD (RELATIVE) VALUE(S) OF TOLERANCE: 6
404 ANRD (ABSOLUTE) VALUE(S) OF TOLERANCE: 12
405
406 THE FOLLOWING LABELS ARE EQUIVALENT
407 PRED=PREDI
408 RES=RESI
409 WRES=WRESI
410 IWRS=IWRESI
411 IPRD=IPREDI
412 IRS=IRESI
413
414 EM/BAYES SETUP:
415 THETAS THAT ARE MU MODELED:
416 1 2 3 6 7 8 9 10 11 12 13 14 15 16 17 18
417 THETAS THAT ARE SIGMA-LIKE:
418 4 5
419
420 MONITORING OF SEARCH:
421
422 Stochastic/Burn-in Mode
423 iteration -3000 SAEMOBJ= 87274.446154680772
424 iteration -2950 SAEMOBJ= 63382.040134968243
425 iteration -2900 SAEMOBJ= 63223.342966300661
426 iteration -2850 SAEMOBJ= 63076.399386978737
427 iteration -2800 SAEMOBJ= 63181.251253389688
428 iteration -2750 SAEMOBJ= 62952.293357295217
429 iteration -2700 SAEMOBJ= 62983.119382505538
430 iteration -2650 SAEMOBJ= 63043.688686895068
431 iteration -2600 SAEMOBJ= 63042.184687491965
432 iteration -2550 SAEMOBJ= 62912.559898850857
433 iteration -2500 SAEMOBJ= 63058.787519545702
434 iteration -2450 SAEMOBJ= 63182.482762401276
435 Convergence achieved
436 Reduced Stochastic/Accumulation Mode
437 iteration 0 SAEMOBJ= 63140.488494599806
438 iteration 50 SAEMOBJ= 62347.537370344711
439 iteration 100 SAEMOBJ= 62334.415933632015
440 iteration 150 SAEMOBJ= 62327.918142434042
441 iteration 200 SAEMOBJ= 62326.351656772902
442 iteration 250 SAEMOBJ= 62324.465067571509
443
444 #TERM:
445 STOCHASTIC PORTION WAS COMPLETED

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```
*****
507
508
509
510
511
512
513 #OBJV:***** 62324.465 *****
*****
514 1
515 *****
*****
516 *****
*****
*****
517 ***** STOCHASTIC APPROXIMATION EXPECTATION-MAXIMIZATION
*****
518 ***** FINAL PARAMETER ESTIMATE
*****
519 *****
*****
520 *****
*****
521
522
523
524 THETA - VECTOR OF FIXED EFFECTS PARAMETERS *****
525
526
527 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 TH 8 TH 9
TH13 TH10 TH11 TH12 TH16 TH17 TH18
528 1.40E-01 1.61E+00 3.98E+00 8.13E-02 2.26E+00 5.08E-02 3.55E-01 -7.75E-02 9.70E
-03 -7.73E-02 -9.00E-02 -3.13E-02
529 6.43E-02 9.23E-02 1.83E-01 -4.13E-01 5.32E-02 6.20E-02
530
531
532
533
534
535 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS *****
536
537
538 ETA1 ETA2 ETA3
539
540 ETA1
541 + 2.35E+00
542
543 ETA2
544 + 0.00E+00 8.42E-01
545
546 ETA3
547 + 0.00E+00 0.00E+00 1.68E+00
548
549
550
551 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****
552
553
554 EPS1
555
556 EPS1
557 + 1.00E+00
558
559 1
560
561
562 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS *****
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563
564
565          ETA1          ETA2          ETA3
566
567  ETA1
568  +      1.53E+00
569
570  ETA2
571  +      0.00E+00    9.17E-01
572
573  ETA3
574  +      0.00E+00    0.00E+00    1.30E+00
575
576
577
578  SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS  ***
579
580
581          EPS1
582
583  EPS1
584  +      1.00E+00
585
586  1
587  *****
588  *****
589  *****
590  *****
591  *****
592  *****
593
594
595
596  THETA - VECTOR OF FIXED EFFECTS PARAMETERS  *****
597
598
599          TH 1          TH 2          TH 3          TH 4          TH 5          TH 6          TH 7          TH 8          TH 9
600          TH13          TH10          TH11          TH12          TH17          TH18
601
602          1.46E-02    8.20E-02    3.77E-01    1.95E-04    1.67E-02    9.74E-03    2.84E-02    4.71E-02    2.74E
-02    2.00E-02    2.72E-02    5.24E-02
603          3.52E-02    2.73E-02    9.10E-02    9.74E-02    6.99E-02    4.67E-02
604
605
606
607  OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS  *****
608
609
610          ETA1          ETA2          ETA3
611
612  ETA1
613  +      2.37E-01
614
615  ETA2
616  +      0.00E+00    5.78E-02
617
618  ETA3
619  +      0.00E+00    0.00E+00    1.52E-01
620

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```
621
622
623 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS  ****
624
625
626 EPS1
627
628 EPS1
629 + 0.00E+00
630
631 1
632
633
634 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS  ****
635
636
637 ETA1 ETA2 ETA3
638
639 ETA1
640 + 7.73E-02
641
642 ETA2
643 + ..... 3.15E-02
644
645 ETA3
646 + ..... 5.88E-02
647
648
649
650 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS  ***
651
652
653 EPS1
654
655 EPS1
656 + .....
657
658 1
659 *****
660 *****
661 *****
662 *****
663 *****
664 *****
665
666
667 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 TH 8 TH
668 9 TH10 TH11 TH12 TH17 TH18 OM11 OM12
669 OM13 OM22 OM23 OM33
670 SG11
671 TH 1
672 + 2.12E-04
673
674 TH 2
675 + -8.63E-05 6.72E-03
676
677 TH 3
678 + -2.02E-03 1.10E-02 1.42E-01
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679
680 TH 4
681 + -7.63E-09 -4.27E-07 3.77E-06 3.81E-08
682
683 TH 5
684 + 8.05E-06 -2.22E-04 -1.41E-04 -1.37E-06 2.80E-04
685
686 TH 6
687 + 2.15E-07 4.72E-05 3.52E-04 -4.72E-08 1.25E-05 9.49E-05
688
689 TH 7
690 + -1.91E-05 9.35E-04 -2.66E-04 9.85E-08 -1.63E-05 -2.49E-05 8.09E-04
691
692 TH 8
693 + 1.43E-05 5.28E-04 -5.53E-04 1.70E-07 5.19E-05 -1.10E-05 1.62E-04 2.22E-03
694
695 TH 9
696 + -5.08E-06 8.44E-04 4.36E-04 1.72E-07 -1.07E-05 -1.15E-05 1.89E-04 1.33E-04 7.52E
-04
697
698 TH10
699 + -5.98E-06 9.03E-04 1.08E-03 4.73E-08 4.17E-06 3.39E-05 1.43E-04 1.14E-04 1.34E
-04 4.00E-04
700
701 TH11
702 + 1.65E-04 -8.02E-05 -1.61E-03 1.27E-10 6.74E-06 -1.59E-06 1.35E-04 6.74E-06 -4.03E
-07 -4.67E-06 7.37E-04
703
704 TH12
705 + 2.05E-04 3.59E-05 -1.48E-03 1.10E-08 -1.20E-05 8.54E-06 8.30E-07 -3.42E-05 -3.73E
-06 -4.63E-07 1.97E-04 2.75E-03
706
707 TH13
708 + 1.78E-04 4.34E-05 -1.25E-03 3.60E-10 -1.66E-05 6.01E-06 9.41E-06 -1.08E-05 7.64E
-05 3.48E-06 2.30E-04 2.31E-04
709 1.24E-03
710
711 TH14
712 + 1.71E-04 9.70E-05 -8.92E-04 -1.56E-07 4.19E-06 9.02E-06 9.18E-06 -1.44E-05 2.03E
-06 5.30E-05 2.37E-04 2.34E-04
713 2.90E-04 7.46E-04
714
715 TH15
716 + -6.93E-05 -2.62E-04 8.77E-03 7.12E-07 1.04E-04 -1.19E-05 6.62E-04 5.25E-05 7.06E
-06 -2.20E-05 -5.88E-04 -1.33E-04
717 -2.28E-04 -2.46E-04 8.29E-03
718
719 TH16
720 + 1.12E-06 -5.13E-04 2.88E-03 5.44E-07 1.48E-04 2.26E-05 -2.42E-05 2.16E-04 6.35E
-07 -3.31E-08 -6.92E-05 -2.64E-03
721 -1.33E-04 -1.51E-04 7.62E-04 9.49E-03
722
723 TH17
724 + -1.17E-04 3.09E-04 1.04E-02 1.56E-10 6.08E-05 1.40E-05 -2.12E-06 1.81E-05 -6.99E
-05 4.36E-05 -1.53E-04 -1.41E-04
725 -9.05E-04 -1.69E-04 1.10E-03 5.45E-04 4.89E-03
726
727 TH18
728 + -1.55E-04 4.19E-04 1.10E-02 5.86E-07 -2.07E-05 1.01E-05 2.97E-06 3.23E-06 3.20E
-05 3.54E-05 -1.47E-04 -1.56E-04
729 -1.54E-04 -3.78E-04 1.02E-03 4.78E-04 9.97E-04 2.18E-03
730
731 OM11
732 + -1.67E-03 2.33E-03 2.23E-02 -2.10E-06 -2.54E-04 9.18E-05 2.38E-04 -2.87E-04 1.76E
-04 3.02E-04 3.81E-04 -7.19E-04
733 8.55E-04 1.22E-03 -2.95E-03 -1.98E-03 -4.28E-04 8.12E-04 5.62E-02
734
735 1

```

```

736          TH 1      TH 2      TH 3      TH 4      TH 5      TH 6      TH 7      TH 8      TH
737              9      TH10     TH11     TH12
738          TH13     TH14     TH15     TH16     TH17     TH18     OM11     OM12
739              OM13           OM22           OM23           OM33
740          SG11
741 OM12
742 + .....
743 .....
744 .....
745 OM13
746 + .....
747 .....
748 .....
749 OM22
750 + 2.05E-05 -2.23E-03 -9.75E-03 -5.36E-08 1.16E-04 -2.02E-05 3.75E-04 5.90E-05 -7.79E
751 -05 -2.45E-04 7.20E-05 1.20E-05
752 -1.18E-06 -4.44E-05 5.52E-04 2.87E-04 -2.50E-04 -3.53E-04 -1.95E-03 0.00E+00 0.00
753 E+00 3.34E-03
754 OM23
755 + .....
756 .....
757 .....
758 .....
759 OM33
760 + -4.09E-04 6.52E-03 2.72E-02 -4.13E-06 -9.03E-04 3.13E-05 1.15E-04 -8.48E-04 7.89E
761 -05 2.87E-04 -2.17E-04 1.62E-04
762 2.31E-04 4.01E-04 -9.66E-04 -2.33E-03 3.51E-04 7.11E-04 9.04E-03 0.00E+00 0.00
763 E+00 -4.13E-03 0.00E+00 2.32E-02
764 SG11
765 + .....
766 .....
767 .....
768 .....
769 .....
770 .....
771 .....
772 .....
773 .....
774 .....
775 TH 1      TH 2      TH 3      TH 4      TH 5      TH 6      TH 7      TH 8      TH
776              9      TH10     TH11     TH12
777          TH13     TH14     TH15     TH16     TH17     TH18     OM11     OM12
778              OM13           OM22           OM23           OM33
779          SG11
780 TH 1
781 + 1.46E-02

```

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```

781
782 TH 2
783 + -7.23E-02 8.20E-02
784
785 TH 3
786 + -3.68E-01 3.57E-01 3.77E-01
787
788 TH 4
789 + -2.68E-03 -2.67E-02 5.12E-02 1.95E-04
790
791 TH 5
792 + 3.30E-02 -1.62E-01 -2.24E-02 -4.19E-01 1.67E-02
793
794 TH 6
795 + 1.52E-03 5.91E-02 9.58E-02 -2.48E-02 7.64E-02 9.74E-03
796
797 TH 7
798 + -4.60E-02 4.01E-01 -2.48E-02 1.77E-02 -3.42E-02 -8.99E-02 2.84E-02
799
800 TH 8
801 + 2.08E-02 1.37E-01 -3.11E-02 1.85E-02 6.58E-02 -2.39E-02 1.21E-01 4.71E-02
802
803 TH 9
804 + -1.27E-02 3.75E-01 4.22E-02 3.21E-02 -2.34E-02 -4.31E-02 2.42E-01 1.03E-01 2.74E
      -02
805
806 TH10
807 + -2.05E-02 5.51E-01 1.43E-01 1.21E-02 1.24E-02 1.74E-01 2.51E-01 1.21E-01 2.45E
      -01 2.00E-02
808
809 TH11
810 + 4.16E-01 -3.60E-02 -1.57E-01 2.40E-05 1.48E-02 -6.00E-03 1.75E-01 5.27E-03 -5.41E
      -04 -8.61E-03 2.72E-02
811
812 TH12
813 + 2.69E-01 8.35E-03 -7.49E-02 1.08E-03 -1.37E-02 1.67E-02 5.57E-04 -1.39E-02 -2.59E
      -03 -4.42E-04 1.38E-01 5.24E-02
814
815 TH13
816 + 3.47E-01 1.50E-02 -9.38E-02 5.24E-05 -2.81E-02 1.75E-02 9.39E-03 -6.49E-03 7.91E
      -02 4.94E-03 2.41E-01 1.25E-01
817 3.52E-02
818
819 TH14
820 + 4.29E-01 4.33E-02 -8.66E-02 -2.93E-02 9.17E-03 3.39E-02 1.18E-02 -1.12E-02 2.70E
      -03 9.70E-02 3.19E-01 1.63E-01
821 3.01E-01 2.73E-02
822
823 TH15
824 + -5.22E-02 -3.51E-02 2.55E-01 4.00E-02 6.82E-02 -1.34E-02 2.56E-01 1.22E-02 2.83E
      -03 -1.21E-02 -2.38E-01 -2.78E-02
825 -7.11E-02 -9.89E-02 9.10E-02
826
827 TH16
828 + 7.86E-04 -6.42E-02 7.84E-02 2.86E-02 9.06E-02 2.38E-02 -8.72E-03 4.71E-02 2.38E
      -04 -1.70E-05 -2.62E-02 -5.16E-01
829 -3.88E-02 -5.67E-02 8.59E-02 9.74E-02
830
831 TH17
832 + -1.15E-01 5.40E-02 3.94E-01 1.14E-05 5.20E-02 2.06E-02 -1.06E-03 5.49E-03 -3.65E
      -02 3.12E-02 -8.04E-02 -3.85E-02
833 -3.68E-01 -8.87E-02 1.73E-01 8.00E-02 6.99E-02
834
835 TH18
836 + -2.27E-01 1.09E-01 6.27E-01 6.43E-02 -2.64E-02 2.22E-02 2.23E-03 1.47E-03 2.50E
      -02 3.79E-02 -1.16E-01 -6.35E-02
837 -9.36E-02 -2.96E-01 2.41E-01 1.05E-01 3.05E-01 4.67E-02
838

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	TH13	TH14	TH15	TH16	TH17	TH18	OM11	OM12		
	OM13	OM22	OM23	OM33						
884										
885	SG11									
886										
887	TH 1									
888	+	1.70E+04								
889										
890	TH 2									
891	+	-3.70E+02	5.62E+02							
892										
893	TH 3									
894	+	2.35E+02	-1.12E+01	2.92E+01						
895										
896	TH 4									
897	+	2.30E+04	-4.49E+02	-7.83E+03	3.97E+07					
898										
899	TH 5									
900	+	2.17E+02	-1.20E+01	-1.15E+02	2.75E+05	6.24E+03				
901										
902	TH 6									
903	+	-5.07E+02	-1.26E+02	-4.82E+01	-1.07E+03	-4.12E+02	1.14E+04			
904										
905	TH 7									
906	+	9.36E+02	-6.42E+02	3.23E+01	-8.48E+03	2.42E+00	7.18E+02	2.65E+03		
907										
908	TH 8									
909	+	2.49E+00	-8.02E+01	3.91E-01	-5.36E+02	-3.77E+01	8.70E+01	0.00E+00	4.86E+02	
910										
911	TH 9									
912	+	1.50E+02	-3.03E+02	-1.86E+00	-4.05E+02	6.01E+01	3.16E+02	0.00E+00	0.00E+00	1.67E
	+03									
913										
914	TH10									
915	+	5.59E+02	-6.75E+02	2.97E+00	-3.15E+02	-6.17E+01	-1.14E+03	0.00E+00	0.00E+00	0.00E
	+00	4.09E+03								
916										
917	TH11									
918	+	-2.45E+03	2.06E+02	-2.43E+01	-5.44E+03	-9.01E+01	-7.74E+01	-8.51E+02	0.00E+00	0.00E
	+00	0.00E+00	2.23E+03							
919										
920	TH12									
921	+	-6.56E+02	3.52E-01	-9.23E+00	-2.35E+03	-2.63E+01	-5.52E+01	0.00E+00	-2.13E+00	0.00E
	+00	0.00E+00	0.00E+00	5.61E+02						
922										
923	TH13									
924	+	-1.57E+03	2.12E+01	-2.35E+01	-2.20E+03	-5.98E+00	-4.09E+00	0.00E+00	0.00E+00	-1.17E
	+02	0.00E+00	0.00E+00	0.00E+00						
925		1.22E+03								
926										
927	TH14									
928	+	-3.42E+03	6.99E+01	-5.34E+01	-1.17E+04	-1.72E+02	1.58E+02	0.00E+00	0.00E+00	0.00E
	+00	-4.23E+02	0.00E+00	0.00E+00						
929		0.00E+00	2.59E+03							
930										
931	TH15									
932	+	-2.31E+02	6.76E+01	-2.13E+01	2.04E+03	1.21E+01	-1.17E+01	-2.79E+02	0.00E+00	0.00E
	+00	0.00E+00	2.10E+02	0.00E+00						
933		0.00E+00	0.00E+00	1.84E+02						
934										
935	TH16									
936	+	-1.88E+02	1.13E+00	-9.10E+00	4.72E+02	-3.83E+00	-3.00E+01	0.00E+00	-6.82E+00	0.00E
	+00	0.00E+00	0.00E+00	1.61E+02						
937		0.00E+00	0.00E+00	0.00E+00	1.59E+02					
938										
939	TH17									
940	+	-2.93E+02	-3.26E+00	-3.10E+01	7.26E+03	5.92E+01	4.20E+01	0.00E+00	0.00E+00	1.80E
	+01	0.00E+00	0.00E+00	0.00E+00						
941		2.28E+02	0.00E+00	0.00E+00	0.00E+00	3.01E+02				

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942
943 TH18
944 +      -6.78E+02  4.72E+00 -1.01E+02  1.73E+04  3.75E+02  1.62E+02  0.00E+00  0.00E+00  0.00E
          +00 -2.86E+01  0.00E+00  0.00E+00
945          0.00E+00  5.14E+02  0.00E+00  0.00E+00  0.00E+00  9.75E+02
946
947 OM11
948 +      5.28E+02  1.13E+00  1.53E+00  2.63E+03  2.50E+01 -2.77E+01 -3.26E+00 -1.07E+00 -2.73E
          -01  8.94E+00 -6.99E+01 -5.30E+00
949          -5.54E+01 -1.44E+02  6.52E+00  2.21E+00 -2.03E+00 -1.87E+01  3.88E+01
950
951 1
952
953          TH 1      TH 2      TH 3      TH 4      TH 5      TH 6      TH 7      TH 8      TH
          9      TH10      TH11      TH12
954          TH13      TH14      TH15      TH16      TH17      TH18      OM11      OM12
          OM13      OM22      OM23      OM33
955          SG11
956
957 OM12
958 +      .....
          .....
959          .....
960
961 OM13
962 +      .....
          .....
963          .....
          .....
964
965 OM22
966 +      6.57E+02  2.26E+02  3.90E+01  5.67E+03  4.09E+00 -2.64E+02 -5.33E+02 -1.60E+01 -7.86E
          +01  3.71E+01  4.70E+01 -3.35E+01
967          -8.00E+01 -1.78E+02 -2.57E+00 -1.53E+01 -4.39E+01 -1.15E+02  2.19E+01  0.00E+00  0.00
          E+00  6.36E+02
968
969 OM23
970 +      .....
          .....
971          .....
          .....
972
973 OM33
974 +      9.35E+01 -9.90E+01 -2.38E+01  2.71E+04  4.15E+02  1.57E+01  3.05E+01  3.50E+01  7.29E
          +01  1.56E+02 -7.61E+00  6.10E+00
975          -1.46E+01 -5.72E+01  1.07E+01  1.80E+01  2.18E+01  7.13E+01  8.37E-01  0.00E+00  0.00
          E+00  1.73E+01  0.00E+00  1.24E+02
976
977 SG11
978 +      .....
          .....
979          .....
          .....
980          .....
981
982 1
983
984
985
986
987
988
989
990
991
992
993
994

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```
995
996
997
998
999
1000
1001
1002
1003 *****
      *****
1004 *****
                                     *****
      *****
1005 ***** STOCHASTIC APPROXIMATION EXPECTATION-MAXIMIZATION
      *****
1006 ***** EIGENVALUES OF COR MATRIX OF ESTIMATE (S)
      *****
1007 *****
                                     *****
      *****
1008 ***** *****
      *****
1009
1010
1011          1          2          3          4          5          6          7          8          9
              10         11         12
1012          13         14         15         16         17         18         19         20
              21
1013
1014          1.27E-01  1.53E-01  1.97E-01  3.25E-01  4.02E-01  4.27E-01  4.53E-01  5.53E-01  6.77E
              -01  7.96E-01  8.67E-01  9.76E-01
1015          1.03E+00  1.06E+00  1.23E+00  1.36E+00  1.45E+00  1.47E+00  1.80E+00  2.48E+00  3.17
              E+00
1016
1017 1
1018
1019
1020 #TBLN:          2
1021 #METH: Objective Function Evaluation by Importance Sampling
1022
1023 ESTIMATION STEP OMITTED:          NO
1024 ANALYSIS TYPE:          POPULATION
1025 NUMBER OF SADDLE POINT RESET ITERATIONS:          0
1026 GRADIENT METHOD USED:          NOSLOW
1027 CONDITIONAL ESTIMATES USED:          YES
1028 CENTERED ETA:          NO
1029 EPS-ETA INTERACTION:          YES
1030 LAPLACIAN OBJ. FUNC.:          NO
1031 NO. OF FUNCT. EVALS. ALLOWED:          2400
1032 NO. OF SIG. FIGURES REQUIRED:          3
1033 INTERMEDIATE PRINTOUT:          YES
1034 ESTIMATE OUTPUT TO MSF:          YES
1035 IND. OBJ. FUNC. VALUES SORTED:          NO
1036 NUMERICAL DERIVATIVE
1037     FILE REQUEST (NUMBER):          NONE
1038 MAP (ETAHAT) ESTIMATION METHOD (OPTMAP):          0
1039 ETA HESSIAN EVALUATION METHOD (ETADER):          0
1040 INITIAL ETA FOR MAP ESTIMATION (MCETA):          0
1041 SIGDIGITS FOR MAP ESTIMATION (SIGLO):          100
1042 GRADIENT SIGDIGITS OF
1043     FIXED EFFECTS PARAMETERS (SIGL):          100
1044 NOPRIOR SETTING (NOPRIOR):          OFF
1045 NOCOV SETTING (NOCOV):          OFF
1046 DERCONT SETTING (DERCONT):          OFF
1047 FINAL ETA RE-EVALUATION (FNLETA):          ON
1048 EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS
1049     IN SHRINKAGE (ETATYPE):          NO
1050 NON-INFL. ETA CORRECTION (NONINFETA):          OFF
```

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1051 RAW OUTPUT FILE (FILE): run13.ext
1052 EXCLUDE TITLE (NOTITLE): NO
1053 EXCLUDE COLUMN LABELS (NOLABEL): NO
1054 FORMAT FOR ADDITIONAL FILES (FORMAT): S1PE12.5
1055 PARAMETER ORDER FOR OUTPUTS (ORDER): TSOL
1056 WISHART PRIOR DF INTERPRETATION (WISHTYPE): 0
1057 KNUTHSUMOFF: 0
1058 INCLUDE LNTWOPI: NO
1059 INCLUDE CONSTANT TERM TO PRIOR (PRIORC): NO
1060 INCLUDE CONSTANT TERM TO OMEGA (ETA) (OLNTWOPI): NO
1061 EM OR BAYESIAN METHOD USED: IMPORTANCE SAMPLING (IMP)
1062 MU MODELING PATTERN (MUM):
1063 GRADIENT/GIBBS PATTERN (GRD): DDDSS
1064 AUTOMATIC SETTING FEATURE (AUTO): OFF
1065 CONVERGENCE TYPE (CTYPE): 3
1066 CONVERGENCE INTERVAL (CINTERVAL): 1
1067 CONVERGENCE ITERATIONS (CITER): 10
1068 CONVERGENCE ALPHA ERROR (CALPHA): 5.000000000000000E-02
1069 ITERATIONS (NITER): 5
1070 ANEAL SETTING (CONSTRAIN): 1
1071 STARTING SEED FOR MC METHODS (SEED): 2019
1072 MC SAMPLES PER SUBJECT (ISAMPLE): 4000
1073 RANDOM SAMPLING METHOD (RANMETHOD): 3U
1074 EXPECTATION ONLY (EONLY): 1
1075 PROPOSAL DENSITY SCALING RANGE
1076 (ISCALE_MIN, ISCALE_MAX): 0.1000000000000000 ,10.00000000000000
1077 SAMPLE ACCEPTANCE RATE (IACCEPT): 1.000000000000000
1078 LONG TAIL SAMPLE ACCEPT. RATE (IACCEPTL): 0.000000000000000
1079 T-DIST. PROPOSAL DENSITY (DF): 4
1080 NO. ITERATIONS FOR MAP (MAPITER): 0
1081 INTERVAL ITER. FOR MAP (MAPINTER): 0
1082 MAP COVARIANCE/MODE SETTING (MAPCOV): 1
1083 Gradient Quick Value (GRDQ): 0.000000000000000
1084
1085 TOLERANCES FOR ESTIMATION/EVALUATION STEP:
1086 NRD (RELATIVE) VALUE(S) OF TOLERANCE: 6
1087 ANRD (ABSOLUTE) VALUE(S) OF TOLERANCE: 12
1088 TOLERANCES FOR COVARIANCE STEP:
1089 NRD (RELATIVE) VALUE(S) OF TOLERANCE: 6
1090 ANRD (ABSOLUTE) VALUE(S) OF TOLERANCE: 12
1091 TOLERANCES FOR TABLE/SCATTER STEP:
1092 NRD (RELATIVE) VALUE(S) OF TOLERANCE: 6
1093 ANRD (ABSOLUTE) VALUE(S) OF TOLERANCE: 12
1094
1095 THE FOLLOWING LABELS ARE EQUIVALENT
1096 PRED=PREDI
1097 RES=RESI
1098 WRES=WRESI
1099 IWRS=IWRESI
1100 IPRD=IPREDI
1101 IRS=IRESI
1102
1103 EM/BAYES SETUP:
1104 THETAS THAT ARE MU MODELED:
1105 1 2 3 6 7 8 9 10 11 12 13 14 15 16 17 18
1106 THETAS THAT ARE SIGMA-LIKE:
1107 4 5
1108
1109 MONITORING OF SEARCH:
1110
1111 iteration 0 OBJ= 65929.582753925293 eff.= 2145. Smpl.= 4000. Fit.=
1112 0.91892
1112 iteration 1 OBJ= 65930.137972741766 eff.= 2615. Smpl.= 4000. Fit.=
1113 0.91841
1113 iteration 2 OBJ= 65928.092607747836 eff.= 2655. Smpl.= 4000. Fit.=
1114 0.91809
1114 iteration 3 OBJ= 65933.556805435044 eff.= 2642. Smpl.= 4000. Fit.=
1115 0.91852

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1115 iteration          4 OBJ= 65933.646150501023 eff.= 2637. Smpl.= 4000. Fit.=
      0.91855
1116 iteration          5 OBJ= 65923.893857959090 eff.= 2672. Smpl.= 4000. Fit.=
      0.91842
1117
1118 #TERM:
1119 EXPECTATION ONLY PROCESS COMPLETED
1120
1121
1122 ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,
1123 AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.
1124
1125 ETABAR:          4.5661E-03  3.0260E-03 -3.1034E-03
1126 SE:             2.3084E-02  1.6643E-02  1.9231E-02
1127 N:              1839        1839        1839
1128
1129 P VAL.:          8.4320E-01  8.5573E-01  8.7180E-01
1130
1131 ETASHRINKSD (%)  3.5386E+01  2.2175E+01  3.6367E+01
1132 ETASHRINKVR (%)  5.8251E+01  3.9432E+01  5.9509E+01
1133 EBVSHRINKSD (%)  3.5599E+01  2.2069E+01  3.6512E+01
1134 EBVSHRINKVR (%)  5.8526E+01  3.9267E+01  5.9693E+01
1135 EPSSHRINKSD (%)  7.9524E-04
1136 EPSSHRINKVR (%)  1.5905E-03
1137
1138
1139 TOTAL DATA POINTS NORMALLY DISTRIBUTED (N):          12356
1140 N*LOG(2PI) CONSTANT TO OBJECTIVE FUNCTION:          22708.809032553872
1141 OBJECTIVE FUNCTION VALUE WITHOUT CONSTANT:          65923.893857959090
1142 OBJECTIVE FUNCTION VALUE WITH CONSTANT:          88632.702890512970
1143 REPORTED OBJECTIVE FUNCTION DOES NOT CONTAIN CONSTANT
1144
1145 TOTAL EFFECTIVE ETAS (NIND*NETA):          5517
1146
1147 #TERE:
1148 Elapsed estimation time in seconds: 1036.38
1149 Elapsed covariance time in seconds: 1248.07
1150 1
1151
1152
1153
1154
1155
1156
1157
1158
1159
1160
1161
1162
1163
1164
1165
1166
1167
1168
1169
1170
1171 *****
      *****
1172 *****
      *****
      *****
1173 *****
      *****
      *****
1174 #OBJT:*****
      *****
      *****
1175 *****

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```

*****
*****
1176 *****
*****
1177
1178
1179
1180
1181
1182
1183 #OBJV: ***** 65923.894 *****
*****
1184 1
1185 *****
*****
1186 *****
*****
*****
1187 ***** OBJECTIVE FUNCTION EVALUATION BY IMPORTANCE SAMPLING
*****
1188 ***** FINAL PARAMETER ESTIMATE
*****
1189 *****
*****
1190 *****
*****
1191
1192
1193
1194 THETA - VECTOR OF FIXED EFFECTS PARAMETERS *****
1195
1196
1197 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 TH 8 TH 9
TH10 TH11 TH12
1198 TH13 TH14 TH15 TH16 TH17 TH18
1199
1200 1.40E-01 1.61E+00 3.98E+00 8.13E-02 2.26E+00 5.08E-02 3.55E-01 -7.75E-02 9.70E
-03 -7.73E-02 -9.00E-02 -3.13E-02
1201 6.43E-02 9.23E-02 1.83E-01 -4.13E-01 5.32E-02 6.20E-02
1202
1203
1204
1205 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS *****
1206
1207
1208 ETA1 ETA2 ETA3
1209
1210 ETA1
1211 + 2.35E+00
1212
1213 ETA2
1214 + 0.00E+00 8.42E-01
1215
1216 ETA3
1217 + 0.00E+00 0.00E+00 1.68E+00
1218
1219
1220
1221 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****
1222
1223
1224 EPS1
1225
1226 EPS1
1227 + 1.00E+00
1228
1229 1
```

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1230
1231
1232 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS  *****
1233
1234
1235          ETA1          ETA2          ETA3
1236
1237  ETA1
1238 +          1.53E+00
1239
1240  ETA2
1241 +          0.00E+00   9.17E-01
1242
1243  ETA3
1244 +          0.00E+00   0.00E+00   1.30E+00
1245
1246
1247
1248 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS  ***
1249
1250
1251          EPS1
1252
1253  EPS1
1254 +          1.00E+00
1255
1256 1
1257 *****
1258 *****
1259 *****
1260 *****
1261 *****
1262 *****
1263 *****
1264 *****
1265 *****
1266 THETA - VECTOR OF FIXED EFFECTS PARAMETERS  *****
1267
1268
1269          TH 1          TH 2          TH 3          TH 4          TH 5          TH 6          TH 7          TH 8          TH 9
1270          TH10         TH11         TH12
1271          TH13         TH14         TH15         TH16         TH17         TH18
1272          1.63E-02   8.44E-02   3.66E-01   5.35E-03   1.97E-01   1.06E-02   4.21E-02   5.94E-02   3.14E
1273          -02   2.01E-02   2.42E-02   3.52E-02
1274          3.72E-02   2.95E-02   1.45E-01   1.19E-01   7.30E-02   5.19E-02
1275
1276
1277 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS  *****
1278
1279
1280          ETA1          ETA2          ETA3
1281
1282  ETA1
1283 +          1.76E-01
1284
1285  ETA2
1286 +          0.00E+00   6.19E-02
1287
```

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```
1288   ETA3
1289 +      0.00E+00  0.00E+00  2.56E-01
1290
1291
1292
1293   SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS   ****
1294
1295
1296           EPS1
1297
1298   EPS1
1299 +      0.00E+00
1300
1301   1
1302
1303
1304   OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS   *****
1305
1306
1307           ETA1      ETA2      ETA3
1308
1309   ETA1
1310 +      5.74E-02
1311
1312   ETA2
1313 +      .....  3.38E-02
1314
1315   ETA3
1316 +      .....  .....  9.87E-02
1317
1318
1319
1320   SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS   ***
1321
1322
1323           EPS1
1324
1325   EPS1
1326 +      .....
1327
1328   1
1329   *****
1330   *****
1331   *****
1332   *****
1333   *****
1334   *****
1335
1336
1337           TH 1      TH 2      TH 3      TH 4      TH 5      TH 6      TH 7      TH 8      TH
1338           9      TH10      TH11      TH12      TH17      TH18      OM11      OM12
1339           TH13      TH14      TH15      TH16      TH17      TH18      OM11      OM12
1340           OM13      OM22      OM23      OM33
1341   SG11
1342
1343   TH 1
1344 +      2.67E-04
1345
1346   TH 2
1347 +      1.72E-05  7.12E-03
```


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1346																				
1347	TH 3																			
1348	+	-2.14E-03	1.71E-02	1.34E-01																
1349																				
1350	TH 4																			
1351	+	-1.64E-05	1.32E-05	1.71E-04	2.86E-05															
1352																				
1353	TH 5																			
1354	+	3.21E-04	2.54E-04	-7.88E-03	-6.71E-04	3.87E-02														
1355																				
1356	TH 6																			
1357	+	-1.44E-05	-4.91E-06	1.06E-04	6.29E-06	-3.48E-04	1.12E-04													
1358																				
1359	TH 7																			
1360	+	3.53E-05	1.26E-03	2.80E-03	-2.77E-05	4.76E-04	-9.16E-06	1.77E-03												
1361																				
1362	TH 8																			
1363	+	-1.53E-06	1.19E-03	3.03E-03	2.90E-05	-9.00E-04	-2.37E-05	2.31E-04	3.53E-03											
1364																				
1365	TH 9																			
1366	+	1.72E-05	1.19E-03	2.94E-03	-2.10E-06	6.68E-05	-3.37E-05	2.70E-04	1.93E-04	9.89E-04										
	-04																			
1367																				
1368	TH10																			
1369	+	4.17E-06	9.80E-04	2.42E-03	8.37E-07	-1.01E-04	3.35E-05	2.54E-04	1.61E-04	1.74E-04										
	-04	4.06E-04																		
1370																				
1371	TH11																			
1372	+	1.57E-04	1.04E-04	-1.03E-03	3.30E-06	-1.22E-04	2.37E-06	5.66E-05	1.05E-05	1.20E-05										
	-05	1.42E-05	5.88E-04																	
1373																				
1374	TH12																			
1375	+	2.20E-04	1.97E-05	-2.03E-03	-3.89E-06	2.00E-04	-1.71E-05	2.60E-05	2.30E-04	1.53E-05										
	-05	5.07E-06	1.89E-04	1.24E-03																
1376																				
1377	TH13																			
1378	+	2.23E-04	5.42E-05	-1.89E-03	-5.33E-06	9.32E-05	-8.86E-06	1.72E-05	2.08E-05	9.62E-06										
	-06	1.00E-05	2.08E-04	2.40E-04																
1379		1.38E-03																		
1380																				
1381	TH14																			
1382	+	2.13E-04	4.57E-05	-1.91E-03	-1.51E-05	3.13E-04	-1.03E-05	2.38E-05	7.52E-06	1.54E-06										
	-05	-1.13E-05	2.15E-04	2.38E-04																
1383		2.53E-04	8.69E-04																	
1384																				
1385	TH15																			
1386	+	1.98E-04	3.87E-04	6.49E-03	-4.89E-05	9.98E-06	-4.72E-05	3.48E-03	2.52E-04	2.83E-05										
	-04	2.63E-04	-9.82E-04	2.14E-05																
1387		-8.37E-05	-1.62E-04	2.11E-02																
1388																				
1389	TH16																			
1390	+	-1.04E-04	9.83E-04	7.40E-03	3.75E-05	-2.11E-03	-3.10E-06	2.29E-04	5.57E-03	1.49E-05										
	-04	1.41E-04	-8.03E-05	4.51E-04																
1391		-6.00E-05	-8.46E-05	9.60E-04	1.41E-02															
1392																				
1393	TH17																			
1394	+	-1.74E-04	1.64E-03	1.36E-02	6.20E-06	-7.87E-04	-8.83E-07	3.74E-04	2.60E-04	1.33E-05										
	-03	2.61E-04	-1.23E-04	-1.76E-04																
1395		-4.92E-04	-1.74E-04	1.20E-03	7.19E-04	5.33E-03														
1396																				
1397	TH18																			
1398	+	-1.89E-04	1.71E-03	1.39E-02	8.55E-06	-3.36E-04	1.38E-05	3.54E-04	2.69E-04	2.97E-05										
	-04	5.50E-04	-1.20E-04	-1.87E-04																
1399		-1.81E-04	-4.02E-04	1.06E-03	7.13E-04	1.41E-03	2.70E-03													
1400																				
1401	OM11																			
1402	+	-1.77E-03	1.23E-04	1.15E-02	-1.18E-04	1.21E-03	3.47E-05	1.77E-04	-8.27E-05	-1.18E-05										
	-04	7.68E-06	-4.65E-06	-5.68E-04																

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```
1403      -4.85E-04 -9.91E-05 -3.87E-03  8.29E-04  8.30E-04  7.90E-04  3.10E-02
1404
1405 1
1406
1407      TH 1      TH 2      TH 3      TH 4      TH 5      TH 6      TH 7      TH 8      TH
1408          9      TH10      TH11      TH12
1408      TH13      TH14      TH15      TH16      TH17      TH18      OM11      OM12
1408          OM13      OM22      OM23      OM33
1409      SG11
1410
1411 OM12
1412 + .....
1412 .....
1413 .....
1414 .....
1415 OM13
1416 + .....
1416 .....
1417 .....
1417 .....
1418
1419 OM22
1420 + .....
1420 .....
1421      -6.93E-05 -1.60E-03 -1.01E-03 -1.15E-04  1.18E-03 -3.64E-06  3.00E-04 -2.62E-04 -5.38E
1421      -05  8.42E-05  2.34E-05 -9.63E-05
1421      -6.61E-05  3.23E-05  6.19E-04 -2.91E-04  1.05E-04  9.11E-05  2.59E-03  0.00E+00  0.00
1421      E+00  3.84E-03
1422
1423 OM23
1424 + .....
1424 .....
1425 .....
1425 .....
1426
1427 OM33
1428 + .....
1428 .....
1429      -6.54E-04  5.43E-03  2.62E-02  1.03E-05  7.80E-03  1.33E-04 -1.11E-03  3.04E-04  3.30E
1429      -04  1.15E-04  3.33E-04 -8.45E-04
1429      -4.73E-04 -1.70E-04 -9.95E-03 -1.44E-03  7.85E-04  1.68E-03  1.45E-03  0.00E+00  0.00
1429      E+00 -1.09E-03  0.00E+00  6.54E-02
1430
1431 SG11
1432 + .....
1432 .....
1433 .....
1433 .....
1434 .....
1435
1436 1
1437 *****
1437 *****
1438 *****
1438 *****
1439 *****
1439 *****
1440 *****
1440 *****
1441 *****
1441 *****
1442 *****
1442 *****
1443
1444
1445      TH 1      TH 2      TH 3      TH 4      TH 5      TH 6      TH 7      TH 8      TH
1445          9      TH10      TH11      TH12
1446      TH13      TH14      TH15      TH16      TH17      TH18      OM11      OM12
1446          OM13      OM22      OM23      OM33
1447      SG11
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1448																				
1449	TH 1																			
1450	+	1.63E-02																		
1451																				
1452	TH 2																			
1453	+	1.25E-02	8.44E-02																	
1454																				
1455	TH 3																			
1456	+	-3.59E-01	5.53E-01	3.66E-01																
1457																				
1458	TH 4																			
1459	+	-1.87E-01	2.93E-02	8.73E-02	5.35E-03															
1460																				
1461	TH 5																			
1462	+	9.99E-02	1.53E-02	-1.09E-01	-6.38E-01	1.97E-01														
1463																				
1464	TH 6																			
1465	+	-8.34E-02	-5.50E-03	2.73E-02	1.11E-01	-1.67E-01	1.06E-02													
1466																				
1467	TH 7																			
1468	+	5.14E-02	3.56E-01	1.82E-01	-1.23E-01	5.76E-02	-2.06E-02	4.21E-02												
1469																				
1470	TH 8																			
1471	+	-1.58E-03	2.37E-01	1.39E-01	9.14E-02	-7.70E-02	-3.78E-02	9.25E-02	5.94E-02											
1472																				
1473	TH 9																			
1474	+	3.35E-02	4.47E-01	2.56E-01	-1.25E-02	1.08E-02	-1.01E-01	2.04E-01	1.03E-01	3.14E-02										
1475	-02																			
1476	TH10																			
1477	+	1.27E-02	5.76E-01	3.28E-01	7.78E-03	-2.54E-02	1.58E-01	2.99E-01	1.34E-01	2.75E-01										
1478	-01	2.01E-02																		
1479	TH11																			
1480	+	3.97E-01	5.08E-02	-1.16E-01	2.55E-02	-2.56E-02	9.23E-03	5.56E-02	7.30E-03	1.57E-01										
1481	-02	2.91E-02	2.42E-02																	
1482	TH12																			
1483	+	3.82E-01	6.62E-03	-1.58E-01	-2.07E-02	2.89E-02	-4.59E-02	1.75E-02	1.10E-01	1.38E-01										
1484	-02	7.14E-03	2.21E-01	3.52E-02																
1485	TH13																			
1486	+	3.67E-01	1.72E-02	-1.39E-01	-2.68E-02	1.27E-02	-2.25E-02	1.10E-02	9.41E-03	8.22E-02										
1487	-03	1.34E-02	2.30E-01	1.84E-01																
1488		3.72E-02																		
1489	TH14																			
1490	+	4.42E-01	1.84E-02	-1.77E-01	-9.60E-02	5.40E-02	-3.30E-02	1.92E-02	4.29E-03	1.66E-01										
1491	-02	-1.90E-02	3.01E-01	2.29E-01																
1492		2.31E-01	2.95E-02																	
1493	TH15																			
1494	+	8.34E-02	3.16E-02	1.22E-01	-6.30E-02	3.49E-04	-3.07E-02	5.71E-01	2.92E-02	6.19E-01										
1495	-02	8.99E-02	-2.79E-01	4.19E-03																
1496		-1.55E-02	-3.79E-02	1.45E-01																
1497	TH16																			
1498	+	-5.34E-02	9.81E-02	1.70E-01	5.91E-02	-9.02E-02	-2.47E-03	4.59E-02	7.89E-01	3.99E-01										
1499	-02	5.89E-02	-2.79E-02	1.08E-01																
1500		-1.36E-02	-2.42E-02	5.56E-02	1.19E-01															
1501	TH17																			
1502	+	-1.46E-01	2.66E-01	5.07E-01	1.59E-02	-5.48E-02	-1.14E-03	1.22E-01	6.00E-02	5.80E-01										
1503	-01	1.77E-01	-6.95E-02	-6.86E-02																
1504		-1.81E-01	-8.08E-02	1.13E-01	8.29E-02	7.30E-02														
1505	TH18																			
1506	+	-2.23E-01	3.89E-01	7.31E-01	3.08E-02	-3.29E-02	2.52E-02	1.62E-01	8.72E-02	1.82E-01										

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-01  5.26E-01 -9.54E-02 -1.02E-01
1507  -9.39E-02 -2.63E-01  1.40E-01  1.16E-01  3.71E-01  5.19E-02
1508
1509  OM11
1510  +  -6.15E-01  8.31E-03  1.78E-01 -1.25E-01  3.50E-02  1.87E-02  2.39E-02 -7.92E-03 -2.13E
      -02  2.17E-03 -1.09E-03 -9.17E-02
1511  -7.41E-02 -1.91E-02 -1.51E-01  3.97E-02  6.46E-02  8.64E-02  1.76E-01
1512
1513  1
1514
1515      TH 1      TH 2      TH 3      TH 4      TH 5      TH 6      TH 7      TH 8      TH
      9      TH10      TH11      TH12
1516      TH13      TH14      TH15      TH16      TH17      TH18      OM11      OM12
      OM13      OM22      OM23      OM33
1517  SG11
1518
1519  OM12
1520  +  .....
      .....
1521  .....
1522
1523  OM13
1524  +  .....
      .....
1525  .....
      .....
1526
1527  OM22
1528  +  -6.85E-02 -3.06E-01 -4.46E-02 -3.47E-01  9.70E-02 -5.56E-03  1.15E-01 -7.12E-02 -2.76E
      -02  6.75E-02  1.56E-02 -4.42E-02
1529  -2.87E-02  1.77E-02  6.89E-02 -3.96E-02  2.33E-02  2.83E-02  2.38E-01  0.00E+00  0.00
      E+00  6.19E-02
1530
1531  OM23
1532  +  .....
      .....
1533  .....
      .....
1534
1535  OM33
1536  +  -1.57E-01  2.52E-01  2.80E-01  7.54E-03  1.55E-01  4.93E-02 -1.03E-01  2.00E-02  4.11E
      -02  2.23E-02  5.36E-02 -9.38E-02
1537  -4.97E-02 -2.25E-02 -2.68E-01 -4.73E-02  4.20E-02  1.26E-01  3.23E-02  0.00E+00  0.00
      E+00 -6.88E-02  0.00E+00  2.56E-01
1538
1539  SG11
1540  +  .....
      .....
1541  .....
      .....
1542  .....
1543
1544  1
1545  *****
      *****
1546  *****
      *****
1547  *****
      *****
      *****
1548  *****
      *****
      *****
1549  *****
      *****
1550  *****
      *****
1551
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1552										
1553		TH 1	TH 2	TH 3	TH 4	TH 5	TH 6	TH 7	TH 8	TH
		9	TH10	TH11	TH12					
1554		TH13	TH14	TH15	TH16	TH17	TH18	OM11	OM12	
		OM13	OM22	OM23	OM33					
1555		SG11								
1556										
1557	TH 1									
1558	+	1.91E+04								
1559										
1560	TH 2									
1561	+	-8.22E+02	6.19E+02							
1562										
1563	TH 3									
1564	+	2.56E+02	-8.62E+01	3.70E+01						
1565										
1566	TH 4									
1567	+	1.50E+04	3.51E+02	8.98E+01	8.44E+04					
1568										
1569	TH 5									
1570	+	1.27E+02	-5.50E+00	6.87E+00	1.29E+03	5.01E+01				
1571										
1572	TH 6									
1573	+	7.31E+02	1.69E+02	-8.66E+00	9.80E+02	9.70E+01	1.01E+04			
1574										
1575	TH 7									
1576	+	6.18E+02	-2.95E+02	2.37E+01	6.23E+02	-1.73E+00	1.43E+01	1.23E+03		
1577										
1578	TH 8									
1579	+	7.81E+01	-1.56E+02	2.03E+01	-6.77E+02	-1.04E+00	1.85E+02	1.80E-01	8.53E+02	
1580										
1581	TH 9									
1582	+	3.31E+02	-3.93E+02	5.82E+01	-2.66E+02	5.56E-01	5.51E+02	5.24E-01	1.27E+01	2.04E
	+03									
1583										
1584	TH10									
1585	+	9.08E+02	-1.10E+03	1.78E+02	-1.54E+03	5.01E+00	-1.84E+03	-3.26E+01	3.07E+01	5.51E
	+01	6.39E+03								
1586										
1587	TH11									
1588	+	-3.49E+03	1.49E+02	-3.02E+01	-3.35E+03	-1.16E+01	-1.95E+02	-5.74E+02	-2.64E+00	-9.47E
	+00	-2.79E+01	3.01E+03							
1589										
1590	TH12									
1591	+	-1.31E+03	1.96E+01	9.49E-01	-1.05E+03	-1.34E+01	2.67E+01	-9.90E-01	-1.59E+01	-1.56E
	+01	-3.79E+01	1.13E+01	1.02E+03						
1592										
1593	TH13									
1594	+	-1.25E+03	4.04E+01	-1.38E+01	-7.73E+02	-4.80E+00	-5.63E+01	2.85E+00	-5.43E+00	-1.53E
	+02	-4.07E+01	5.63E+00	7.35E+00						
1595		9.19E+02								
1596										
1597	TH14									
1598	+	-2.52E+03	7.54E+01	-4.27E+01	-1.22E+03	-1.47E+01	2.93E+01	6.42E+00	-8.32E+00	-1.72E
	+01	-3.84E+02	1.71E+01	1.43E+01						
1599		1.11E+01	1.80E+03							
1600										
1601	TH15									
1602	+	-2.36E+02	5.56E+01	-1.08E+01	-1.54E+02	-2.13E+00	-6.24E+00	-2.28E+02	-6.81E-01	-1.00E
	+00	-1.66E-02	2.25E+02	-1.90E-01						
1603		6.68E-02	-8.76E-01	1.04E+02						
1604										
1605	TH16									
1606	+	-3.05E+00	6.05E+01	-1.33E+01	2.85E+02	3.17E+00	-6.38E+01	7.19E-02	-3.36E+02	-3.21E
	+00	-1.54E+01	5.76E+00	-3.25E+01						
1607		2.00E+00	4.28E+00	-5.31E-01	2.08E+02					
1608										
1609	TH17									

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```

1610 +      -2.06E+02  1.06E+02 -4.62E+01  3.57E+01 -1.67E+00 -1.36E+02  4.53E-01 -1.75E+00 -5.45E
      +02 -2.70E+01  7.61E+00  2.77E+00
1611      1.15E+02  4.65E+00 -6.60E-01  2.17E+00  4.10E+02
1612
1613 TH18
1614 +      -6.53E+02  2.58E+02 -1.41E+02 -1.84E+02 -2.33E+01  3.41E+02  1.27E+01 -1.74E+00 -2.22E
      +00 -1.52E+03  1.53E+01  1.13E+00
1615      7.26E+00  3.94E+02 -2.74E+00  6.14E+00  1.49E+01  1.24E+03
1616
1617 OM11
1618 +      1.00E+03 -4.09E+01  7.24E+00  8.65E+02  6.13E+00  2.39E+01  5.83E+00  1.07E+01  2.74E
      +01  6.89E+01 -1.68E+02 -6.11E+01
1619      -6.01E+01 -1.37E+02  2.83E+00 -4.25E+00 -8.56E+00 -2.41E+01  9.12E+01
1620
1621 1
1622
1623      TH 1      TH 2      TH 3      TH 4      TH 5      TH 6      TH 7      TH 8      TH
      9      TH10      TH11      TH12
1624      TH13      TH14      TH15      TH16      TH17      TH18      OM11      OM12
      OM13      OM22      OM23      OM33
1625      SG11
1626
1627 OM12
1628 +      .....
      .....
1629      .....
1630
1631 OM13
1632 +      .....
      .....
1633      .....
      .....
1634
1635 OM22
1636 +      -1.82E+02  2.73E+02 -2.51E+01  1.94E+03  1.97E+01  1.14E+02 -1.44E+02 -5.54E+01 -1.27E
      +02 -5.77E+02 -7.58E+00  2.18E+01
1637      1.99E+01  1.50E+01  1.23E+01  2.60E+01  2.12E+01  7.80E+01 -3.39E+01  0.00E+00  0.00
      E+00  4.54E+02
1638
1639 OM23
1640 +      .....
      .....
1641      .....
      .....
1642
1643 OM33
1644 +      8.80E+01 -1.78E+01 -4.62E+00 -7.13E+01 -7.07E+00 -4.27E+01  7.63E+00 -7.49E+00  3.33E
      +00  4.70E+01 -2.01E+01  9.44E-01
1645      -1.71E+00 -1.36E+01  8.68E+00  5.99E+00  6.93E+00  3.88E+00  7.11E+00  0.00E+00  0.00
      E+00 -8.84E+00  0.00E+00  2.15E+01
1646
1647 SG11
1648 +      .....
      .....
1649      .....
      .....
1650      .....
1651
1652 1
1653
1654
1655
1656
1657
1658
1659
1660
1661

```

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```
1662
1663
1664
1665
1666
1667
1668
1669
1670
1671
1672
1673 *****
1674 *****
1675 *****
1676 *****
1677 *****
1678 *****
1679
1680
1681      1      2      3      4      5      6      7      8      9
1682      10     11     12     13     14     15     16     17     18     19     20
1683      21
1684      8.19E-02 1.36E-01 1.88E-01 2.29E-01 2.62E-01 2.76E-01 3.80E-01 6.38E-01 6.90E
1685      -01 7.75E-01 7.99E-01 8.02E-01
1686      9.04E-01 9.68E-01 1.19E+00 1.30E+00 1.61E+00 1.72E+00 2.00E+00 2.47E+00 3.57
1687      E+00
1688 Elapsed postprocess time in seconds: 3.27
1689 Elapsed finaloutput time in seconds: 0.46
1690 #CPUT: Total CPU Time in Seconds, 3724.619
1691 Stop Time:
1692 Mon Feb 24 13:19:38 EST 2020
```

Repository artifact ID FI-482536.

Appendix 7. Data Manipulation Log

Creation of the simulation dataset is presented below:

```
1  remove(list=ls())
2
3  library(tidyverse)
4  library(readxl)
5  library(magrittr)
6  library(lattice)
7  library(gridExtra)
8  library(GGally)
9  library(psych)
10 library(reshape2)
11 library(zoo)
12 library(survival)
13
14
15 as.num<-function(x){as.numeric(as.character(x))}
16 as.fac<-function(x){as.numeric(as.factor(x))}
17
18 # define equations for geometric mean, geometric cv%, and outliers
19 gm_mean<-function(x,na.rm=T){
20   a <- mean(log(x[x>0]),na.rm=T)
21   exp(a)
22 }
23
24 geocv<-function(x, na.rm = TRUE){
25   sdlog <- sd(log(x[x > 0]), na.rm = na.rm)
26   geosd <- exp(sdlog)
27   100*(sqrt(exp(log(geosd)^2)-1))
28 }
29
30 is_outlier <- function(x, na.rm=T) {
31   a<-quantile(x, 0.25,na.rm=T) - 1.5 * IQR(x,na.rm=T)
32   b<-quantile(x, 0.75,na.rm=T) + 1.5 * IQR(x,na.rm=T)
33   return(x < a | x > b)
34 }
35
36 `%!in%`=Negate(`%in%`)
37
38
39
40
41 #####
42 #
43 #---- Read in file
44 #
45 #####
46
47 #----Load in datafile
48 d1<-read.csv("RCC_COMBINED_PD_2_31OCT2019.csv",header=T,stringsAsFactors=F)
49
50
51 length(unique(d1$ID))
52 # [1] 1979
53
54 #####
55 #
56 # Explore SLD
57 #
58 #####
59
60
61 # Subset FLAGE = 3 for SLD
62 sld1<-d1 %>% subset(FLAGE==3) %>% subset(C==".")
63
```


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```
64 length(unique(sld1$ID)) # [1] 1842
65
66
67 summary(as.numeric(sld1$BSLD))
68 # Min. 1st Qu. Median Mean 3rd Qu. Max. NA's
69 # 10.00 45.00 79.65 106.35 141.00 707.50 11
70
71
72 # 11 missing baseline SLD, remove for now
73 sld1$C<-ifelse(sld1$BSLD=="", "CBSLD", sld1$C)
74
75 sld2<-sld1 %>% subset(C=="")
76 length(unique(sld2$ID)) # [1] 1839
77
78 summary(as.numeric(sld1$TAFD))
79 # Min. 1st Qu. Median Mean 3rd Qu. Max.
80 # 0.00 6.00 18.14 24.08 36.00 125.29
81 # Max time for tumor collection is 125, can go to 144 which is divisible by 6 or 8
82
83
84
85 # Expand grid
86 ini<-sld2 %>% select(ID) %>% distinct()
87 ini<-expand.grid(ID=ini$ID,
88 TTIME=seq(0,144,by=6)) %>%
89 arrange(ID,TTIME) %>%
90 distinct()
91
92
93 sld3<-sld2 %>% select(C,PROT,NSID,ID,STID,TRT,TRTG,FLAGE,
94 AGE,SEX,RACE,ETHN,RACD,BWT,SMOK,BBMI,
95 BCCL,BCAL,BPLT,BNEU,BHGB,BALB,BLDH,BALT,BAST,
96 BBIL,BSLD,SURT,CENS,ECOG,METS,LIVMET,
97 LNGMET,BONMET,MSKCC,HENG,EGFR,EVID,EVNT,
98 DOSRED,DOSINT,BLYM) %>%
99 distinct()
100
101
102 cd1<-merge(sld3,ini,by=c("ID"))
103 cd2<-cd1 %>% select(C,PROT,NSID,ID,STID,TRT,TRTG,FLAGE,
104 AGE,SEX,RACE,ETHN,RACD,BWT,SMOK,BBMI,
105 BCCL,BCAL,BPLT,BNEU,BHGB,BALB,BLDH,BALT,BAST,
106 BBIL,BSLD,SURT,CENS,ECOG,METS,LIVMET,
107 LNGMET,BONMET,MSKCC,HENG,EGFR,EVID,EVNT,
108 DOSRED,DOSINT,BLYM,TTIME) %>%
109 mutate(DV="") %>%
110 arrange(ID,TTIME) %>%
111 distinct()
112
113
114
115
116 write.csv(cd2,"SIM_RCC_COMBINED_PD2_SLD_31OCT2019.csv",quote=F,na="",
117 row.names= F)
118
119
```

Repository artifact ID FI-432756.

Example code for diagnostic plots is presented below:

```
1
2 rm(list=ls())
3
4 library(tidyverse)
5 library(gridExtra)
6 library(GGally)
7 library(psych)
```

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```
8
9
10
11 # load in datafile
12 dat1 <- read.table("tgil3.fit", na=".", header=T, skip=1)
13 dat1<-dat1 %>% mutate(SLD=DV)
14
15
16 # define aesthetics
17 size<- theme(axis.title.x=element_text(size=20),
18             axis.text.x=element_text(size=20),
19             axis.title.y=element_text(size=20),
20             axis.text.y=element_text(size=20),
21             legend.text=element_text(size=20),
22             legend.title=element_text(size=20),
23             plot.title=element_text(size=20),
24             strip.text.x=element_text(size=20),
25             strip.text.y=element_text(size=20))
26
27 size1<- theme(axis.title.x=element_text(size=28),
28             axis.text.x=element_text(size=24),
29             axis.title.y=element_text(size=28),
30             axis.text.y=element_text(size=24),
31             legend.text=element_text(size=20),
32             legend.title=element_text(size=24),
33             plot.title=element_text(size=28),
34             strip.text.x=element_text(size=24),
35             strip.text.y=element_text(size=24))
36
37
38
39
40
41 dat1$TREAT<-ifelse(dat1$TRT==1,"IFNa",
42                  ifelse(dat1$TRT==2,"Sunitinib",
43                        ifelse(dat1$TRT==3,"Sorafenib",
44                              ifelse(dat1$TRT==4,"Axitinib","Ave+Axi"))))
45
46
47 #####ETAs#####
48 #ETAS - histograms
49
50 #ETA1
51 p1<-ggplot(dat1, aes(x=ETA1)) +
52   geom_histogram(aes(y=..density..), # Histogram with density instead of count on y-axis
53                 colour="black", fill="#3399FF") +
54   geom_density(alpha=.2) + theme_bw() + labs(x=expression("ETA on KL")) + ylab("Density") +
55   geom_vline(aes(xintercept=0), color="red",
56             linetype="dashed", size=1)+size
57
58
59
60 #ETA2
61 p2<-ggplot(dat1, aes(x=ETA2)) +
62   geom_histogram(aes(y=..density..), # Histogram with density instead of count on y-axis
63                 colour="black", fill="#3399FF") +
64   geom_density(alpha=.2) + theme_bw() + labs(x=expression("ETA on KD")) + ylab("Density") +
65   geom_vline(aes(xintercept=0), color="red",
66             linetype="dashed", size=1)+size
67
68
69
70 #ETA3
71 p3<-ggplot(dat1, aes(x=ETA3)) +
72   geom_histogram(aes(y=..density..), # Histogram with density instead of count on y-axis
73                 colour="black", fill="#3399FF") +
74   geom_density(alpha=.2) + theme_bw() + labs(x=expression("ETA on LAM")) + ylab("Density") +
75   geom_vline(aes(xintercept=0), color="red",
```

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```
76         linetype="dashed", size=1)+size
77
78
79
80 grid.arrange(p1,p2,p3, ncol=2)
81
82
83 dev.print(file="ETA_Histogram.png", device=png, width=1200,height=1200)
84
85
86
87 #####error distribution
88
89 e1<-ggplot(dat1, aes(x=IWRES)) +
90   geom_histogram(aes(y=..density..),           # Histogram with density instead of count on y-axis
91                 colour="black", fill="#3399FF") +
92   geom_density(alpha=.2) + theme_bw() + xlab("IWRES") + ylab("Density") +
93   geom_vline(aes(xintercept=0), color="red",
94             linetype="dashed", size=1)+size
95
96
97
98 e2<-ggplot(dat1, aes(x=CWRES)) +
99   geom_histogram(aes(y=..density..),           # Histogram with density instead of count on y-axis
100                colour="black", fill="#3399FF") +
101   geom_density(alpha=.2) + theme_bw() + xlab("CWRES") + ylab("Density") +
102   geom_vline(aes(xintercept=0), color="red",
103             linetype="dashed", size=1)+size
104
105
106
107
108 grid.arrange(e1,e2, ncol=2)
109
110
111 dev.print(file="error_Histogram.png", device=png, width=1200,height=800)
112
113
114
115 ##### Fitting
116 #####
117
118 dat1$PROT<-as.character(as.numeric(dat1$PROT))
119
120 #DV versus predictions
121
122 pepred<-ggplot(data=dat1, aes(x=PRED, y=DV, colour=TREAT)) +
123   geom_point(shape=1)+
124   theme_bw() +
125   theme(panel.border = element_blank(), panel.grid.major = element_blank(),
126         panel.grid.minor = element_blank(),
127         axis.line = element_line(colour = "black"))+
128   geom_abline(intercept = 0,slope = 1, colour = "red", linetype = 2,size=1)+
129   stat_smooth(method = "lm", se = F, colour = "black")+
130   xlab(bquote('Population predicted SLD (mm)')) +
131   ylab(bquote('Observed SLD (mm)')) +
132   scale_colour_discrete(name="")+size
133
134 pipred<-ggplot(data=dat1, aes(x=IPRED, y=DV, colour=TREAT)) +
135   geom_point(shape=1)+
136   theme_bw() +
137   theme(panel.border = element_blank(), panel.grid.major = element_blank(),
138         panel.grid.minor = element_blank(),
139         axis.line = element_line(colour = "black"))+
140   geom_abline(intercept = 0,slope = 1, colour = "red", linetype = 2,size = 1)+
141   stat_smooth(method = "lm", se = F, colour = "black")+
142   xlab(bquote('Individual predicted SLD (mm)')) +
```

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```
143   ylab(bquote('Observed SLD (mm)')) +
144     scale_colour_discrete(name="")+size
145
146
147   grid.arrange(pepred, pipred, ncol=1)
148
149
150   dev.print(file="DV_Pop-Predictions.png", device=png, width=1200,height=800)
151
152
153
154
155   ##### Plots of residuals
156   #####
157   # identify the outlier (|WRES|>6 and |IWRES|>6)
158
159   OUT2<-dat1[dat1$IWRES>6 | dat1$IWRES< -6,]
160   length(OUT2$ID)
161   # [1] 16
162   write.table(OUT2,file="outIWRES.csv",sep=" ",row.names=F)
163   OUT3<-dat1[dat1$CWRES>6 | dat1$CWRES< -6,]
164   length(OUT3$ID)
165   # [1] 14
166   write.table(OUT3,file="outCWRES.csv",sep=" ",row.names=F)
167
168
169
170   #CWRES versus TIME
171
172   CWREStime <- ggplot(data=dat1, aes(x=TIME, y=CWRES, colour=TREAT)) +
173     theme_bw() +
174     theme(panel.border = element_blank(), panel.grid.major = element_blank(),
175           panel.grid.minor = element_blank(),
176           axis.line = element_line(colour = "black"))+
177     xlab("Time (weeks)") +
178     geom_point(shape=1)+
179     geom_hline(yintercept = 0) +
180     geom_hline(yintercept = c(-6,6),linetype = 2,colour="red") +
181     geom_text(data=OUT3, aes(x=TIME, y=CWRES, label=ID, colour=TREAT), vjust=1, size=3,show.
182               legend=FALSE)+
183     scale_colour_discrete(name="")+size
184
185
186   #IWRES versus TIME
187   iwrestime <- ggplot(data=dat1, aes(x=TIME, y=IWRES, colour=TREAT)) +
188     theme_bw() +
189     theme(panel.border = element_blank(), panel.grid.major = element_blank(),
190           panel.grid.minor = element_blank(),
191           axis.line = element_line(colour = "black"))+
192     xlab("Time after first dose (hrs)") +
193     geom_point(shape=1)+
194     geom_hline(yintercept = 0) +
195     geom_hline(yintercept = c(-6,6),linetype = 2,colour="red") +
196     geom_text(data=OUT2, aes(x=TIME, y=IWRES, label=ID, colour=TREAT), vjust=1, size=3,show.
197               legend=FALSE)+
198     scale_colour_discrete(name="")+size
199
200
201
202   grid.arrange(CWREStime,iwrestime, ncol=1)
203
204   dev.print(file="RES_time.png", device=png, width=1200,height=800)
205
206   #####
207   #####
```

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```
207 # log time
208 #CWRES versus TIME
209 CWREStimelog <- ggplot(data=dat1, aes(x=TIME, y=CWRES, colour=TREAT)) +
210   theme_bw() +
211   theme(panel.border = element_blank(), panel.grid.major = element_blank(),
212         panel.grid.minor = element_blank(),
213         axis.line = element_line(colour = "black"))+
214   xlab("Time on Log (weeks)") +
215   scale_x_log10()+
216   geom_point(shape=1)+
217   geom_hline(yintercept = 0) +
218   geom_hline(yintercept = c(-6,6), linetype = 2, colour="red") +
219   geom_text(data=OUT3, aes(x=TIME, y=CWRES, label=ID, colour=TREAT), vjust=1, size=3, show.
220             legend=FALSE)+
221   scale_colour_discrete(name="")+size
222
223
224 #IWRES versus TIME
225 iwrestimelog <- ggplot(data=dat1, aes(x=TIME, y=IWRES, colour=TREAT)) +
226   theme_bw() +
227   theme(panel.border = element_blank(), panel.grid.major = element_blank(),
228         panel.grid.minor = element_blank(),
229         axis.line = element_line(colour = "black"))+
230   xlab("Time on Log (weeks)") +
231   scale_x_log10()+
232   geom_point(shape=1)+
233   geom_hline(yintercept = 0) +
234   geom_hline(yintercept = c(-6,6), linetype = 2, colour="red") +
235   geom_text(data=OUT2, aes(x=TIME, y=IWRES, label=ID, colour=TREAT), vjust=1, size=3, show.
236             legend=FALSE)+
237   scale_colour_discrete(name="")+size
238
239
240
241 grid.arrange(CWREStimelog, iwrestimelog, ncol=1)
242
243 dev.print(file="RES_logtime.png", device=png, width=1200,height=800)
244 #####
245
246
247 #CWRES versus Population predictions (log Population prediction)
248 CWRESpred <- ggplot(data=dat1, aes(x=PRED, y=CWRES, colour=TREAT)) +
249   theme_bw() +
250   theme(panel.border = element_blank(), panel.grid.major = element_blank(),
251         panel.grid.minor = element_blank(),
252         axis.line = element_line(colour = "black"))+
253   xlab(bquote('Population Predicted(mm)')) +
254   geom_point(shape=1)+
255   geom_hline(yintercept = 0) +
256   geom_hline(yintercept = c(-6,6), linetype = 2, colour="red") +
257   geom_text(data=OUT3, aes(x=PRED, y=CWRES, label=ID, colour=TREAT), vjust=1, size=3, show.
258             legend=FALSE)+
259   scale_colour_discrete(name="")+size
260
261 #IWRES versus Population predictions (log Population prediction)
262 iwrespred <- ggplot(data=dat1, aes(x=PRED, y=IWRES, colour=TREAT)) +
263   theme_bw() +
264   theme(panel.border = element_blank(), panel.grid.major = element_blank(),
265         panel.grid.minor = element_blank(),
266         axis.line = element_line(colour = "black"))+
267   xlab(bquote('Population Predicted(mm)')) +
268   geom_point(shape=1)+
269   geom_hline(yintercept = 0) +
270   geom_hline(yintercept = c(-6,6), linetype = 2, colour="red") +
271   geom_text(data=OUT2, aes(x=PRED, y=IWRES, label=ID, colour=TREAT), vjust=1, size=3, show.
```

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```
      legend=FALSE) +
272   scale_colour_discrete(name="")+size
273
274   grid.arrange(CWRESpred,iwresipred, ncol=1)
275
276   dev.print(file="RES_pred.png", device=png, width=1200,height=800)
277
278
279
280
281
282   #####
283
284
285
286   ##### Fitting
287   #####
288
289
290   #####individual plots#####
291   pdf("individual_plots.pdf")
292   par(mfrow=c(3,4), mar=c(2,2,2,2))
293   for(i in sort(unique(dat1$ID))) {
294     temp<-dat1 [dat1$ID==i,]
295     plot(temp$TIME, temp$DV, type="n", ylab="SLD (mm)",
296          xlab="Time (weeks)",
297          main=paste("ID=",i),cex=0.5)
298     points(temp$TIME, temp$DV, type="p", cex=0.7, col="blue")
299     points(temp$TIME, temp$IPRED, type="l", cex=1.2, lwd=1.5,col="red")
300     points(temp$TIME, temp$PRED, type="l", lty=3, cex=1.2, lwd=1, col="black")
301
302     legend("topright",c("Individual Pred", "Pop Pred"), bty="n", cex=0.7,
303            lty=c(1,3), col=c("red","black"))
304   }
305
306
307
308
309   dev.off()
310   #####
311
312   # per treatment and study
313
314   studies<-ggplot(dat1, aes(x=TIME, y=DV, group=ID, color=TREAT)) +
315     geom_point() +
316     facet_wrap(~PROT)+
317     theme_bw() +
318     xlab("Time (weeks)") +
319     ylab(bquote('Observed SLD (mm)')) +
320     #scale_y_log10()+
321     theme(legend.position = "none")+size
322   print(studies)
323
324   dev.print(file="perstudydose.png", device=png, width=1200,height=800)
325
326
327
328   ##### ETAs VS covariates
329   #####
330   ##### Relationship between ETAs and demographics (Age, BWT, SEX)
331
332
333   ##### BSLD #####
334
335   bsld1<-ggplot(data=dat1, aes(x=BSLD, y=ETA1, colour=TREAT)) +
336     geom_point(size=3)+
```

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```

337   theme_bw() +
338   theme(panel.border = element_blank(), panel.grid.major = element_blank(),
339         panel.grid.minor = element_blank(),
340         axis.line = element_line(colour = "black"))+
341   theme(legend.position = "none")+
342   geom_abline(intercept = 0,slope = 0, colour = "black", linetype = 2,size = 1)+
343   stat_smooth( method="loess",se = F, colour = "red",span=1,size=1)+
344   xlab("Baseline SLD (mm)") +
345   labs(y=expression("ETA on KL")) +size1
346
347   bsld2<-ggplot(data=dat1, aes(x=BSLD, y=ETA2, colour=TREAT)) +
348   geom_point(size=3)+
349   theme_bw() +
350   theme(panel.border = element_blank(), panel.grid.major = element_blank(),
351         panel.grid.minor = element_blank(),
352         axis.line = element_line(colour = "black"))+
353   theme(legend.position = "none")+
354   geom_abline(intercept = 0,slope = 0, colour = "black", linetype = 2,size = 1)+
355   stat_smooth( method="loess",se = F, colour = "red",span=1,size=1)+
356   xlab("Baseline SLD (mm)") +
357   labs(y=expression("ETA on KD")) +size1
358
359
360
361   bsld3<-ggplot(data=dat1, aes(x=BSLD, y=ETA3, colour=TREAT)) +
362   geom_point(size=3)+
363   theme_bw() +
364   theme(panel.border = element_blank(), panel.grid.major = element_blank(),
365         panel.grid.minor = element_blank(),
366         axis.line = element_line(colour = "black"))+
367   theme(legend.position = "none")+
368   geom_abline(intercept = 0,slope = 0, colour = "black", linetype = 2,size = 1)+
369   stat_smooth( method="loess",se = F, colour = "red",span=1,size=1)+
370   xlab("Baseline SLD (mm)") +
371   ylab("ETA on LAM") +size1
372
373
374
375   grid.arrange(bsld1,bsld2,bsld3, ncol=2)
376
377
378   dev.print(file="BSLD_ETA.png", device=png, width=1200,height=1200)
379
380
381
382
383   ##### boxplot to see ETA versus TREAT#####
384
385   trt1<-ggplot(data=dat1, aes(x=TREAT, y=ETA1, fill=TREAT)) +
386   geom_boxplot()+
387   theme_bw() +
388   theme(panel.border = element_blank(), panel.grid.major = element_blank(),
389         panel.grid.minor = element_blank(),
390         axis.line = element_line(colour = "black"))+
391   theme(legend.position = "none")+
392   geom_abline(intercept = 0,slope = 0, colour = "black", linetype = 2,size = 1)+
393   xlab("Treatment") +
394   ylab("ETA on KL") +
395   size
396
397
398   trt2<-ggplot(data=dat1, aes(x=TREAT, y=ETA2, fill=TREAT)) +
399   geom_boxplot()+
400   theme_bw() +
401   theme(panel.border = element_blank(), panel.grid.major = element_blank(),
402         panel.grid.minor = element_blank(),
403         axis.line = element_line(colour = "black"))+
404   theme(legend.position = "none")+

```

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```
405   geom_abline(intercept = 0,slope = 0, colour = "black", linetype = 2,size = 1)+
406   xlab("Treatment") +
407   ylab("ETA on KD") +
408   size
409
410 trt3<-ggplot(data=dat1, aes(x=TREAT, y=ETA3, fill=TREAT)) +
411   geom_boxplot()+
412   theme_bw() +
413   theme(panel.border = element_blank(), panel.grid.major = element_blank(),
414         panel.grid.minor = element_blank(),
415         axis.line = element_line(colour = "black"))+
416   theme(legend.position = "none")+
417   geom_abline(intercept = 0,slope = 0, colour = "black", linetype = 2,size = 1)+
418   xlab("Treatment") +
419   ylab("ETA on LAM") +
420   size
421
422
423 grid.arrange(trt1,trt2,trt3, ncol=2)
424
425 dev.print(file="TRT_ETA.png", device=png, width=1200,height=1200)
426
427
428
429 #####
430 #
431 # Exploratory plotting of TGI metrics
432 #
433 #####
434
435 dat2<-dat1 %>% select (PROT, ID, TRT, TREAT, KL, KD, LAM, TTG, TR6, TR8) %>% distinct()
436
437 summary(dat2$KL)
438 # Min. 1st Qu. Median Mean 3rd Qu. Max.
439 # 0.000389 0.001886 0.003101 0.008318 0.007947 0.187668
440
441 # TVKL = 0.145 ( in rate / year)
442 0.144/52
443 # [1] 0.002769231 now this is in /week so same as the individual KL units
444
445 # Histograms of parameters
446 kl<-ggplot(dat2, aes(x=KL)) +
447   geom_histogram(aes(y=..density..), # Histogram with density instead of count on y-axis
448                 colour="black", fill="#3399FF") +
449   geom_density(alpha=.2) + theme_bw() + labs(x=expression("KL")) + ylab("Density") +
450   size
451
452
453 kd<-ggplot(dat2, aes(x=KD)) +
454   geom_histogram(aes(y=..density..), # Histogram with density instead of count on y-axis
455                 colour="black", fill="#3399FF") +
456   geom_density(alpha=.2) + theme_bw() + labs(x=expression("KD")) + ylab("Density") +
457   size
458
459
460 lam<-ggplot(dat2, aes(x=LAM)) +
461   geom_histogram(aes(y=..density..), # Histogram with density instead of count on y-axis
462                 colour="black", fill="#3399FF") +
463   geom_density(alpha=.2) + theme_bw() + labs(x=expression("LAM")) + ylab("Density") +
464   size
465
466
467 ttg1<-ggplot(dat2, aes(x=TTG)) +
468   geom_histogram(aes(y=..density..), # Histogram with density instead of count on y-axis
469                 colour="black", fill="#3399FF") +
470   geom_density(alpha=.2) + theme_bw() + labs(x=expression("TTG")) + ylab("Density") +
471   geom_vline(aes(xintercept=0), color="red", linetype="dashed", size=1)+
472   size
```


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```
473
474
475 tr6.1<-ggplot(dat2, aes(x=TR6)) +
476   geom_histogram(aes(y=..density..),           # Histogram with density instead of count on y-axis
477                 colour="black", fill="#3399FF") +
478   geom_density(alpha=.2) + theme_bw() + labs(x=expression("TR6")) + ylab("Density") +
479   #geom_vline(aes(xintercept=0), color="red", linetype="dashed", size=1)+
480   size
481
482
483 tr8.1<-ggplot(dat2, aes(x=TR8)) +
484   geom_histogram(aes(y=..density..),           # Histogram with density instead of count on y-axis
485                 colour="black", fill="#3399FF") +
486   geom_density(alpha=.2) + theme_bw() + labs(x=expression("TR8")) + ylab("Density") +
487   #geom_vline(aes(xintercept=0), color="red", linetype="dashed", size=1)+
488   size
489
490
491
492 grid.arrange(kl,kd,lam,ttgl,tr6.1,tr8.1,ncol=2)
493
494 dev.print(file="Histogram_TGIparam.png", device=png, width=1200,height=1800)
495
496
497 # Boxplots of metrics
498
499 ttg<-ggplot(data=dat2, aes(x=TREAT, y=TTG, fill=TREAT)) +
500   geom_boxplot()+
501   theme_bw() +
502   theme(panel.border = element_blank(), panel.grid.major = element_blank(),
503         panel.grid.minor = element_blank(),
504         axis.line = element_line(colour = "black"))+
505   theme(legend.position = "none")+
506   xlab("Treatment") +
507   scale_y_continuous(limits=c(-10,60),breaks = seq(-10, 60, by = 10))+
508   ylab("Time to tumor growth (weeks)")+
509   size
510
511
512
513 grid.arrange(ttg,ncol=1)
514
515 dev.print(file="TTG_byTRT.png", device=png, width=600,height=600)
516
517
518
519 tr6<-ggplot(data=dat2, aes(x=TREAT, y=TR6, fill=TREAT)) +
520   geom_boxplot()+
521   theme_bw() +
522   theme(panel.border = element_blank(), panel.grid.major = element_blank(),
523         panel.grid.minor = element_blank(),
524         axis.line = element_line(colour = "black"))+
525   theme(legend.position = "none")+
526   #geom_abline(intercept = 0,slope = 0, colour = "black", linetype = 2,size = 1)+
527   xlab("Treatment") +
528   ylab("Tumor Ratio Week 6") +
529   size
530
531
532 tr8<-ggplot(data=dat2, aes(x=TREAT, y=TR8, fill=TREAT)) +
533   geom_boxplot()+
534   theme_bw() +
535   theme(panel.border = element_blank(), panel.grid.major = element_blank(),
536         panel.grid.minor = element_blank(),
537         axis.line = element_line(colour = "black"))+
538   theme(legend.position = "none")+
539   #geom_abline(intercept = 0,slope = 0, colour = "black", linetype = 2,size = 1)+
540   xlab("Treatment") +
```

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```
541   ylab("Tumor Ratio Week 8") +
542   size
543
544
545   grid.arrange(tr6,tr8,ncol=2)
546
547   dev.print(file="TumorRatio_byTRT.png", device=png, width=1200,height=600)
548
549
550   #####
551
552   # BSLD by treatment and protocol
553
554   bsldtrt1<-ggplot(data=dat1, aes(x=TREAT, y=BSLD, fill=TREAT)) +
555     geom_boxplot() +
556     #facet_wrap(~PROT) +
557     theme_bw() +
558     theme(panel.border = element_blank(), panel.grid.major = element_blank(),
559           panel.grid.minor = element_blank(),
560           axis.line = element_line(colour = "black")) +
561     theme(legend.position = "none") +
562     xlab("Treatment") +
563     ylab("BSLD") +
564     ylim(0,200)
565
566
567   bsldtrt2<-ggplot(data=dat1, aes(x=TREAT, y=BSLD, fill=TREAT)) +
568     geom_boxplot() +
569     facet_wrap(~PROT) +
570     theme_bw() +
571     theme(panel.border = element_blank(), panel.grid.major = element_blank(),
572           panel.grid.minor = element_blank(),
573           axis.line = element_line(colour = "black")) +
574     theme(legend.position = "none") +
575     xlab("Treatment") +
576     ylab("BSLD") +
577     ylim(0,200)
578
579
580   grid.arrange(bsldtrt1,bsldtrt2,ncol=2)
581
582   dev.print(file="BSLDboxplot_byTRT.png", device=png, width=1200,height=600)
583
584   ##### Summary tables of tumor ratio and TTG
585
586   # Geometric mean
587   gm_mean<-function(x,na.rm=T){
588     a <- mean(log(x[x>0]),na.rm=T)
589     exp(a)
590   }
591
592   # Geometric CV%
593   geocv<-function(x, na.rm = TRUE){
594     sdlog <- sd(log(x[x > 0]), na.rm = na.rm)
595     geosd <- exp(sdlog)
596     100*(sqrt(exp(log(geosd)^2)-1))
597   }
598
599
600   ## Tumor ratio week 6
601   tr6sum<-dat2 %>%
602     group_by(TREAT) %>%
603     summarise(n=length(TR6),
604               Median=sprintf("%.1f",median(TR6)),
605               Min=sprintf("%.1f",min(TR6)),
606               Max=sprintf("%.1f",max(TR6)),
607               Mean=sprintf("%.1f",mean(TR6)),
608               SD=sprintf("%.2f",sd(TR6)),
```

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```
609         GM=sprintf("%.1f", gm_mean(TR6)),
610         GeoCV=sprintf("%.2f", geocv(TR6))
611 tr6sum
612
613 ## Tumor ratio week 8
614 tr8sum<-dat2 %>%
615   group_by(TREAT) %>%
616   summarise(n=length(TR8),
617             Median=sprintf("%.1f", median(TR8)),
618             Min=sprintf("%.1f", min(TR8)),
619             Max=sprintf("%.1f", max(TR8)),
620             Mean=sprintf("%.1f", mean(TR8)),
621             SD=sprintf("%.2f", sd(TR8)),
622             GM=sprintf("%.1f", gm_mean(TR8)),
623             GeoCV=sprintf("%.2f", geocv(TR8)))
624 tr8sum
625
626
627 trsum<-cbind(tr6sum[,c(1,2,8,9)], tr8sum[,c(8,9)])
628 trsum
629 names(trsum)<-c("Treatment", "N", "A", "B", "C", "D")
630 trsum$'Tumor Ratio Week 6'<-paste0(trsum$A, " (", trsum$B, "\\%)" )
631 trsum$'Tumor Ratio Week 8'<-paste0(trsum$C, " (", trsum$D, "\\%)" )
632 trsum<-trsum[,c(1,2,7,8)]
633 trsum
634
635 ### TTG
636 ttgsum<-dat2 %>%
637   group_by(TREAT) %>%
638   summarise(n=length(TTG),
639             Median=sprintf("%.1f", median(TTG)),
640             Min=sprintf("%.1f", min(TTG)),
641             Max=sprintf("%.1f", max(TTG)),
642             Mean=sprintf("%.1f", mean(TTG)),
643             SD=sprintf("%.2f", sd(TTG)),
644             GM=sprintf("%.1f", gm_mean(TTG)),
645             GeoCV=sprintf("%.2f", geocv(TTG)))
646 ttgsum$'Time to tumor growth'<-paste0(ttgsum$GM, " (", ttgsum$GeoCV, "\\%)" )
647
648
649 met.sum<-cbind(trsum, ttgsum[,10])
650 met.sum
651
652 write.csv(met.sum, file="SummaryTumorMetrics.csv", quote=F, row.names=F, na="NA")
653
654
655 ##### end of script #####
656 sessionInfo()
657 # R version 3.6.1 (2019-07-05)
658 # Platform: x86_64-w64-mingw32/x64 (64-bit)
659 # Running under: Windows >= 8 x64 (build 9200)
660 #
661 # Matrix products: default
662 #
663 # Random number generation:
664 #   RNG:      Mersenne-Twister
665 # Normal:    Inversion
666 # Sample:    Rounding
667 #
668 # locale:
669 #   [1] LC_COLLATE=English_United States.1252  LC_CTYPE=English_United States.1252
670 #   [3] LC_MONETARY=English_United States.1252 LC_NUMERIC=C
671 #   [5] LC_TIME=English_United States.1252
672 #
673 # attached base packages:
674 #   [1] stats      graphics  grDevices  utils      datasets  methods   base
675 #
676 # other attached packages:
```

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```
677 # [1] psych_1.8.12      GGally_1.4.0      gridExtra_2.3     forcats_0.4.0     stringr_1.4.0     dplyr_
        0.8.3
678 # [7] purrr_0.3.2      readr_1.3.1      tidyr_1.0.0      tibble_2.1.3      ggplot2_3.2.1
        tidyverse_1.2.1
679 #
680 # loaded via a namespace (and not attached):
681 # [1] tidyselect_0.2.5  haven_2.1.1      lattice_0.20-38   colorspace_1.4-1  vctrs_
        0.2.0
682 # [6] generics_0.0.2    yaml_2.2.0        utf8_1.1.4        rlang_0.4.0        pillar_1.4.2
683 # [11] foreign_0.8-71    glue_1.3.1        withr_2.1.2        RColorBrewer_1.1-2 modelr_
        0.1.5
684 # [16] readxl_1.3.1      lifecycle_0.1.0   plyr_1.8.4        munsell_0.5.0      gtable_
        0.3.0
685 # [21] cellranger_1.1.0  rvest_0.3.4        labeling_0.3       parallel_3.6.1     fansi_0.4.0
686 # [26] broom_0.5.2       Rcpp_1.0.2         backports_1.1.4    scales_1.0.0       jsonlite_
        1.6
687 # [31] mnormt_1.5-5      hms_0.5.1          digest_0.6.20      stringi_1.4.3      grid_3.6.1
688 # [36] cli_1.1.0         tools_3.6.1        magrittr_1.5       lazyeval_0.2.2     crayon_
        1.3.4
689 # [41] pkgconfig_2.0.2    zeallot_0.1.0      xml2_1.2.2         lubridate_1.7.4    assertthat_
        0.2.1
690 # [46] reshape_0.8.8     httr_1.4.1         rstudioapi_0.10    R6_2.4.0           nlme_
        3.1-140
691 # [51] compiler_3.6.1
```

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Appendix 8. Simulations

The VPCs code is listed here:

```
1 Mon Feb 24 12:23:58 EST 2020
2 $SIZES PD=-150
3
4 $PROB run16.mod; Claret TGI model
5
6
7
8
9 $INPUT
10
11
12 C PROT NSID ID STID DOSE DOSEP DOSIV
13 DOSIVP DOS2 DOS2P TRT TRTG=DROP PERD NTPD DAY
14 TIME FLAGE AGE SEX RACE ETHN RACD BWT
15 SMOK BBMI BCCL BCAL BPLT BNEU BHGB BALB
16 BLDH BALT BAST BBIL BSLD DV SURT CENS
17 ECOG METS LIVMET LNGMET BONMET MSKCC HENG EGFR
18 EVID EVNT DOSRED DOSINT BLYM
19 DSLD TREAT=DROP TREAT2=DROP LBSLD LSLD
20
21
22 ;TAFD is time in weeks
23 ;DV is the SLD column in mm
24
25
26 $DATA RCC_COMBINED_PD2_SLD_31OCT2019.csv
27 IGNORE=@
28
29 $SUBROUTINE ADVAN 13 TOL=6
30
31 $MODEL
32 COMP=TUMOR
33
34 $PK
35 ;;; LAMTRT-DEFINITION START
36 IF (TRT.EQ.2) LAMTRT = 1
37 IF (TRT.EQ.1) LAMTRT = (1+THETA(15))
38 IF (TRT.EQ.3) LAMTRT = (1+THETA(16))
39 IF (TRT.EQ.4) LAMTRT = (1+THETA(17))
40 IF (TRT.EQ.5) LAMTRT = (1+THETA(18))
41 ;;; LAMTRT-DEFINITION END
42
43 ;;; LAM-RELATION START
44 LAMCOV=LAMTRT
45 ;;; LAM-RELATION END
46
47
48 ;;; KLTRT-DEFINITION START
49 IF (TRT.EQ.2) KLTRT = 1
50 IF (TRT.EQ.1) KLTRT = (1+THETA(11))
51 IF (TRT.EQ.3) KLTRT = (1+THETA(12))
52 IF (TRT.EQ.4) KLTRT = (1+THETA(13))
53 IF (TRT.EQ.5) KLTRT = (1+THETA(14))
54 ;;; KLTRT-DEFINITION END
55
56 ;;; KL-RELATION START
57 KLCOV=KLTRT
58 ;;; KL-RELATION END
59
60
61 ;;; KDTRT-DEFINITION START
62 IF (TRT.EQ.2) KDTRT = 1
63 IF (TRT.EQ.1) KDTRT = (1+THETA(7))
```

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```

64 IF (TRT.EQ.3)      KDTRT = (1+THETA(8))
65 IF (TRT.EQ.4)      KDTRT = (1+THETA(9))
66 IF (TRT.EQ.5)      KDTRT = (1+THETA(10))
67 ;;; KDTRT-DEFINITION END
68
69
70 ;;; KDBSLD-DEFINITION START
71      KDBSLD = ((BSLD/91)**THETA(6))
72 ;;; KDBSLD-DEFINITION END
73
74 ;;; KD-RELATION START
75 KDCOV=KDBSLD*KDTRT
76 ;;; KD-RELATION END
77
78
79
80 TVKL=LOG(THETA(1)/52)      ; change to rate/year from /weeks
81
82 TVKL = KLCOV*TVKL
83 MU_1=TVKL
84 KL = EXP (MU_1+ETA(1))
85
86 TVKD=LOG(THETA(2)/52)
87
88 TVKD = KDCOV*TVKD
89 MU_2=TVKD
90 KD = EXP (MU_2+ETA(2))
91
92 TVLAM=LOG(THETA(3)/52)
93
94 TVLAM = LAMCOV*TVLAM
95 MU_3=TVLAM
96 LAM = EXP (MU_3+ETA(3))
97
98 A_0(1)=BSLD
99
100
101
102 $DES
103
104      ;y(t) = y(0) exp[ kL t - (kD Treatment/lam)(1-exp(-lam t)) ].
105      ;dy/dt = [kL t - kD/lam Treatment (exp(-lam t))] y(t).
106
107
108 DADT(1) = (KL - KD*EXP(-LAM*T))*A(1)
109
110
111
112
113 $ERROR
114
115 IPRED=A(1)
116 W = SQRT(THETA(4)**2*IPRED**2+THETA(5)**2)
117
118 Y=IPRED+W*ERR(1)
119
120 IWRES=(DV-IPRED)/W
121
122
123 XL=LOG(KL)
124 XD=LOG(LAM*KD)
125
126 IF (XL.GT.XD) THEN
127      TTG=0
128 ELSE
129      TTG=(LOG(LAM*KD)-LOG(KL))/LAM ; added lam for KD term to adjust
130 ENDIF
131

```

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```

132
133      W6 = BSLD*EXP (KL*6-(KD/LAM) *(1-EXP (-LAM*6)))
134      W8 = BSLD*EXP (KL*8-(KD/LAM) *(1-EXP (-LAM*8)))
135      TR6= W6/BSLD
136      TR8= W8/BSLD
137
138      REP=IREP
139
140
141      $THETA  (0,0.143663) ; KL
142      (0,1.60217) ; KD
143      (0,3.939) ; LAM
144      (0.01,0.0811432) ; Proportional Error
145      (0.01,2.26872) ; Additive Error
146
147      $THETA  (-100,0.0506293,100000) ; KDBSLD1
148
149      $THETA  (-100000,0.352134,100000) ; KDTRT1
150      (-100000,-0.0745063,100000) ; KDTRT2
151      (-100000,0.0073258,100000) ; KDTRT3
152      (-100000,-0.0769689,100000) ; KDTRT4
153
154      $THETA  (-100000,-0.0946182,100000) ; KLTRT1
155      (-100000,-0.036812,100000) ; KLTRT2
156      (-100000,0.0612846,100000) ; KLTRT3
157      (-100000,0.0898521,100000) ; KLTRT4
158
159      $THETA  (-100000,0.212748,100000) ; LAMTRT1
160      (-100000,-0.397089,100000) ; LAMTRT2
161      (-100000,0.0522,100000) ; LAMTRT3
162      (-100000,0.0611664,100000) ; LAMTRT4
163
164      $OMEGA  2.26315 ; ETA(KL)
165      0.839075 ; ETA(KD)
166      1.66932 ; ETA(LAM)
167
168      $SIGMA  1  FIX
169
170      $SIMULATION (20200224) ONLYSIM SUBPROB=500
171
172
173
174      $TABLE REP ID PROT TIME
175      KL KD LAM TTG TR6 TR8
176      BSLD DV TRT
177      NOAPPEND NOHEADER NOPRINT FORMAT=sF14.4 FILE=simul6
178
179
180      NM-TRAN MESSAGES
181
182      WARNINGS AND ERRORS (IF ANY) FOR PROBLEM 1
183
184      (WARNING 2) NM-TRAN INFERS THAT THE DATA ARE POPULATION.
185
186      (MU_WARNING 26) DATA ITEM(S) USED IN DEFINITION OF MU_(S) SHOULD BE CONSTANT FOR INDIV. REC.:
187      BSLD
188
189      License Registered to: Pfizer
190      Expiration Date: 14 JUN 2020
191      Current Date: 24 FEB 2020
192      Days until program expires : 110
193      1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.4.3
194      ORIGINALLY DEVELOPED BY STUART BEAL, LEWIS SHEINER, AND ALISON BOECKMANN
195      CURRENT DEVELOPERS ARE ROBERT BAUER, ICON DEVELOPMENT SOLUTIONS,
196      AND ALISON BOECKMANN. IMPLEMENTATION, EFFICIENCY, AND STANDARDIZATION
197      PERFORMED BY NOUS INFOSYSTEMS.
198
199      PROBLEM NO.: 1

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```

200  run16.mod; Claret TGI model
201  ODATA CHECKOUT RUN:          NO
202  DATA SET LOCATED ON UNIT NO.: 2
203  THIS UNIT TO BE REWOUND:    NO
204  NO. OF DATA RECS IN DATA SET: 12356
205  NO. OF DATA ITEMS IN DATA SET: 56
206  ID DATA ITEM IS DATA ITEM NO.: 4
207  DEP VARIABLE IS DATA ITEM NO.: 37
208  MDV DATA ITEM IS DATA ITEM NO.: 56
209  OINDICES PASSED TO SUBROUTINE PRED:
210  48 16 0 0 0 0 0 0 0 0 0 0
211  OLABELS FOR DATA ITEMS:
212  C PROT NSID ID STID DOSE DOSEP DOSIV DOSIVP DOS2 DOS2P TRT PERD NTPD DAY TIME FLAGE AGE SEX
    RACE ETHN RACD BWT SMOK BBMI
213  BCCL BCAL BPLT BNEU BHGB BALB BLDH BALT BAST BBIL BSLD DV SURT CENS ECOG METS LIVMET LNGMET
    BONMET MSKCC HENG EGFR EVID
214  EVNT DOSRED DOSINT BLYM DSLD LBSLD LSLD MDV
215  0(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:
216  KL KD LAM TTG TR6 TR8 REP
217  OFORMAT FOR DATA:
218  (18(3E20.0/),1E20.0,1F2.0)
219
220  TOT. NO. OF OBS RECS: 12356
221  TOT. NO. OF INDIVIDUALS: 1839
222  OLENGTH OF THETA: 18
223  ODEFAULT THETA BOUNDARY TEST OMITTED: NO
224  OOMEGA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 3
225  ODEFAULT OMEGA BOUNDARY TEST OMITTED: NO
226  OSIGMA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 1
227  ODEFAULT SIGMA BOUNDARY TEST OMITTED: NO
228  OINITIAL ESTIMATE OF THETA:
229  LOWER BOUND INITIAL EST UPPER BOUND
230  0.0000E+00 0.1437E+00 0.1000E+07
231  0.0000E+00 0.1602E+01 0.1000E+07
232  0.0000E+00 0.3939E+01 0.1000E+07
233  0.1000E-01 0.8114E-01 0.1000E+07
234  0.1000E-01 0.2269E+01 0.1000E+07
235  -0.1000E+03 0.5063E-01 0.1000E+06
236  -0.1000E+06 0.3521E+00 0.1000E+06
237  -0.1000E+06 -0.7451E-01 0.1000E+06
238  -0.1000E+06 0.7326E-02 0.1000E+06
239  -0.1000E+06 -0.7697E-01 0.1000E+06
240  -0.1000E+06 -0.9462E-01 0.1000E+06
241  -0.1000E+06 -0.3681E-01 0.1000E+06
242  -0.1000E+06 0.6128E-01 0.1000E+06
243  -0.1000E+06 0.8985E-01 0.1000E+06
244  -0.1000E+06 0.2127E+00 0.1000E+06
245  -0.1000E+06 -0.3971E+00 0.1000E+06
246  -0.1000E+06 0.5220E-01 0.1000E+06
247  -0.1000E+06 0.6117E-01 0.1000E+06
248  OINITIAL ESTIMATE OF OMEGA:
249  0.2263E+01
250  0.0000E+00 0.8391E+00
251  0.0000E+00 0.0000E+00 0.1669E+01
252  OINITIAL ESTIMATE OF SIGMA:
253  0.1000E+01
254  OSIGMA CONSTRAINED TO BE THIS INITIAL ESTIMATE
255  OSIMULATION STEP OMITTED: NO
256  OBJ FUNC EVALUATED: NO
257  ORIGINAL DATA USED ON EACH NEW SIMULATION: NO
258  SEEDS RESET ON EACH NEW SUPERSET ITERATION: YES
259  OSIMULATION RANDOM METHOD SELECTED (RANMETHOD): 4U
260  SEED 1 RESET TO INITIAL: YES
261  SOURCE 1:
262  SEED1: 20200224 SEED2: 0 PSEUDO-NORMAL
263  NUMBER OF SUBPROBLEMS: 500
264  OTABLES STEP OMITTED: NO
265  NO. OF TABLES: 1

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266 SEED NUMBER (SEED):      11456
267 RANMETHOD:                3U
268 MC SAMPLES (ESAMPLE):     300
269 WRES SQUARE ROOT TYPE (WRESCHOL): EIGENVALUE
270 0-- TABLE 1 --
271 0RECORDS ONLY:            ALL
272 04 COLUMNS APPENDED:      NO
273 PRINTED:                  NO
274 HEADERS:                  NO
275 FILE TO BE FORWARDED:      NO
276 FORMAT:                   SF14.4
277 LFORMAT:
278 RFORMAT:
279 FIXED_EFFECT_ETAS:
280 0USER-CHOSEN ITEMS:
281 REP ID PROT TIME KL KD LAM TTG TR6 TR8 BSLD DV TRT
282 1DOUBLE PRECISION PREDPP VERSION 7.4.3
283
284 GENERAL NONLINEAR KINETICS MODEL WITH STIFF/NONSTIFF EQUATIONS (LSODA, ADVAN13)
285 0MODEL SUBROUTINE USER-SUPPLIED - ID NO. 9999
286 0MAXIMUM NO. OF BASIC PK PARAMETERS: 3
287 0COMPARTMENT ATTRIBUTES
288 COMPT. NO.  FUNCTION  INITIAL  ON/OFF  DOSE  DEFAULT  DEFAULT
289              STATUS  ALLOWED  ALLOWED  FOR DOSE  FOR OBS.
290      1          TUMOR      ON      YES      YES      YES      YES
291      2          OUTPUT     OFF     YES      NO      NO      NO
292 INITIAL (BASE) TOLERANCE SETTINGS:
293 NRD (RELATIVE) VALUE(S) OF TOLERANCE: 6
294 ANRD (ABSOLUTE) VALUE(S) OF TOLERANCE: 12
295 1
296 ADDITIONAL PK PARAMETERS - ASSIGNMENT OF ROWS IN GG
297 COMPT. NO.  INDICES
298              SCALE  BIOAVAIL.  ZERO-ORDER  ZERO-ORDER  ABSORB
299              FRACTION  RATE  DURATION  LAG
300      1          *      *      *      *      *
301      2          *      -      -      -      -
302      - PARAMETER IS NOT ALLOWED FOR THIS MODEL
303      * PARAMETER IS NOT SUPPLIED BY PK SUBROUTINE;
304      WILL DEFAULT TO ONE IF APPLICABLE
305 0DATA ITEM INDICES USED BY PRED ARE:
306 EVENT ID DATA ITEM IS DATA ITEM NO.: 48
307 TIME DATA ITEM IS DATA ITEM NO.: 16
308
309 0PK SUBROUTINE CALLED WITH EVERY EVENT RECORD.
310 PK SUBROUTINE NOT CALLED AT NONEVENT (ADDITIONAL OR LAGGED) DOSE TIMES.
311 0PK SUBROUTINE INDICATES THAT COMPARTMENT AMOUNTS ARE INITIALIZED.
312 0ERROR SUBROUTINE CALLED WITH EVERY EVENT RECORD.
313 0ERROR SUBROUTINE INDICATES THAT DERIVATIVES OF COMPARTMENT AMOUNTS ARE USED.
314 0DES SUBROUTINE USES COMPACT STORAGE MODE.
315 TOLERANCES FOR SIMULATION STEP:
316 NRD (RELATIVE) VALUE(S) OF TOLERANCE: 6
317 ANRD (ABSOLUTE) VALUE(S) OF TOLERANCE: 12
318 TOLERANCES FOR TABLE/SCATTER STEP:
319 NRD (RELATIVE) VALUE(S) OF TOLERANCE: 6
320 ANRD (ABSOLUTE) VALUE(S) OF TOLERANCE: 12
321 1
322 PROBLEM NO.: 1 SUBPROBLEM NO.: 1
323
324 SIMULATION STEP PERFORMED
325 SOURCE 1:
326 SEED1: 161864711 SEED2: 1058137485
327 Elapsed simulation time in seconds: 0.15
328 ESTIMATION STEP OMITTED: YES
329 Elapsed finaloutput time in seconds: 0.32
330
331 1
332 PROBLEM NO.: 1 SUBPROBLEM NO.: 2
333

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334 SIMULATION STEP PERFORMED
335 SOURCE 1:
336 SEED1: 2020403526 SEED2: 0
337 Elapsed simulation time in seconds: 0.15
338 ESTIMATION STEP OMITTED: YES
339 Elapsed finaloutput time in seconds: 0.28
340
341 1
342 PROBLEM NO.: 1 SUBPROBLEM NO.: 3
343
344 SIMULATION STEP PERFORMED
345 SOURCE 1:
346 SEED1: 798963013 SEED2: -1089133599
347 Elapsed simulation time in seconds: 0.16
348 ESTIMATION STEP OMITTED: YES
349 Elapsed finaloutput time in seconds: 0.28
350
351 1
352 PROBLEM NO.: 1 SUBPROBLEM NO.: 4
353
354 SIMULATION STEP PERFORMED
355 SOURCE 1:
356 SEED1: 1733547310 SEED2: 0
357 Elapsed simulation time in seconds: 0.18
358 ESTIMATION STEP OMITTED: YES
359 Elapsed finaloutput time in seconds: 0.28
360
361 1
362 PROBLEM NO.: 1 SUBPROBLEM NO.: 5
363
364 SIMULATION STEP PERFORMED
365 SOURCE 1:
366 SEED1: 1201871379 SEED2: -1078430383
367 Elapsed simulation time in seconds: 0.21
368 ESTIMATION STEP OMITTED: YES
369 Elapsed finaloutput time in seconds: 0.28
370
371 1
372 PROBLEM NO.: 1 SUBPROBLEM NO.: 6
373
374 SIMULATION STEP PERFORMED
375 SOURCE 1:
376 SEED1: 1261120543 SEED2: 0
377 Elapsed simulation time in seconds: 0.15
378 ESTIMATION STEP OMITTED: YES
379 Elapsed finaloutput time in seconds: 0.28
380
381 1
382 PROBLEM NO.: 1 SUBPROBLEM NO.: 7
383
384 SIMULATION STEP PERFORMED
385 SOURCE 1:
386 SEED1: 860053880 SEED2: -1090394926
387 Elapsed simulation time in seconds: 0.15
388 ESTIMATION STEP OMITTED: YES
389 Elapsed finaloutput time in seconds: 0.28
390
391 1
392 PROBLEM NO.: 1 SUBPROBLEM NO.: 8
393
394 SIMULATION STEP PERFORMED
395 SOURCE 1:
396 SEED1: 191875168 SEED2: 0
397 Elapsed simulation time in seconds: 0.27
398 ESTIMATION STEP OMITTED: YES
399 Elapsed finaloutput time in seconds: 0.28
400
401 1

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402 PROBLEM NO.:          1          SUBPROBLEM NO.:          9
403
404 SIMULATION STEP PERFORMED
405 SOURCE 1:
406     SEED1:    1276401627    SEED2:    -1092127754
407 Elapsed simulation time in seconds:    0.19
408 ESTIMATION STEP OMITTED:    YES
409 Elapsed finaloutput time in seconds:    0.28
410
411 1
412 PROBLEM NO.:          1          SUBPROBLEM NO.:          10
413
414 SIMULATION STEP PERFORMED
415 SOURCE 1:
416     SEED1:    1608834690    SEED2:          0
417 Elapsed simulation time in seconds:    0.15
418 ESTIMATION STEP OMITTED:    YES
419 Elapsed finaloutput time in seconds:    0.28
420
421 1
422 PROBLEM NO.:          1          SUBPROBLEM NO.:          11
423
424 SIMULATION STEP PERFORMED
425 SOURCE 1:
426     SEED1:    1034075544    SEED2:    -1083344309
427 Elapsed simulation time in seconds:    0.15
428 ESTIMATION STEP OMITTED:    YES
429 Elapsed finaloutput time in seconds:    0.28
430
431 1
432 PROBLEM NO.:          1          SUBPROBLEM NO.:          12
433
434 SIMULATION STEP PERFORMED
435 SOURCE 1:
436     SEED1:    1827220989    SEED2:          0
437 Elapsed simulation time in seconds:    0.14
438 ESTIMATION STEP OMITTED:    YES
439 Elapsed finaloutput time in seconds:    0.28
440
441 1
442 PROBLEM NO.:          1          SUBPROBLEM NO.:          13
443
444 SIMULATION STEP PERFORMED
445 SOURCE 1:
446     SEED1:    488561450    SEED2:    1037159680
447 Elapsed simulation time in seconds:    0.14
448 ESTIMATION STEP OMITTED:    YES
449 Elapsed finaloutput time in seconds:    0.28
450
451 1
452 PROBLEM NO.:          1          SUBPROBLEM NO.:          14
453
454 SIMULATION STEP PERFORMED
455 SOURCE 1:
456     SEED1:    600860836    SEED2:          0
457 Elapsed simulation time in seconds:    0.13
458 ESTIMATION STEP OMITTED:    YES
459 Elapsed finaloutput time in seconds:    0.28
460
461 1
462 PROBLEM NO.:          1          SUBPROBLEM NO.:          15
463
464 SIMULATION STEP PERFORMED
465 SOURCE 1:
466     SEED1:    1034225012    SEED2:    -1070674607
467 Elapsed simulation time in seconds:    0.15
468 ESTIMATION STEP OMITTED:    YES
469 Elapsed finaloutput time in seconds:    0.28

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470
471 1
472 PROBLEM NO.:          1          SUBPROBLEM NO.:          16
473
474 SIMULATION STEP PERFORMED
475 SOURCE 1:
476     SEED1:      490894781    SEED2:          0
477 Elapsed simulation time in seconds:      0.14
478 ESTIMATION STEP OMITTED:          YES
479 Elapsed finaloutput time in seconds:      0.28
480
481 1
482 PROBLEM NO.:          1          SUBPROBLEM NO.:          17
483
484 SIMULATION STEP PERFORMED
485 SOURCE 1:
486     SEED1:      1724289681    SEED2:      1049043233
487 Elapsed simulation time in seconds:      0.12
488 ESTIMATION STEP OMITTED:          YES
489 Elapsed finaloutput time in seconds:      0.28
490
491 1
492 PROBLEM NO.:          1          SUBPROBLEM NO.:          18
493
494 SIMULATION STEP PERFORMED
495 SOURCE 1:
496     SEED1:      284463769    SEED2:          0
497 Elapsed simulation time in seconds:      0.13
498 ESTIMATION STEP OMITTED:          YES
499 Elapsed finaloutput time in seconds:      0.28
500
501 1
502 PROBLEM NO.:          1          SUBPROBLEM NO.:          19
503
504 SIMULATION STEP PERFORMED
505 SOURCE 1:
506     SEED1:      1751457187    SEED2:      1056162979
507 Elapsed simulation time in seconds:      0.13
508 ESTIMATION STEP OMITTED:          YES
509 Elapsed finaloutput time in seconds:      0.28
510
511 1
512 PROBLEM NO.:          1          SUBPROBLEM NO.:          20
513
514 SIMULATION STEP PERFORMED
515 SOURCE 1:
516     SEED1:      425291421    SEED2:          0
517 Elapsed simulation time in seconds:      0.13
518 ESTIMATION STEP OMITTED:          YES
519 Elapsed finaloutput time in seconds:      0.28
520
521 1
522 PROBLEM NO.:          1          SUBPROBLEM NO.:          21
523
524 SIMULATION STEP PERFORMED
525 SOURCE 1:
526     SEED1:      2090669699    SEED2:      1071542921
527 Elapsed simulation time in seconds:      0.14
528 ESTIMATION STEP OMITTED:          YES
529 Elapsed finaloutput time in seconds:      0.28
530
531 1
532 PROBLEM NO.:          1          SUBPROBLEM NO.:          22
533
534 SIMULATION STEP PERFORMED
535 SOURCE 1:
536     SEED1:      1466308682    SEED2:          0
537 Elapsed simulation time in seconds:      0.13

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538 ESTIMATION STEP OMITTED: YES
539 Elapsed finaloutput time in seconds: 0.28
540
541 1
542 PROBLEM NO.: 1 SUBPROBLEM NO.: 23
543
544 SIMULATION STEP PERFORMED
545 SOURCE 1:
546 SEED1: 1738993712 SEED2: 1061702664
547 Elapsed simulation time in seconds: 0.13
548 ESTIMATION STEP OMITTED: YES
549 Elapsed finaloutput time in seconds: 0.28
550
551 1
552 PROBLEM NO.: 1 SUBPROBLEM NO.: 24
553
554 SIMULATION STEP PERFORMED
555 SOURCE 1:
556 SEED1: 1460696029 SEED2: 0
557 Elapsed simulation time in seconds: 0.13
558 ESTIMATION STEP OMITTED: YES
559 Elapsed finaloutput time in seconds: 0.28
560
561 1
562 PROBLEM NO.: 1 SUBPROBLEM NO.: 25
563
564 SIMULATION STEP PERFORMED
565 SOURCE 1:
566 SEED1: 1909116348 SEED2: 1065605440
567 Elapsed simulation time in seconds: 0.13
568 ESTIMATION STEP OMITTED: YES
569 Elapsed finaloutput time in seconds: 0.28
570
571 1
572 PROBLEM NO.: 1 SUBPROBLEM NO.: 26
573
574 SIMULATION STEP PERFORMED
575 SOURCE 1:
576 SEED1: 2109412283 SEED2: 0
577 Elapsed simulation time in seconds: 0.14
578 ESTIMATION STEP OMITTED: YES
579 Elapsed finaloutput time in seconds: 0.28
580
581 1
582 PROBLEM NO.: 1 SUBPROBLEM NO.: 27
583
584 SIMULATION STEP PERFORMED
585 SOURCE 1:
586 SEED1: 2067566681 SEED2: 1074021055
587 Elapsed simulation time in seconds: 0.16
588 ESTIMATION STEP OMITTED: YES
589 Elapsed finaloutput time in seconds: 0.28
590
591 1
592 PROBLEM NO.: 1 SUBPROBLEM NO.: 28
593
594 SIMULATION STEP PERFORMED
595 SOURCE 1:
596 SEED1: 956482669 SEED2: 0
597 Elapsed simulation time in seconds: 0.15
598 ESTIMATION STEP OMITTED: YES
599 Elapsed finaloutput time in seconds: 0.28
600
601 1
602 PROBLEM NO.: 1 SUBPROBLEM NO.: 29
603
604 SIMULATION STEP PERFORMED
605 SOURCE 1:

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606     SEED1:      64343401    SEED2:    1068400638
607 Elapsed simulation  time in seconds:    0.16
608 ESTIMATION STEP OMITTED:    YES
609 Elapsed finaloutput  time in seconds:    0.28
610
611 1
612 PROBLEM NO.:      1          SUBPROBLEM NO.:    30
613
614 SIMULATION STEP PERFORMED
615 SOURCE 1:
616     SEED1:    1795846301    SEED2:      0
617 Elapsed simulation  time in seconds:    0.20
618 ESTIMATION STEP OMITTED:    YES
619 Elapsed finaloutput  time in seconds:    0.28
620
621 1
622 PROBLEM NO.:      1          SUBPROBLEM NO.:    31
623
624 SIMULATION STEP PERFORMED
625 SOURCE 1:
626     SEED1:    1264479957    SEED2:   -1072157176
627 Elapsed simulation  time in seconds:    0.14
628 ESTIMATION STEP OMITTED:    YES
629 Elapsed finaloutput  time in seconds:    0.28
630
631 1
632 PROBLEM NO.:      1          SUBPROBLEM NO.:    32
633
634 SIMULATION STEP PERFORMED
635 SOURCE 1:
636     SEED1:    1844199865    SEED2:      0
637 Elapsed simulation  time in seconds:    0.13
638 ESTIMATION STEP OMITTED:    YES
639 Elapsed finaloutput  time in seconds:    0.28
640
641 1
642 PROBLEM NO.:      1          SUBPROBLEM NO.:    33
643
644 SIMULATION STEP PERFORMED
645 SOURCE 1:
646     SEED1:    1006115004    SEED2:   -1081454986
647 Elapsed simulation  time in seconds:    0.14
648 ESTIMATION STEP OMITTED:    YES
649 Elapsed finaloutput  time in seconds:    0.28
650
651 1
652 PROBLEM NO.:      1          SUBPROBLEM NO.:    34
653
654 SIMULATION STEP PERFORMED
655 SOURCE 1:
656     SEED1:    1662737738    SEED2:      0
657 Elapsed simulation  time in seconds:    0.14
658 ESTIMATION STEP OMITTED:    YES
659 Elapsed finaloutput  time in seconds:    0.28
660
661 1
662 PROBLEM NO.:      1          SUBPROBLEM NO.:    35
663
664 SIMULATION STEP PERFORMED
665 SOURCE 1:
666     SEED1:    1662274237    SEED2:    1038884670
667 Elapsed simulation  time in seconds:    0.13
668 ESTIMATION STEP OMITTED:    YES
669 Elapsed finaloutput  time in seconds:    0.28
670
671 1
672 PROBLEM NO.:      1          SUBPROBLEM NO.:    36
673

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674 SIMULATION STEP PERFORMED
675 SOURCE 1:
676 SEED1: 2113795193 SEED2: 0
677 Elapsed simulation time in seconds: 0.13
678 ESTIMATION STEP OMITTED: YES
679 Elapsed finaloutput time in seconds: 0.28
680
681 1
682 PROBLEM NO.: 1 SUBPROBLEM NO.: 37
683
684 SIMULATION STEP PERFORMED
685 SOURCE 1:
686 SEED1: 1076061941 SEED2: -1082192601
687 Elapsed simulation time in seconds: 0.13
688 ESTIMATION STEP OMITTED: YES
689 Elapsed finaloutput time in seconds: 0.28
690
691 1
692 PROBLEM NO.: 1 SUBPROBLEM NO.: 38
693
694 SIMULATION STEP PERFORMED
695 SOURCE 1:
696 SEED1: 677686850 SEED2: 0
697 Elapsed simulation time in seconds: 0.13
698 ESTIMATION STEP OMITTED: YES
699 Elapsed finaloutput time in seconds: 0.28
700
701 1
702 PROBLEM NO.: 1 SUBPROBLEM NO.: 39
703
704 SIMULATION STEP PERFORMED
705 SOURCE 1:
706 SEED1: 157720352 SEED2: 1062410845
707 Elapsed simulation time in seconds: 0.12
708 ESTIMATION STEP OMITTED: YES
709 Elapsed finaloutput time in seconds: 0.28
710
711 1
712 PROBLEM NO.: 1 SUBPROBLEM NO.: 40
713
714 SIMULATION STEP PERFORMED
715 SOURCE 1:
716 SEED1: 845379091 SEED2: 0
717 Elapsed simulation time in seconds: 0.14
718 ESTIMATION STEP OMITTED: YES
719 Elapsed finaloutput time in seconds: 0.28
720
721 1
722 PROBLEM NO.: 1 SUBPROBLEM NO.: 41
723
724 SIMULATION STEP PERFORMED
725 SOURCE 1:
726 SEED1: 2079844007 SEED2: 1062515678
727 Elapsed simulation time in seconds: 0.13
728 ESTIMATION STEP OMITTED: YES
729 Elapsed finaloutput time in seconds: 0.28
730
731 1
732 PROBLEM NO.: 1 SUBPROBLEM NO.: 42
733
734 SIMULATION STEP PERFORMED
735 SOURCE 1:
736 SEED1: 45844697 SEED2: 0
737 Elapsed simulation time in seconds: 0.14
738 ESTIMATION STEP OMITTED: YES
739 Elapsed finaloutput time in seconds: 0.28
740
741 1

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742 PROBLEM NO.:          1          SUBPROBLEM NO.:          43
743
744 SIMULATION STEP PERFORMED
745 SOURCE 1:
746     SEED1:    427460931    SEED2:    1047600081
747 Elapsed simulation  time in seconds:    0.14
748 ESTIMATION STEP OMITTED:    YES
749 Elapsed finaloutput  time in seconds:    0.28
750
751 1
752 PROBLEM NO.:          1          SUBPROBLEM NO.:          44
753
754 SIMULATION STEP PERFORMED
755 SOURCE 1:
756     SEED1:    1381775991    SEED2:          0
757 Elapsed simulation  time in seconds:    0.13
758 ESTIMATION STEP OMITTED:    YES
759 Elapsed finaloutput  time in seconds:    0.28
760
761 1
762 PROBLEM NO.:          1          SUBPROBLEM NO.:          45
763
764 SIMULATION STEP PERFORMED
765 SOURCE 1:
766     SEED1:    422435095    SEED2:    1045736056
767 Elapsed simulation  time in seconds:    0.15
768 ESTIMATION STEP OMITTED:    YES
769 Elapsed finaloutput  time in seconds:    0.28
770
771 1
772 PROBLEM NO.:          1          SUBPROBLEM NO.:          46
773
774 SIMULATION STEP PERFORMED
775 SOURCE 1:
776     SEED1:    434870867    SEED2:          0
777 Elapsed simulation  time in seconds:    0.13
778 ESTIMATION STEP OMITTED:    YES
779 Elapsed finaloutput  time in seconds:    0.28
780
781 1
782 PROBLEM NO.:          1          SUBPROBLEM NO.:          47
783
784 SIMULATION STEP PERFORMED
785 SOURCE 1:
786     SEED1:    1917391846    SEED2:    1075717057
787 Elapsed simulation  time in seconds:    0.13
788 ESTIMATION STEP OMITTED:    YES
789 Elapsed finaloutput  time in seconds:    0.28
790
791 1
792 PROBLEM NO.:          1          SUBPROBLEM NO.:          48
793
794 SIMULATION STEP PERFORMED
795 SOURCE 1:
796     SEED1:    1520075750    SEED2:          0
797 Elapsed simulation  time in seconds:    0.17
798 ESTIMATION STEP OMITTED:    YES
799 Elapsed finaloutput  time in seconds:    0.28
800
801 1
802 PROBLEM NO.:          1          SUBPROBLEM NO.:          49
803
804 SIMULATION STEP PERFORMED
805 SOURCE 1:
806     SEED1:    2036107958    SEED2:    1063251713
807 Elapsed simulation  time in seconds:    0.13
808 ESTIMATION STEP OMITTED:    YES
809 Elapsed finaloutput  time in seconds:    0.28

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810
811 1
812 PROBLEM NO.:          1          SUBPROBLEM NO.:          50
813
814 SIMULATION STEP PERFORMED
815 SOURCE 1:
816     SEED1:    1607631210    SEED2:          0
817 Elapsed simulation time in seconds:    0.12
818 ESTIMATION STEP OMITTED:          YES
819 Elapsed finaloutput time in seconds:    0.28
820
821 1
822 PROBLEM NO.:          1          SUBPROBLEM NO.:          51
823
824 SIMULATION STEP PERFORMED
825 SOURCE 1:
826     SEED1:    1640759816    SEED2:    1045845822
827 Elapsed simulation time in seconds:    0.12
828 ESTIMATION STEP OMITTED:          YES
829 Elapsed finaloutput time in seconds:    0.28
830
831 1
832 PROBLEM NO.:          1          SUBPROBLEM NO.:          52
833
834 SIMULATION STEP PERFORMED
835 SOURCE 1:
836     SEED1:    855410099    SEED2:          0
837 Elapsed simulation time in seconds:    0.13
838 ESTIMATION STEP OMITTED:          YES
839 Elapsed finaloutput time in seconds:    0.28
840
841 1
842 PROBLEM NO.:          1          SUBPROBLEM NO.:          53
843
844 SIMULATION STEP PERFORMED
845 SOURCE 1:
846     SEED1:    1949786876    SEED2:    1067314261
847 Elapsed simulation time in seconds:    0.13
848 ESTIMATION STEP OMITTED:          YES
849 Elapsed finaloutput time in seconds:    0.28
850
851 1
852 PROBLEM NO.:          1          SUBPROBLEM NO.:          54
853
854 SIMULATION STEP PERFORMED
855 SOURCE 1:
856     SEED1:    848571363    SEED2:          0
857 Elapsed simulation time in seconds:    0.16
858 ESTIMATION STEP OMITTED:          YES
859 Elapsed finaloutput time in seconds:    0.28
860
861 1
862 PROBLEM NO.:          1          SUBPROBLEM NO.:          55
863
864 SIMULATION STEP PERFORMED
865 SOURCE 1:
866     SEED1:    1494107830    SEED2:    -1104929999
867 Elapsed simulation time in seconds:    0.14
868 ESTIMATION STEP OMITTED:          YES
869 Elapsed finaloutput time in seconds:    0.28
870
871 1
872 PROBLEM NO.:          1          SUBPROBLEM NO.:          56
873
874 SIMULATION STEP PERFORMED
875 SOURCE 1:
876     SEED1:    2095853779    SEED2:          0
877 Elapsed simulation time in seconds:    0.14

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878 ESTIMATION STEP OMITTED: YES
879 Elapsed finaloutput time in seconds: 0.28
880
881 1
882 PROBLEM NO.: 1 SUBPROBLEM NO.: 57
883
884 SIMULATION STEP PERFORMED
885 SOURCE 1:
886 SEED1: 303621865 SEED2: 1065681674
887 Elapsed simulation time in seconds: 0.14
888 ESTIMATION STEP OMITTED: YES
889 Elapsed finaloutput time in seconds: 0.28
890
891 1
892 PROBLEM NO.: 1 SUBPROBLEM NO.: 58
893
894 SIMULATION STEP PERFORMED
895 SOURCE 1:
896 SEED1: 1349738909 SEED2: 0
897 Elapsed simulation time in seconds: 0.12
898 ESTIMATION STEP OMITTED: YES
899 Elapsed finaloutput time in seconds: 0.28
900
901 1
902 PROBLEM NO.: 1 SUBPROBLEM NO.: 59
903
904 SIMULATION STEP PERFORMED
905 SOURCE 1:
906 SEED1: 210848942 SEED2: 1058907712
907 Elapsed simulation time in seconds: 0.13
908 ESTIMATION STEP OMITTED: YES
909 Elapsed finaloutput time in seconds: 0.28
910
911 1
912 PROBLEM NO.: 1 SUBPROBLEM NO.: 60
913
914 SIMULATION STEP PERFORMED
915 SOURCE 1:
916 SEED1: 145599708 SEED2: 0
917 Elapsed simulation time in seconds: 0.12
918 ESTIMATION STEP OMITTED: YES
919 Elapsed finaloutput time in seconds: 0.28
920
921 1
922 PROBLEM NO.: 1 SUBPROBLEM NO.: 61
923
924 SIMULATION STEP PERFORMED
925 SOURCE 1:
926 SEED1: 2026296246 SEED2: 1061237625
927 Elapsed simulation time in seconds: 0.12
928 ESTIMATION STEP OMITTED: YES
929 Elapsed finaloutput time in seconds: 0.28
930
931 1
932 PROBLEM NO.: 1 SUBPROBLEM NO.: 62
933
934 SIMULATION STEP PERFORMED
935 SOURCE 1:
936 SEED1: 965788917 SEED2: 0
937 Elapsed simulation time in seconds: 0.13
938 ESTIMATION STEP OMITTED: YES
939 Elapsed finaloutput time in seconds: 0.28
940
941 1
942 PROBLEM NO.: 1 SUBPROBLEM NO.: 63
943
944 SIMULATION STEP PERFORMED
945 SOURCE 1:

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946     SEED1:    2077686325    SEED2:    1063252409
947 Elapsed simulation  time in seconds:    0.13
948 ESTIMATION STEP OMITTED:    YES
949 Elapsed finaloutput  time in seconds:    0.28
950
951 1
952 PROBLEM NO.:    1    SUBPROBLEM NO.:    64
953
954 SIMULATION STEP PERFORMED
955 SOURCE 1:
956     SEED1:    2078566271    SEED2:    0
957 Elapsed simulation  time in seconds:    0.14
958 ESTIMATION STEP OMITTED:    YES
959 Elapsed finaloutput  time in seconds:    0.28
960
961 1
962 PROBLEM NO.:    1    SUBPROBLEM NO.:    65
963
964 SIMULATION STEP PERFORMED
965 SOURCE 1:
966     SEED1:    234093189    SEED2:    1062457771
967 Elapsed simulation  time in seconds:    0.14
968 ESTIMATION STEP OMITTED:    YES
969 Elapsed finaloutput  time in seconds:    0.28
970
971 1
972 PROBLEM NO.:    1    SUBPROBLEM NO.:    66
973
974 SIMULATION STEP PERFORMED
975 SOURCE 1:
976     SEED1:    1491567217    SEED2:    0
977 Elapsed simulation  time in seconds:    0.12
978 ESTIMATION STEP OMITTED:    YES
979 Elapsed finaloutput  time in seconds:    0.28
980
981 1
982 PROBLEM NO.:    1    SUBPROBLEM NO.:    67
983
984 SIMULATION STEP PERFORMED
985 SOURCE 1:
986     SEED1:    1827976059    SEED2:    1061229893
987 Elapsed simulation  time in seconds:    0.13
988 ESTIMATION STEP OMITTED:    YES
989 Elapsed finaloutput  time in seconds:    0.28
990
991 1
992 PROBLEM NO.:    1    SUBPROBLEM NO.:    68
993
994 SIMULATION STEP PERFORMED
995 SOURCE 1:
996     SEED1:    1365755186    SEED2:    0
997 Elapsed simulation  time in seconds:    0.14
998 ESTIMATION STEP OMITTED:    YES
999 Elapsed finaloutput  time in seconds:    0.29
1000
1001 1
1002 PROBLEM NO.:    1    SUBPROBLEM NO.:    69
1003
1004 SIMULATION STEP PERFORMED
1005 SOURCE 1:
1006     SEED1:    685004665    SEED2:    -1093383147
1007 Elapsed simulation  time in seconds:    0.16
1008 ESTIMATION STEP OMITTED:    YES
1009 Elapsed finaloutput  time in seconds:    0.28
1010
1011 1
1012 PROBLEM NO.:    1    SUBPROBLEM NO.:    70
1013

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1014 SIMULATION STEP PERFORMED
1015 SOURCE 1:
1016 SEED1: 825902556 SEED2: 0
1017 Elapsed simulation time in seconds: 0.13
1018 ESTIMATION STEP OMITTED: YES
1019 Elapsed finaloutput time in seconds: 0.28
1020
1021 1
1022 PROBLEM NO.: 1 SUBPROBLEM NO.: 71
1023
1024 SIMULATION STEP PERFORMED
1025 SOURCE 1:
1026 SEED1: 284142785 SEED2: 1036862256
1027 Elapsed simulation time in seconds: 0.14
1028 ESTIMATION STEP OMITTED: YES
1029 Elapsed finaloutput time in seconds: 0.28
1030
1031 1
1032 PROBLEM NO.: 1 SUBPROBLEM NO.: 72
1033
1034 SIMULATION STEP PERFORMED
1035 SOURCE 1:
1036 SEED1: 1465655428 SEED2: 0
1037 Elapsed simulation time in seconds: 0.14
1038 ESTIMATION STEP OMITTED: YES
1039 Elapsed finaloutput time in seconds: 0.28
1040
1041 1
1042 PROBLEM NO.: 1 SUBPROBLEM NO.: 73
1043
1044 SIMULATION STEP PERFORMED
1045 SOURCE 1:
1046 SEED1: 711835985 SEED2: -1084885226
1047 Elapsed simulation time in seconds: 0.13
1048 ESTIMATION STEP OMITTED: YES
1049 Elapsed finaloutput time in seconds: 0.28
1050
1051 1
1052 PROBLEM NO.: 1 SUBPROBLEM NO.: 74
1053
1054 SIMULATION STEP PERFORMED
1055 SOURCE 1:
1056 SEED1: 1261842859 SEED2: 0
1057 Elapsed simulation time in seconds: 0.13
1058 ESTIMATION STEP OMITTED: YES
1059 Elapsed finaloutput time in seconds: 0.28
1060
1061 1
1062 PROBLEM NO.: 1 SUBPROBLEM NO.: 75
1063
1064 SIMULATION STEP PERFORMED
1065 SOURCE 1:
1066 SEED1: 1381302334 SEED2: -1078725960
1067 Elapsed simulation time in seconds: 0.15
1068 ESTIMATION STEP OMITTED: YES
1069 Elapsed finaloutput time in seconds: 0.28
1070
1071 1
1072 PROBLEM NO.: 1 SUBPROBLEM NO.: 76
1073
1074 SIMULATION STEP PERFORMED
1075 SOURCE 1:
1076 SEED1: 1007474036 SEED2: 0
1077 Elapsed simulation time in seconds: 0.20
1078 ESTIMATION STEP OMITTED: YES
1079 Elapsed finaloutput time in seconds: 0.28
1080
1081 1

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1082 PROBLEM NO.:          1          SUBPROBLEM NO.:          77
1083
1084 SIMULATION STEP PERFORMED
1085 SOURCE 1:
1086     SEED1:    1623641511    SEED2:    1028516878
1087 Elapsed simulation  time in seconds:    0.19
1088 ESTIMATION STEP OMITTED:          YES
1089 Elapsed finaloutput  time in seconds:    0.28
1090
1091 1
1092 PROBLEM NO.:          1          SUBPROBLEM NO.:          78
1093
1094 SIMULATION STEP PERFORMED
1095 SOURCE 1:
1096     SEED1:    1032185020    SEED2:          0
1097 Elapsed simulation  time in seconds:    0.16
1098 ESTIMATION STEP OMITTED:          YES
1099 Elapsed finaloutput  time in seconds:    0.28
1100
1101 1
1102 PROBLEM NO.:          1          SUBPROBLEM NO.:          79
1103
1104 SIMULATION STEP PERFORMED
1105 SOURCE 1:
1106     SEED1:    866664143    SEED2:   -1088245936
1107 Elapsed simulation  time in seconds:    0.16
1108 ESTIMATION STEP OMITTED:          YES
1109 Elapsed finaloutput  time in seconds:    0.28
1110
1111 1
1112 PROBLEM NO.:          1          SUBPROBLEM NO.:          80
1113
1114 SIMULATION STEP PERFORMED
1115 SOURCE 1:
1116     SEED1:    838931450    SEED2:          0
1117 Elapsed simulation  time in seconds:    0.13
1118 ESTIMATION STEP OMITTED:          YES
1119 Elapsed finaloutput  time in seconds:    0.28
1120
1121 1
1122 PROBLEM NO.:          1          SUBPROBLEM NO.:          81
1123
1124 SIMULATION STEP PERFORMED
1125 SOURCE 1:
1126     SEED1:    1242004651    SEED2:   -1082942137
1127 Elapsed simulation  time in seconds:    0.14
1128 ESTIMATION STEP OMITTED:          YES
1129 Elapsed finaloutput  time in seconds:    0.28
1130
1131 1
1132 PROBLEM NO.:          1          SUBPROBLEM NO.:          82
1133
1134 SIMULATION STEP PERFORMED
1135 SOURCE 1:
1136     SEED1:    1883073180    SEED2:          0
1137 Elapsed simulation  time in seconds:    0.13
1138 ESTIMATION STEP OMITTED:          YES
1139 Elapsed finaloutput  time in seconds:    0.28
1140
1141 1
1142 PROBLEM NO.:          1          SUBPROBLEM NO.:          83
1143
1144 SIMULATION STEP PERFORMED
1145 SOURCE 1:
1146     SEED1:    2078257851    SEED2:    1068790176
1147 Elapsed simulation  time in seconds:    0.14
1148 ESTIMATION STEP OMITTED:          YES
1149 Elapsed finaloutput  time in seconds:    0.28

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1150
1151 1
1152 PROBLEM NO.:          1          SUBPROBLEM NO.:          84
1153
1154 SIMULATION STEP PERFORMED
1155 SOURCE 1:
1156     SEED1:    1524115839    SEED2:          0
1157 Elapsed simulation time in seconds:    0.17
1158 ESTIMATION STEP OMITTED:          YES
1159 Elapsed finaloutput time in seconds:    0.28
1160
1161 1
1162 PROBLEM NO.:          1          SUBPROBLEM NO.:          85
1163
1164 SIMULATION STEP PERFORMED
1165 SOURCE 1:
1166     SEED1:    1140735976    SEED2:   -1088029932
1167 Elapsed simulation time in seconds:    0.14
1168 ESTIMATION STEP OMITTED:          YES
1169 Elapsed finaloutput time in seconds:    0.28
1170
1171 1
1172 PROBLEM NO.:          1          SUBPROBLEM NO.:          86
1173
1174 SIMULATION STEP PERFORMED
1175 SOURCE 1:
1176     SEED1:    425452606    SEED2:          0
1177 Elapsed simulation time in seconds:    0.13
1178 ESTIMATION STEP OMITTED:          YES
1179 Elapsed finaloutput time in seconds:    0.28
1180
1181 1
1182 PROBLEM NO.:          1          SUBPROBLEM NO.:          87
1183
1184 SIMULATION STEP PERFORMED
1185 SOURCE 1:
1186     SEED1:    1181098860    SEED2:   -1091419348
1187 Elapsed simulation time in seconds:    0.16
1188 ESTIMATION STEP OMITTED:          YES
1189 Elapsed finaloutput time in seconds:    0.28
1190
1191 1
1192 PROBLEM NO.:          1          SUBPROBLEM NO.:          88
1193
1194 SIMULATION STEP PERFORMED
1195 SOURCE 1:
1196     SEED1:    2086264248    SEED2:          0
1197 Elapsed simulation time in seconds:    0.12
1198 ESTIMATION STEP OMITTED:          YES
1199 Elapsed finaloutput time in seconds:    0.28
1200
1201 1
1202 PROBLEM NO.:          1          SUBPROBLEM NO.:          89
1203
1204 SIMULATION STEP PERFORMED
1205 SOURCE 1:
1206     SEED1:    2103070784    SEED2:   1054254545
1207 Elapsed simulation time in seconds:    0.14
1208 ESTIMATION STEP OMITTED:          YES
1209 Elapsed finaloutput time in seconds:    0.28
1210
1211 1
1212 PROBLEM NO.:          1          SUBPROBLEM NO.:          90
1213
1214 SIMULATION STEP PERFORMED
1215 SOURCE 1:
1216     SEED1:    1654610581    SEED2:          0
1217 Elapsed simulation time in seconds:    0.15

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1218 ESTIMATION STEP OMITTED: YES
1219 Elapsed finaloutput time in seconds: 0.28
1220
1221 1
1222 PROBLEM NO.: 1 SUBPROBLEM NO.: 91
1223
1224 SIMULATION STEP PERFORMED
1225 SOURCE 1:
1226 SEED1: 1326319201 SEED2: -1090041870
1227 Elapsed simulation time in seconds: 0.13
1228 ESTIMATION STEP OMITTED: YES
1229 Elapsed finaloutput time in seconds: 0.28
1230
1231 1
1232 PROBLEM NO.: 1 SUBPROBLEM NO.: 92
1233
1234 SIMULATION STEP PERFORMED
1235 SOURCE 1:
1236 SEED1: 1120260784 SEED2: 0
1237 Elapsed simulation time in seconds: 0.13
1238 ESTIMATION STEP OMITTED: YES
1239 Elapsed finaloutput time in seconds: 0.28
1240
1241 1
1242 PROBLEM NO.: 1 SUBPROBLEM NO.: 93
1243
1244 SIMULATION STEP PERFORMED
1245 SOURCE 1:
1246 SEED1: 273164722 SEED2: 1067780977
1247 Elapsed simulation time in seconds: 0.16
1248 ESTIMATION STEP OMITTED: YES
1249 Elapsed finaloutput time in seconds: 0.28
1250
1251 1
1252 PROBLEM NO.: 1 SUBPROBLEM NO.: 94
1253
1254 SIMULATION STEP PERFORMED
1255 SOURCE 1:
1256 SEED1: 71178287 SEED2: 0
1257 Elapsed simulation time in seconds: 0.15
1258 ESTIMATION STEP OMITTED: YES
1259 Elapsed finaloutput time in seconds: 0.29
1260
1261 1
1262 PROBLEM NO.: 1 SUBPROBLEM NO.: 95
1263
1264 SIMULATION STEP PERFORMED
1265 SOURCE 1:
1266 SEED1: 1552384940 SEED2: -1099682207
1267 Elapsed simulation time in seconds: 0.14
1268 ESTIMATION STEP OMITTED: YES
1269 Elapsed finaloutput time in seconds: 0.28
1270
1271 1
1272 PROBLEM NO.: 1 SUBPROBLEM NO.: 96
1273
1274 SIMULATION STEP PERFORMED
1275 SOURCE 1:
1276 SEED1: 310619418 SEED2: 0
1277 Elapsed simulation time in seconds: 0.14
1278 ESTIMATION STEP OMITTED: YES
1279 Elapsed finaloutput time in seconds: 0.28
1280
1281 1
1282 PROBLEM NO.: 1 SUBPROBLEM NO.: 97
1283
1284 SIMULATION STEP PERFORMED
1285 SOURCE 1:

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1286     SEED1:    2063383412    SEED2:    1067786582
1287 Elapsed simulation  time in seconds:    0.15
1288 ESTIMATION STEP OMITTED:    YES
1289 Elapsed finaloutput  time in seconds:    0.28
1290
1291 1
1292 PROBLEM NO.:          1          SUBPROBLEM NO.:          98
1293
1294 SIMULATION STEP PERFORMED
1295 SOURCE 1:
1296     SEED1:    1388274140    SEED2:          0
1297 Elapsed simulation  time in seconds:    0.19
1298 ESTIMATION STEP OMITTED:    YES
1299 Elapsed finaloutput  time in seconds:    0.28
1300
1301 1
1302 PROBLEM NO.:          1          SUBPROBLEM NO.:          99
1303
1304 SIMULATION STEP PERFORMED
1305 SOURCE 1:
1306     SEED1:    93813710    SEED2:    1074094064
1307 Elapsed simulation  time in seconds:    0.13
1308 ESTIMATION STEP OMITTED:    YES
1309 Elapsed finaloutput  time in seconds:    0.28
1310
1311 1
1312 PROBLEM NO.:          1          SUBPROBLEM NO.:          100
1313
1314 SIMULATION STEP PERFORMED
1315 SOURCE 1:
1316     SEED1:    34966499    SEED2:          0
1317 Elapsed simulation  time in seconds:    0.14
1318 ESTIMATION STEP OMITTED:    YES
1319 Elapsed finaloutput  time in seconds:    0.28
1320
1321 1
1322 PROBLEM NO.:          1          SUBPROBLEM NO.:          101
1323
1324 SIMULATION STEP PERFORMED
1325 SOURCE 1:
1326     SEED1:    1368880882    SEED2:    -1092420075
1327 Elapsed simulation  time in seconds:    0.14
1328 ESTIMATION STEP OMITTED:    YES
1329 Elapsed finaloutput  time in seconds:    0.28
1330
1331 1
1332 PROBLEM NO.:          1          SUBPROBLEM NO.:          102
1333
1334 SIMULATION STEP PERFORMED
1335 SOURCE 1:
1336     SEED1:    1229420459    SEED2:          0
1337 Elapsed simulation  time in seconds:    0.15
1338 ESTIMATION STEP OMITTED:    YES
1339 Elapsed finaloutput  time in seconds:    0.28
1340
1341 1
1342 PROBLEM NO.:          1          SUBPROBLEM NO.:          103
1343
1344 SIMULATION STEP PERFORMED
1345 SOURCE 1:
1346     SEED1:    1554303167    SEED2:    -1102405197
1347 Elapsed simulation  time in seconds:    0.18
1348 ESTIMATION STEP OMITTED:    YES
1349 Elapsed finaloutput  time in seconds:    0.28
1350
1351 1
1352 PROBLEM NO.:          1          SUBPROBLEM NO.:          104
1353

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1354 SIMULATION STEP PERFORMED
1355 SOURCE 1:
1356 SEED1: 1253682372 SEED2: 0
1357 Elapsed simulation time in seconds: 0.14
1358 ESTIMATION STEP OMITTED: YES
1359 Elapsed finaloutput time in seconds: 0.28
1360
1361 1
1362 PROBLEM NO.: 1 SUBPROBLEM NO.: 105
1363
1364 SIMULATION STEP PERFORMED
1365 SOURCE 1:
1366 SEED1: 144399212 SEED2: 1069353852
1367 Elapsed simulation time in seconds: 0.13
1368 ESTIMATION STEP OMITTED: YES
1369 Elapsed finaloutput time in seconds: 0.28
1370
1371 1
1372 PROBLEM NO.: 1 SUBPROBLEM NO.: 106
1373
1374 SIMULATION STEP PERFORMED
1375 SOURCE 1:
1376 SEED1: 836147816 SEED2: 0
1377 Elapsed simulation time in seconds: 0.15
1378 ESTIMATION STEP OMITTED: YES
1379 Elapsed finaloutput time in seconds: 0.28
1380
1381 1
1382 PROBLEM NO.: 1 SUBPROBLEM NO.: 107
1383
1384 SIMULATION STEP PERFORMED
1385 SOURCE 1:
1386 SEED1: 1492352968 SEED2: -1096727972
1387 Elapsed simulation time in seconds: 0.14
1388 ESTIMATION STEP OMITTED: YES
1389 Elapsed finaloutput time in seconds: 0.28
1390
1391 1
1392 PROBLEM NO.: 1 SUBPROBLEM NO.: 108
1393
1394 SIMULATION STEP PERFORMED
1395 SOURCE 1:
1396 SEED1: 97266753 SEED2: 0
1397 Elapsed simulation time in seconds: 0.13
1398 ESTIMATION STEP OMITTED: YES
1399 Elapsed finaloutput time in seconds: 0.28
1400
1401 1
1402 PROBLEM NO.: 1 SUBPROBLEM NO.: 109
1403
1404 SIMULATION STEP PERFORMED
1405 SOURCE 1:
1406 SEED1: 2051693741 SEED2: 1074554961
1407 Elapsed simulation time in seconds: 0.14
1408 ESTIMATION STEP OMITTED: YES
1409 Elapsed finaloutput time in seconds: 0.29
1410
1411 1
1412 PROBLEM NO.: 1 SUBPROBLEM NO.: 110
1413
1414 SIMULATION STEP PERFORMED
1415 SOURCE 1:
1416 SEED1: 1009524817 SEED2: 0
1417 Elapsed simulation time in seconds: 0.14
1418 ESTIMATION STEP OMITTED: YES
1419 Elapsed finaloutput time in seconds: 0.28
1420
1421 1

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1422 PROBLEM NO.:          1          SUBPROBLEM NO.:          111
1423
1424 SIMULATION STEP PERFORMED
1425 SOURCE 1:
1426     SEED1:      489642691    SEED2:      1020328449
1427 Elapsed simulation  time in seconds:      0.12
1428 ESTIMATION STEP OMITTED:      YES
1429 Elapsed finaloutput  time in seconds:      0.28
1430
1431 1
1432 PROBLEM NO.:          1          SUBPROBLEM NO.:          112
1433
1434 SIMULATION STEP PERFORMED
1435 SOURCE 1:
1436     SEED1:      732156112    SEED2:          0
1437 Elapsed simulation  time in seconds:      0.14
1438 ESTIMATION STEP OMITTED:      YES
1439 Elapsed finaloutput  time in seconds:      0.28
1440
1441 1
1442 PROBLEM NO.:          1          SUBPROBLEM NO.:          113
1443
1444 SIMULATION STEP PERFORMED
1445 SOURCE 1:
1446     SEED1:      752770758    SEED2:     -1102220459
1447 Elapsed simulation  time in seconds:      0.14
1448 ESTIMATION STEP OMITTED:      YES
1449 Elapsed finaloutput  time in seconds:      0.28
1450
1451 1
1452 PROBLEM NO.:          1          SUBPROBLEM NO.:          114
1453
1454 SIMULATION STEP PERFORMED
1455 SOURCE 1:
1456     SEED1:      1443886034    SEED2:          0
1457 Elapsed simulation  time in seconds:      0.15
1458 ESTIMATION STEP OMITTED:      YES
1459 Elapsed finaloutput  time in seconds:      0.28
1460
1461 1
1462 PROBLEM NO.:          1          SUBPROBLEM NO.:          115
1463
1464 SIMULATION STEP PERFORMED
1465 SOURCE 1:
1466     SEED1:      132824775    SEED2:      1054713589
1467 Elapsed simulation  time in seconds:      0.14
1468 ESTIMATION STEP OMITTED:      YES
1469 Elapsed finaloutput  time in seconds:      0.28
1470
1471 1
1472 PROBLEM NO.:          1          SUBPROBLEM NO.:          116
1473
1474 SIMULATION STEP PERFORMED
1475 SOURCE 1:
1476     SEED1:      97014085     SEED2:          0
1477 Elapsed simulation  time in seconds:      0.13
1478 ESTIMATION STEP OMITTED:      YES
1479 Elapsed finaloutput  time in seconds:      0.28
1480
1481 1
1482 PROBLEM NO.:          1          SUBPROBLEM NO.:          117
1483
1484 SIMULATION STEP PERFORMED
1485 SOURCE 1:
1486     SEED1:      688367955    SEED2:     -1090608700
1487 Elapsed simulation  time in seconds:      0.13
1488 ESTIMATION STEP OMITTED:      YES
1489 Elapsed finaloutput  time in seconds:      0.29

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1490
1491 1
1492 PROBLEM NO.:          1          SUBPROBLEM NO.:          118
1493
1494 SIMULATION STEP PERFORMED
1495 SOURCE 1:
1496     SEED1:    1001350432    SEED2:          0
1497 Elapsed simulation time in seconds:    0.13
1498 ESTIMATION STEP OMITTED:          YES
1499 Elapsed finaloutput time in seconds:    0.28
1500
1501 1
1502 PROBLEM NO.:          1          SUBPROBLEM NO.:          119
1503
1504 SIMULATION STEP PERFORMED
1505 SOURCE 1:
1506     SEED1:    756125005    SEED2:   -1080698306
1507 Elapsed simulation time in seconds:    0.15
1508 ESTIMATION STEP OMITTED:          YES
1509 Elapsed finaloutput time in seconds:    0.28
1510
1511 1
1512 PROBLEM NO.:          1          SUBPROBLEM NO.:          120
1513
1514 SIMULATION STEP PERFORMED
1515 SOURCE 1:
1516     SEED1:    1721562170    SEED2:          0
1517 Elapsed simulation time in seconds:    0.14
1518 ESTIMATION STEP OMITTED:          YES
1519 Elapsed finaloutput time in seconds:    0.28
1520
1521 1
1522 PROBLEM NO.:          1          SUBPROBLEM NO.:          121
1523
1524 SIMULATION STEP PERFORMED
1525 SOURCE 1:
1526     SEED1:    1649316376    SEED2:    1011381636
1527 Elapsed simulation time in seconds:    0.13
1528 ESTIMATION STEP OMITTED:          YES
1529 Elapsed finaloutput time in seconds:    0.28
1530
1531 1
1532 PROBLEM NO.:          1          SUBPROBLEM NO.:          122
1533
1534 SIMULATION STEP PERFORMED
1535 SOURCE 1:
1536     SEED1:    1345965209    SEED2:          0
1537 Elapsed simulation time in seconds:    0.14
1538 ESTIMATION STEP OMITTED:          YES
1539 Elapsed finaloutput time in seconds:    0.28
1540
1541 1
1542 PROBLEM NO.:          1          SUBPROBLEM NO.:          123
1543
1544 SIMULATION STEP PERFORMED
1545 SOURCE 1:
1546     SEED1:    629299632    SEED2:   -1094607335
1547 Elapsed simulation time in seconds:    0.13
1548 ESTIMATION STEP OMITTED:          YES
1549 Elapsed finaloutput time in seconds:    0.28
1550
1551 1
1552 PROBLEM NO.:          1          SUBPROBLEM NO.:          124
1553
1554 SIMULATION STEP PERFORMED
1555 SOURCE 1:
1556     SEED1:    1746611977    SEED2:          0
1557 Elapsed simulation time in seconds:    0.14

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1558 ESTIMATION STEP OMITTED: YES
1559 Elapsed finaloutput time in seconds: 0.29
1560
1561 1
1562 PROBLEM NO.: 1 SUBPROBLEM NO.: 125
1563
1564 SIMULATION STEP PERFORMED
1565 SOURCE 1:
1566 SEED1: 1631662598 SEED2: 1034058083
1567 Elapsed simulation time in seconds: 0.14
1568 ESTIMATION STEP OMITTED: YES
1569 Elapsed finaloutput time in seconds: 0.28
1570
1571 1
1572 PROBLEM NO.: 1 SUBPROBLEM NO.: 126
1573
1574 SIMULATION STEP PERFORMED
1575 SOURCE 1:
1576 SEED1: 314829657 SEED2: 0
1577 Elapsed simulation time in seconds: 0.13
1578 ESTIMATION STEP OMITTED: YES
1579 Elapsed finaloutput time in seconds: 0.28
1580
1581 1
1582 PROBLEM NO.: 1 SUBPROBLEM NO.: 127
1583
1584 SIMULATION STEP PERFORMED
1585 SOURCE 1:
1586 SEED1: 1705633624 SEED2: 1049607913
1587 Elapsed simulation time in seconds: 0.13
1588 ESTIMATION STEP OMITTED: YES
1589 Elapsed finaloutput time in seconds: 0.29
1590
1591 1
1592 PROBLEM NO.: 1 SUBPROBLEM NO.: 128
1593
1594 SIMULATION STEP PERFORMED
1595 SOURCE 1:
1596 SEED1: 2075532585 SEED2: 0
1597 Elapsed simulation time in seconds: 0.15
1598 ESTIMATION STEP OMITTED: YES
1599 Elapsed finaloutput time in seconds: 0.28
1600
1601 1
1602 PROBLEM NO.: 1 SUBPROBLEM NO.: 129
1603
1604 SIMULATION STEP PERFORMED
1605 SOURCE 1:
1606 SEED1: 823994086 SEED2: -1078981479
1607 Elapsed simulation time in seconds: 0.14
1608 ESTIMATION STEP OMITTED: YES
1609 Elapsed finaloutput time in seconds: 0.28
1610
1611 1
1612 PROBLEM NO.: 1 SUBPROBLEM NO.: 130
1613
1614 SIMULATION STEP PERFORMED
1615 SOURCE 1:
1616 SEED1: 896028584 SEED2: 0
1617 Elapsed simulation time in seconds: 0.13
1618 ESTIMATION STEP OMITTED: YES
1619 Elapsed finaloutput time in seconds: 0.28
1620
1621 1
1622 PROBLEM NO.: 1 SUBPROBLEM NO.: 131
1623
1624 SIMULATION STEP PERFORMED
1625 SOURCE 1:

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1626     SEED1:    1824980971    SEED2:    1065620498
1627 Elapsed simulation  time in seconds:    0.13
1628 ESTIMATION STEP OMITTED:    YES
1629 Elapsed finaloutput  time in seconds:    0.28
1630
1631 1
1632 PROBLEM NO.:          1          SUBPROBLEM NO.:          132
1633
1634 SIMULATION STEP PERFORMED
1635 SOURCE 1:
1636     SEED1:    1473188721    SEED2:          0
1637 Elapsed simulation  time in seconds:    0.13
1638 ESTIMATION STEP OMITTED:    YES
1639 Elapsed finaloutput  time in seconds:    0.29
1640
1641 1
1642 PROBLEM NO.:          1          SUBPROBLEM NO.:          133
1643
1644 SIMULATION STEP PERFORMED
1645 SOURCE 1:
1646     SEED1:    1926905585    SEED2:    1065659837
1647 Elapsed simulation  time in seconds:    0.13
1648 ESTIMATION STEP OMITTED:    YES
1649 Elapsed finaloutput  time in seconds:    0.28
1650
1651 1
1652 PROBLEM NO.:          1          SUBPROBLEM NO.:          134
1653
1654 SIMULATION STEP PERFORMED
1655 SOURCE 1:
1656     SEED1:    1512811881    SEED2:          0
1657 Elapsed simulation  time in seconds:    0.13
1658 ESTIMATION STEP OMITTED:    YES
1659 Elapsed finaloutput  time in seconds:    0.28
1660
1661 1
1662 PROBLEM NO.:          1          SUBPROBLEM NO.:          135
1663
1664 SIMULATION STEP PERFORMED
1665 SOURCE 1:
1666     SEED1:    1861678215    SEED2:    1056655476
1667 Elapsed simulation  time in seconds:    0.13
1668 ESTIMATION STEP OMITTED:    YES
1669 Elapsed finaloutput  time in seconds:    0.28
1670
1671 1
1672 PROBLEM NO.:          1          SUBPROBLEM NO.:          136
1673
1674 SIMULATION STEP PERFORMED
1675 SOURCE 1:
1676     SEED1:    782807392    SEED2:          0
1677 Elapsed simulation  time in seconds:    0.14
1678 ESTIMATION STEP OMITTED:    YES
1679 Elapsed finaloutput  time in seconds:    0.28
1680
1681 1
1682 PROBLEM NO.:          1          SUBPROBLEM NO.:          137
1683
1684 SIMULATION STEP PERFORMED
1685 SOURCE 1:
1686     SEED1:    40687126    SEED2:    1052623445
1687 Elapsed simulation  time in seconds:    0.16
1688 ESTIMATION STEP OMITTED:    YES
1689 Elapsed finaloutput  time in seconds:    0.28
1690
1691 1
1692 PROBLEM NO.:          1          SUBPROBLEM NO.:          138
1693

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1694 SIMULATION STEP PERFORMED
1695 SOURCE 1:
1696 SEED1: 2075173422 SEED2: 0
1697 Elapsed simulation time in seconds: 0.12
1698 ESTIMATION STEP OMITTED: YES
1699 Elapsed finaloutput time in seconds: 0.29
1700
1701 1
1702 PROBLEM NO.: 1 SUBPROBLEM NO.: 139
1703
1704 SIMULATION STEP PERFORMED
1705 SOURCE 1:
1706 SEED1: 793193495 SEED2: -1089369681
1707 Elapsed simulation time in seconds: 0.15
1708 ESTIMATION STEP OMITTED: YES
1709 Elapsed finaloutput time in seconds: 0.28
1710
1711 1
1712 PROBLEM NO.: 1 SUBPROBLEM NO.: 140
1713
1714 SIMULATION STEP PERFORMED
1715 SOURCE 1:
1716 SEED1: 1448970249 SEED2: 0
1717 Elapsed simulation time in seconds: 0.14
1718 ESTIMATION STEP OMITTED: YES
1719 Elapsed finaloutput time in seconds: 0.28
1720
1721 1
1722 PROBLEM NO.: 1 SUBPROBLEM NO.: 141
1723
1724 SIMULATION STEP PERFORMED
1725 SOURCE 1:
1726 SEED1: 549983442 SEED2: -1121220401
1727 Elapsed simulation time in seconds: 0.14
1728 ESTIMATION STEP OMITTED: YES
1729 Elapsed finaloutput time in seconds: 0.28
1730
1731 1
1732 PROBLEM NO.: 1 SUBPROBLEM NO.: 142
1733
1734 SIMULATION STEP PERFORMED
1735 SOURCE 1:
1736 SEED1: 700663769 SEED2: 0
1737 Elapsed simulation time in seconds: 0.20
1738 ESTIMATION STEP OMITTED: YES
1739 Elapsed finaloutput time in seconds: 0.29
1740
1741 1
1742 PROBLEM NO.: 1 SUBPROBLEM NO.: 143
1743
1744 SIMULATION STEP PERFORMED
1745 SOURCE 1:
1746 SEED1: 1349533586 SEED2: -1074854960
1747 Elapsed simulation time in seconds: 0.16
1748 ESTIMATION STEP OMITTED: YES
1749 Elapsed finaloutput time in seconds: 0.28
1750
1751 1
1752 PROBLEM NO.: 1 SUBPROBLEM NO.: 144
1753
1754 SIMULATION STEP PERFORMED
1755 SOURCE 1:
1756 SEED1: 1248587012 SEED2: 0
1757 Elapsed simulation time in seconds: 0.14
1758 ESTIMATION STEP OMITTED: YES
1759 Elapsed finaloutput time in seconds: 0.28
1760
1761 1

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1762 PROBLEM NO.:          1          SUBPROBLEM NO.:          145
1763
1764 SIMULATION STEP PERFORMED
1765 SOURCE 1:
1766     SEED1:    1155949501    SEED2:    -1089649179
1767 Elapsed simulation  time in seconds:    0.14
1768 ESTIMATION STEP OMITTED:          YES
1769 Elapsed finaloutput  time in seconds:    0.28
1770
1771 1
1772 PROBLEM NO.:          1          SUBPROBLEM NO.:          146
1773
1774 SIMULATION STEP PERFORMED
1775 SOURCE 1:
1776     SEED1:    1921368186    SEED2:          0
1777 Elapsed simulation  time in seconds:    0.14
1778 ESTIMATION STEP OMITTED:          YES
1779 Elapsed finaloutput  time in seconds:    0.28
1780
1781 1
1782 PROBLEM NO.:          1          SUBPROBLEM NO.:          147
1783
1784 SIMULATION STEP PERFORMED
1785 SOURCE 1:
1786     SEED1:    1639506585    SEED2:    1040822363
1787 Elapsed simulation  time in seconds:    0.14
1788 ESTIMATION STEP OMITTED:          YES
1789 Elapsed finaloutput  time in seconds:    0.28
1790
1791 1
1792 PROBLEM NO.:          1          SUBPROBLEM NO.:          148
1793
1794 SIMULATION STEP PERFORMED
1795 SOURCE 1:
1796     SEED1:    1077801981    SEED2:          0
1797 Elapsed simulation  time in seconds:    0.17
1798 ESTIMATION STEP OMITTED:          YES
1799 Elapsed finaloutput  time in seconds:    0.29
1800
1801 1
1802 PROBLEM NO.:          1          SUBPROBLEM NO.:          149
1803
1804 SIMULATION STEP PERFORMED
1805 SOURCE 1:
1806     SEED1:    1009623918    SEED2:    -1072697497
1807 Elapsed simulation  time in seconds:    0.12
1808 ESTIMATION STEP OMITTED:          YES
1809 Elapsed finaloutput  time in seconds:    0.28
1810
1811 1
1812 PROBLEM NO.:          1          SUBPROBLEM NO.:          150
1813
1814 SIMULATION STEP PERFORMED
1815 SOURCE 1:
1816     SEED1:    2131883035    SEED2:          0
1817 Elapsed simulation  time in seconds:    0.14
1818 ESTIMATION STEP OMITTED:          YES
1819 Elapsed finaloutput  time in seconds:    0.28
1820
1821 1
1822 PROBLEM NO.:          1          SUBPROBLEM NO.:          151
1823
1824 SIMULATION STEP PERFORMED
1825 SOURCE 1:
1826     SEED1:    843888933    SEED2:    -1070946295
1827 Elapsed simulation  time in seconds:    0.14
1828 ESTIMATION STEP OMITTED:          YES
1829 Elapsed finaloutput  time in seconds:    0.28

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1830
1831 1
1832 PROBLEM NO.:          1          SUBPROBLEM NO.:          152
1833
1834 SIMULATION STEP PERFORMED
1835 SOURCE 1:
1836     SEED1:    1004510098    SEED2:          0
1837 Elapsed simulation time in seconds:    0.13
1838 ESTIMATION STEP OMITTED:          YES
1839 Elapsed finaloutput time in seconds:    0.28
1840
1841 1
1842 PROBLEM NO.:          1          SUBPROBLEM NO.:          153
1843
1844 SIMULATION STEP PERFORMED
1845 SOURCE 1:
1846     SEED1:    174163717    SEED2:    1061852589
1847 Elapsed simulation time in seconds:    0.30
1848 ESTIMATION STEP OMITTED:          YES
1849 Elapsed finaloutput time in seconds:    0.28
1850
1851 1
1852 PROBLEM NO.:          1          SUBPROBLEM NO.:          154
1853
1854 SIMULATION STEP PERFORMED
1855 SOURCE 1:
1856     SEED1:    95261994    SEED2:          0
1857 Elapsed simulation time in seconds:    0.19
1858 ESTIMATION STEP OMITTED:          YES
1859 Elapsed finaloutput time in seconds:    0.29
1860
1861 1
1862 PROBLEM NO.:          1          SUBPROBLEM NO.:          155
1863
1864 SIMULATION STEP PERFORMED
1865 SOURCE 1:
1866     SEED1:    251630402    SEED2:    1059363753
1867 Elapsed simulation time in seconds:    0.16
1868 ESTIMATION STEP OMITTED:          YES
1869 Elapsed finaloutput time in seconds:    0.28
1870
1871 1
1872 PROBLEM NO.:          1          SUBPROBLEM NO.:          156
1873
1874 SIMULATION STEP PERFORMED
1875 SOURCE 1:
1876     SEED1:    1261458129    SEED2:          0
1877 Elapsed simulation time in seconds:    0.15
1878 ESTIMATION STEP OMITTED:          YES
1879 Elapsed finaloutput time in seconds:    0.28
1880
1881 1
1882 PROBLEM NO.:          1          SUBPROBLEM NO.:          157
1883
1884 SIMULATION STEP PERFORMED
1885 SOURCE 1:
1886     SEED1:    1065053718    SEED2:    -1091899231
1887 Elapsed simulation time in seconds:    0.15
1888 ESTIMATION STEP OMITTED:          YES
1889 Elapsed finaloutput time in seconds:    0.28
1890
1891 1
1892 PROBLEM NO.:          1          SUBPROBLEM NO.:          158
1893
1894 SIMULATION STEP PERFORMED
1895 SOURCE 1:
1896     SEED1:    108132411    SEED2:          0
1897 Elapsed simulation time in seconds:    0.16

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1898 ESTIMATION STEP OMITTED: YES
1899 Elapsed finaloutput time in seconds: 0.28
1900
1901 1
1902 PROBLEM NO.: 1 SUBPROBLEM NO.: 159
1903
1904 SIMULATION STEP PERFORMED
1905 SOURCE 1:
1906 SEED1: 1813151725 SEED2: 1061858898
1907 Elapsed simulation time in seconds: 0.17
1908 ESTIMATION STEP OMITTED: YES
1909 Elapsed finaloutput time in seconds: 0.29
1910
1911 1
1912 PROBLEM NO.: 1 SUBPROBLEM NO.: 160
1913
1914 SIMULATION STEP PERFORMED
1915 SOURCE 1:
1916 SEED1: 1258603861 SEED2: 0
1917 Elapsed simulation time in seconds: 0.19
1918 ESTIMATION STEP OMITTED: YES
1919 Elapsed finaloutput time in seconds: 0.28
1920
1921 1
1922 PROBLEM NO.: 1 SUBPROBLEM NO.: 161
1923
1924 SIMULATION STEP PERFORMED
1925 SOURCE 1:
1926 SEED1: 758618645 SEED2: -1096763442
1927 Elapsed simulation time in seconds: 0.13
1928 ESTIMATION STEP OMITTED: YES
1929 Elapsed finaloutput time in seconds: 0.28
1930
1931 1
1932 PROBLEM NO.: 1 SUBPROBLEM NO.: 162
1933
1934 SIMULATION STEP PERFORMED
1935 SOURCE 1:
1936 SEED1: 1979792596 SEED2: 0
1937 Elapsed simulation time in seconds: 0.18
1938 ESTIMATION STEP OMITTED: YES
1939 Elapsed finaloutput time in seconds: 0.28
1940
1941 1
1942 PROBLEM NO.: 1 SUBPROBLEM NO.: 163
1943
1944 SIMULATION STEP PERFORMED
1945 SOURCE 1:
1946 SEED1: 852224747 SEED2: -1089569028
1947 Elapsed simulation time in seconds: 0.15
1948 ESTIMATION STEP OMITTED: YES
1949 Elapsed finaloutput time in seconds: 0.28
1950
1951 1
1952 PROBLEM NO.: 1 SUBPROBLEM NO.: 164
1953
1954 SIMULATION STEP PERFORMED
1955 SOURCE 1:
1956 SEED1: 1372608032 SEED2: 0
1957 Elapsed simulation time in seconds: 0.14
1958 ESTIMATION STEP OMITTED: YES
1959 Elapsed finaloutput time in seconds: 0.29
1960
1961 1
1962 PROBLEM NO.: 1 SUBPROBLEM NO.: 165
1963
1964 SIMULATION STEP PERFORMED
1965 SOURCE 1:

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1966     SEED1:    1824274344    SEED2:    1055726292
1967 Elapsed simulation  time in seconds:    0.16
1968 ESTIMATION STEP OMITTED:    YES
1969 Elapsed finaloutput  time in seconds:    0.28
1970
1971 1
1972 PROBLEM NO.:          1          SUBPROBLEM NO.:          166
1973
1974 SIMULATION STEP PERFORMED
1975 SOURCE 1:
1976     SEED1:    1158318705    SEED2:          0
1977 Elapsed simulation  time in seconds:    0.16
1978 ESTIMATION STEP OMITTED:    YES
1979 Elapsed finaloutput  time in seconds:    0.28
1980
1981 1
1982 PROBLEM NO.:          1          SUBPROBLEM NO.:          167
1983
1984 SIMULATION STEP PERFORMED
1985 SOURCE 1:
1986     SEED1:    138150911    SEED2:    1061897929
1987 Elapsed simulation  time in seconds:    0.16
1988 ESTIMATION STEP OMITTED:    YES
1989 Elapsed finaloutput  time in seconds:    0.28
1990
1991 1
1992 PROBLEM NO.:          1          SUBPROBLEM NO.:          168
1993
1994 SIMULATION STEP PERFORMED
1995 SOURCE 1:
1996     SEED1:    494544287    SEED2:          0
1997 Elapsed simulation  time in seconds:    0.19
1998 ESTIMATION STEP OMITTED:    YES
1999 Elapsed finaloutput  time in seconds:    0.28
2000
2001 1
2002 PROBLEM NO.:          1          SUBPROBLEM NO.:          169
2003
2004 SIMULATION STEP PERFORMED
2005 SOURCE 1:
2006     SEED1:    2076308562    SEED2:    1074536845
2007 Elapsed simulation  time in seconds:    0.14
2008 ESTIMATION STEP OMITTED:    YES
2009 Elapsed finaloutput  time in seconds:    0.28
2010
2011 1
2012 PROBLEM NO.:          1          SUBPROBLEM NO.:          170
2013
2014 SIMULATION STEP PERFORMED
2015 SOURCE 1:
2016     SEED1:    2010809043    SEED2:          0
2017 Elapsed simulation  time in seconds:    0.16
2018 ESTIMATION STEP OMITTED:    YES
2019 Elapsed finaloutput  time in seconds:    0.28
2020
2021 1
2022 PROBLEM NO.:          1          SUBPROBLEM NO.:          171
2023
2024 SIMULATION STEP PERFORMED
2025 SOURCE 1:
2026     SEED1:    1108668734    SEED2:    -1085698274
2027 Elapsed simulation  time in seconds:    0.16
2028 ESTIMATION STEP OMITTED:    YES
2029 Elapsed finaloutput  time in seconds:    0.28
2030
2031 1
2032 PROBLEM NO.:          1          SUBPROBLEM NO.:          172
2033

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2034 SIMULATION STEP PERFORMED
2035 SOURCE 1:
2036 SEED1: 1923859127 SEED2: 0
2037 Elapsed simulation time in seconds: 0.16
2038 ESTIMATION STEP OMITTED: YES
2039 Elapsed finaloutput time in seconds: 0.28
2040
2041 1
2042 PROBLEM NO.: 1 SUBPROBLEM NO.: 173
2043
2044 SIMULATION STEP PERFORMED
2045 SOURCE 1:
2046 SEED1: 1706710119 SEED2: 1044179999
2047 Elapsed simulation time in seconds: 0.14
2048 ESTIMATION STEP OMITTED: YES
2049 Elapsed finaloutput time in seconds: 0.29
2050
2051 1
2052 PROBLEM NO.: 1 SUBPROBLEM NO.: 174
2053
2054 SIMULATION STEP PERFORMED
2055 SOURCE 1:
2056 SEED1: 146717652 SEED2: 0
2057 Elapsed simulation time in seconds: 0.17
2058 ESTIMATION STEP OMITTED: YES
2059 Elapsed finaloutput time in seconds: 0.28
2060
2061 1
2062 PROBLEM NO.: 1 SUBPROBLEM NO.: 175
2063
2064 SIMULATION STEP PERFORMED
2065 SOURCE 1:
2066 SEED1: 1692961158 SEED2: 1050184769
2067 Elapsed simulation time in seconds: 0.16
2068 ESTIMATION STEP OMITTED: YES
2069 Elapsed finaloutput time in seconds: 0.29
2070
2071 1
2072 PROBLEM NO.: 1 SUBPROBLEM NO.: 176
2073
2074 SIMULATION STEP PERFORMED
2075 SOURCE 1:
2076 SEED1: 382057053 SEED2: 0
2077 Elapsed simulation time in seconds: 0.16
2078 ESTIMATION STEP OMITTED: YES
2079 Elapsed finaloutput time in seconds: 0.29
2080
2081 1
2082 PROBLEM NO.: 1 SUBPROBLEM NO.: 177
2083
2084 SIMULATION STEP PERFORMED
2085 SOURCE 1:
2086 SEED1: 1604362232 SEED2: -1137755024
2087 Elapsed simulation time in seconds: 0.18
2088 ESTIMATION STEP OMITTED: YES
2089 Elapsed finaloutput time in seconds: 0.28
2090
2091 1
2092 PROBLEM NO.: 1 SUBPROBLEM NO.: 178
2093
2094 SIMULATION STEP PERFORMED
2095 SOURCE 1:
2096 SEED1: 1549368348 SEED2: 0
2097 Elapsed simulation time in seconds: 0.15
2098 ESTIMATION STEP OMITTED: YES
2099 Elapsed finaloutput time in seconds: 0.28
2100
2101 1

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2102 PROBLEM NO.:          1          SUBPROBLEM NO.:          179
2103
2104 SIMULATION STEP PERFORMED
2105 SOURCE 1:
2106     SEED1:    1808944350    SEED2:    1065554387
2107 Elapsed simulation  time in seconds:    0.14
2108 ESTIMATION STEP OMITTED:          YES
2109 Elapsed finaloutput  time in seconds:    0.28
2110
2111 1
2112 PROBLEM NO.:          1          SUBPROBLEM NO.:          180
2113
2114 SIMULATION STEP PERFORMED
2115 SOURCE 1:
2116     SEED1:    250950991    SEED2:          0
2117 Elapsed simulation  time in seconds:    0.14
2118 ESTIMATION STEP OMITTED:          YES
2119 Elapsed finaloutput  time in seconds:    0.29
2120
2121 1
2122 PROBLEM NO.:          1          SUBPROBLEM NO.:          181
2123
2124 SIMULATION STEP PERFORMED
2125 SOURCE 1:
2126     SEED1:    2125512959    SEED2:    1044272303
2127 Elapsed simulation  time in seconds:    0.13
2128 ESTIMATION STEP OMITTED:          YES
2129 Elapsed finaloutput  time in seconds:    0.29
2130
2131 1
2132 PROBLEM NO.:          1          SUBPROBLEM NO.:          182
2133
2134 SIMULATION STEP PERFORMED
2135 SOURCE 1:
2136     SEED1:    356921824    SEED2:          0
2137 Elapsed simulation  time in seconds:    0.15
2138 ESTIMATION STEP OMITTED:          YES
2139 Elapsed finaloutput  time in seconds:    0.28
2140
2141 1
2142 PROBLEM NO.:          1          SUBPROBLEM NO.:          183
2143
2144 SIMULATION STEP PERFORMED
2145 SOURCE 1:
2146     SEED1:    620007785    SEED2:   -1094770086
2147 Elapsed simulation  time in seconds:    0.15
2148 ESTIMATION STEP OMITTED:          YES
2149 Elapsed finaloutput  time in seconds:    0.29
2150
2151 1
2152 PROBLEM NO.:          1          SUBPROBLEM NO.:          184
2153
2154 SIMULATION STEP PERFORMED
2155 SOURCE 1:
2156     SEED1:    1141217313    SEED2:          0
2157 Elapsed simulation  time in seconds:    0.14
2158 ESTIMATION STEP OMITTED:          YES
2159 Elapsed finaloutput  time in seconds:    0.29
2160
2161 1
2162 PROBLEM NO.:          1          SUBPROBLEM NO.:          185
2163
2164 SIMULATION STEP PERFORMED
2165 SOURCE 1:
2166     SEED1:    1473505802    SEED2:   -1090524496
2167 Elapsed simulation  time in seconds:    0.16
2168 ESTIMATION STEP OMITTED:          YES
2169 Elapsed finaloutput  time in seconds:    0.28

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2170
2171 1
2172 PROBLEM NO.:          1          SUBPROBLEM NO.:          186
2173
2174 SIMULATION STEP PERFORMED
2175 SOURCE 1:
2176     SEED1:      929769863    SEED2:          0
2177 Elapsed simulation time in seconds:      0.25
2178 ESTIMATION STEP OMITTED:          YES
2179 Elapsed finaloutput time in seconds:      0.28
2180
2181 1
2182 PROBLEM NO.:          1          SUBPROBLEM NO.:          187
2183
2184 SIMULATION STEP PERFORMED
2185 SOURCE 1:
2186     SEED1:     1371452395    SEED2:   -1082671503
2187 Elapsed simulation time in seconds:      0.23
2188 ESTIMATION STEP OMITTED:          YES
2189 Elapsed finaloutput time in seconds:      0.28
2190
2191 1
2192 PROBLEM NO.:          1          SUBPROBLEM NO.:          188
2193
2194 SIMULATION STEP PERFORMED
2195 SOURCE 1:
2196     SEED1:      771653693    SEED2:          0
2197 Elapsed simulation time in seconds:      0.14
2198 ESTIMATION STEP OMITTED:          YES
2199 Elapsed finaloutput time in seconds:      0.29
2200
2201 1
2202 PROBLEM NO.:          1          SUBPROBLEM NO.:          189
2203
2204 SIMULATION STEP PERFORMED
2205 SOURCE 1:
2206     SEED1:     1260786060    SEED2:   -1071092194
2207 Elapsed simulation time in seconds:      0.15
2208 ESTIMATION STEP OMITTED:          YES
2209 Elapsed finaloutput time in seconds:      0.28
2210
2211 1
2212 PROBLEM NO.:          1          SUBPROBLEM NO.:          190
2213
2214 SIMULATION STEP PERFORMED
2215 SOURCE 1:
2216     SEED1:      613208022    SEED2:          0
2217 Elapsed simulation time in seconds:      0.14
2218 ESTIMATION STEP OMITTED:          YES
2219 Elapsed finaloutput time in seconds:      0.29
2220
2221 1
2222 PROBLEM NO.:          1          SUBPROBLEM NO.:          191
2223
2224 SIMULATION STEP PERFORMED
2225 SOURCE 1:
2226     SEED1:      972306771    SEED2:   -1084829499
2227 Elapsed simulation time in seconds:      0.14
2228 ESTIMATION STEP OMITTED:          YES
2229 Elapsed finaloutput time in seconds:      0.29
2230
2231 1
2232 PROBLEM NO.:          1          SUBPROBLEM NO.:          192
2233
2234 SIMULATION STEP PERFORMED
2235 SOURCE 1:
2236     SEED1:     137067531    SEED2:          0
2237 Elapsed simulation time in seconds:      0.16

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2238 ESTIMATION STEP OMITTED: YES
2239 Elapsed finaloutput time in seconds: 0.29
2240
2241 1
2242 PROBLEM NO.: 1 SUBPROBLEM NO.: 193
2243
2244 SIMULATION STEP PERFORMED
2245 SOURCE 1:
2246 SEED1: 430668909 SEED2: 1051750586
2247 Elapsed simulation time in seconds: 0.15
2248 ESTIMATION STEP OMITTED: YES
2249 Elapsed finaloutput time in seconds: 0.28
2250
2251 1
2252 PROBLEM NO.: 1 SUBPROBLEM NO.: 194
2253
2254 SIMULATION STEP PERFORMED
2255 SOURCE 1:
2256 SEED1: 345968181 SEED2: 0
2257 Elapsed simulation time in seconds: 0.15
2258 ESTIMATION STEP OMITTED: YES
2259 Elapsed finaloutput time in seconds: 0.29
2260
2261 1
2262 PROBLEM NO.: 1 SUBPROBLEM NO.: 195
2263
2264 SIMULATION STEP PERFORMED
2265 SOURCE 1:
2266 SEED1: 1384761786 SEED2: -1081700712
2267 Elapsed simulation time in seconds: 0.16
2268 ESTIMATION STEP OMITTED: YES
2269 Elapsed finaloutput time in seconds: 0.28
2270
2271 1
2272 PROBLEM NO.: 1 SUBPROBLEM NO.: 196
2273
2274 SIMULATION STEP PERFORMED
2275 SOURCE 1:
2276 SEED1: 550129949 SEED2: 0
2277 Elapsed simulation time in seconds: 0.16
2278 ESTIMATION STEP OMITTED: YES
2279 Elapsed finaloutput time in seconds: 0.29
2280
2281 1
2282 PROBLEM NO.: 1 SUBPROBLEM NO.: 197
2283
2284 SIMULATION STEP PERFORMED
2285 SOURCE 1:
2286 SEED1: 1037435841 SEED2: -1082851302
2287 Elapsed simulation time in seconds: 0.16
2288 ESTIMATION STEP OMITTED: YES
2289 Elapsed finaloutput time in seconds: 0.36
2290
2291 1
2292 PROBLEM NO.: 1 SUBPROBLEM NO.: 198
2293
2294 SIMULATION STEP PERFORMED
2295 SOURCE 1:
2296 SEED1: 300326306 SEED2: 0
2297 Elapsed simulation time in seconds: 0.12
2298 ESTIMATION STEP OMITTED: YES
2299 Elapsed finaloutput time in seconds: 0.28
2300
2301 1
2302 PROBLEM NO.: 1 SUBPROBLEM NO.: 199
2303
2304 SIMULATION STEP PERFORMED
2305 SOURCE 1:

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2306     SEED1:    1543961530    SEED2:   -1097916714
2307 Elapsed simulation  time in seconds:    0.14
2308 ESTIMATION STEP OMITTED:    YES
2309 Elapsed finaloutput  time in seconds:    0.29
2310
2311 1
2312 PROBLEM NO.:          1          SUBPROBLEM NO.:          200
2313
2314 SIMULATION STEP PERFORMED
2315 SOURCE 1:
2316     SEED1:    1616693724    SEED2:           0
2317 Elapsed simulation  time in seconds:    0.14
2318 ESTIMATION STEP OMITTED:    YES
2319 Elapsed finaloutput  time in seconds:    0.28
2320
2321 1
2322 PROBLEM NO.:          1          SUBPROBLEM NO.:          201
2323
2324 SIMULATION STEP PERFORMED
2325 SOURCE 1:
2326     SEED1:    1240303750    SEED2:  -1088698360
2327 Elapsed simulation  time in seconds:    0.13
2328 ESTIMATION STEP OMITTED:    YES
2329 Elapsed finaloutput  time in seconds:    0.28
2330
2331 1
2332 PROBLEM NO.:          1          SUBPROBLEM NO.:          202
2333
2334 SIMULATION STEP PERFORMED
2335 SOURCE 1:
2336     SEED1:    1198731521    SEED2:           0
2337 Elapsed simulation  time in seconds:    0.14
2338 ESTIMATION STEP OMITTED:    YES
2339 Elapsed finaloutput  time in seconds:    0.29
2340
2341 1
2342 PROBLEM NO.:          1          SUBPROBLEM NO.:          203
2343
2344 SIMULATION STEP PERFORMED
2345 SOURCE 1:
2346     SEED1:    1833926464    SEED2:   1030469207
2347 Elapsed simulation  time in seconds:    0.14
2348 ESTIMATION STEP OMITTED:    YES
2349 Elapsed finaloutput  time in seconds:    0.29
2350
2351 1
2352 PROBLEM NO.:          1          SUBPROBLEM NO.:          204
2353
2354 SIMULATION STEP PERFORMED
2355 SOURCE 1:
2356     SEED1:    797109829    SEED2:           0
2357 Elapsed simulation  time in seconds:    0.13
2358 ESTIMATION STEP OMITTED:    YES
2359 Elapsed finaloutput  time in seconds:    0.29
2360
2361 1
2362 PROBLEM NO.:          1          SUBPROBLEM NO.:          205
2363
2364 SIMULATION STEP PERFORMED
2365 SOURCE 1:
2366     SEED1:    2118613990    SEED2:   1074683155
2367 Elapsed simulation  time in seconds:    0.13
2368 ESTIMATION STEP OMITTED:    YES
2369 Elapsed finaloutput  time in seconds:    0.29
2370
2371 1
2372 PROBLEM NO.:          1          SUBPROBLEM NO.:          206
2373

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2374 SIMULATION STEP PERFORMED
2375 SOURCE 1:
2376 SEED1: 1127229987 SEED2: 0
2377 Elapsed simulation time in seconds: 0.16
2378 ESTIMATION STEP OMITTED: YES
2379 Elapsed finaloutput time in seconds: 0.29
2380
2381 1
2382 PROBLEM NO.: 1 SUBPROBLEM NO.: 207
2383
2384 SIMULATION STEP PERFORMED
2385 SOURCE 1:
2386 SEED1: 1268755019 SEED2: -1074874514
2387 Elapsed simulation time in seconds: 0.13
2388 ESTIMATION STEP OMITTED: YES
2389 Elapsed finaloutput time in seconds: 0.28
2390
2391 1
2392 PROBLEM NO.: 1 SUBPROBLEM NO.: 208
2393
2394 SIMULATION STEP PERFORMED
2395 SOURCE 1:
2396 SEED1: 480868697 SEED2: 0
2397 Elapsed simulation time in seconds: 0.14
2398 ESTIMATION STEP OMITTED: YES
2399 Elapsed finaloutput time in seconds: 0.28
2400
2401 1
2402 PROBLEM NO.: 1 SUBPROBLEM NO.: 209
2403
2404 SIMULATION STEP PERFORMED
2405 SOURCE 1:
2406 SEED1: 1434501739 SEED2: -1088549280
2407 Elapsed simulation time in seconds: 0.14
2408 ESTIMATION STEP OMITTED: YES
2409 Elapsed finaloutput time in seconds: 0.28
2410
2411 1
2412 PROBLEM NO.: 1 SUBPROBLEM NO.: 210
2413
2414 SIMULATION STEP PERFORMED
2415 SOURCE 1:
2416 SEED1: 1300799790 SEED2: 0
2417 Elapsed simulation time in seconds: 0.13
2418 ESTIMATION STEP OMITTED: YES
2419 Elapsed finaloutput time in seconds: 0.28
2420
2421 1
2422 PROBLEM NO.: 1 SUBPROBLEM NO.: 211
2423
2424 SIMULATION STEP PERFORMED
2425 SOURCE 1:
2426 SEED1: 1619835982 SEED2: 1022340001
2427 Elapsed simulation time in seconds: 0.12
2428 ESTIMATION STEP OMITTED: YES
2429 Elapsed finaloutput time in seconds: 0.29
2430
2431 1
2432 PROBLEM NO.: 1 SUBPROBLEM NO.: 212
2433
2434 SIMULATION STEP PERFORMED
2435 SOURCE 1:
2436 SEED1: 579421744 SEED2: 0
2437 Elapsed simulation time in seconds: 0.13
2438 ESTIMATION STEP OMITTED: YES
2439 Elapsed finaloutput time in seconds: 0.28
2440
2441 1

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2442 PROBLEM NO.:          1          SUBPROBLEM NO.:          213
2443
2444 SIMULATION STEP PERFORMED
2445 SOURCE 1:
2446     SEED1:      883537447    SEED2:    -1073658456
2447 Elapsed simulation  time in seconds:      0.13
2448 ESTIMATION STEP OMITTED:      YES
2449 Elapsed finaloutput  time in seconds:      0.28
2450
2451 1
2452 PROBLEM NO.:          1          SUBPROBLEM NO.:          214
2453
2454 SIMULATION STEP PERFORMED
2455 SOURCE 1:
2456     SEED1:      1195278827    SEED2:           0
2457 Elapsed simulation  time in seconds:      0.12
2458 ESTIMATION STEP OMITTED:      YES
2459 Elapsed finaloutput  time in seconds:      0.28
2460
2461 1
2462 PROBLEM NO.:          1          SUBPROBLEM NO.:          215
2463
2464 SIMULATION STEP PERFORMED
2465 SOURCE 1:
2466     SEED1:      57587045    SEED2:    1068147684
2467 Elapsed simulation  time in seconds:      0.13
2468 ESTIMATION STEP OMITTED:      YES
2469 Elapsed finaloutput  time in seconds:      0.28
2470
2471 1
2472 PROBLEM NO.:          1          SUBPROBLEM NO.:          216
2473
2474 SIMULATION STEP PERFORMED
2475 SOURCE 1:
2476     SEED1:      1079108687    SEED2:           0
2477 Elapsed simulation  time in seconds:      0.12
2478 ESTIMATION STEP OMITTED:      YES
2479 Elapsed finaloutput  time in seconds:      0.29
2480
2481 1
2482 PROBLEM NO.:          1          SUBPROBLEM NO.:          217
2483
2484 SIMULATION STEP PERFORMED
2485 SOURCE 1:
2486     SEED1:      1074895835    SEED2:   -1077991462
2487 Elapsed simulation  time in seconds:      0.13
2488 ESTIMATION STEP OMITTED:      YES
2489 Elapsed finaloutput  time in seconds:      0.28
2490
2491 1
2492 PROBLEM NO.:          1          SUBPROBLEM NO.:          218
2493
2494 SIMULATION STEP PERFORMED
2495 SOURCE 1:
2496     SEED1:      1827304340    SEED2:           0
2497 Elapsed simulation  time in seconds:      0.14
2498 ESTIMATION STEP OMITTED:      YES
2499 Elapsed finaloutput  time in seconds:      0.28
2500
2501 1
2502 PROBLEM NO.:          1          SUBPROBLEM NO.:          219
2503
2504 SIMULATION STEP PERFORMED
2505 SOURCE 1:
2506     SEED1:      679328547    SEED2:   -1089477139
2507 Elapsed simulation  time in seconds:      0.12
2508 ESTIMATION STEP OMITTED:      YES
2509 Elapsed finaloutput  time in seconds:      0.28

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2510
2511 1
2512 PROBLEM NO.:          1          SUBPROBLEM NO.:          220
2513
2514 SIMULATION STEP PERFORMED
2515 SOURCE 1:
2516     SEED1:    1717730095    SEED2:          0
2517 Elapsed simulation time in seconds:    0.13
2518 ESTIMATION STEP OMITTED:          YES
2519 Elapsed finaloutput time in seconds:    0.28
2520
2521 1
2522 PROBLEM NO.:          1          SUBPROBLEM NO.:          221
2523
2524 SIMULATION STEP PERFORMED
2525 SOURCE 1:
2526     SEED1:    127721983    SEED2:    1069990576
2527 Elapsed simulation time in seconds:    0.13
2528 ESTIMATION STEP OMITTED:          YES
2529 Elapsed finaloutput time in seconds:    0.28
2530
2531 1
2532 PROBLEM NO.:          1          SUBPROBLEM NO.:          222
2533
2534 SIMULATION STEP PERFORMED
2535 SOURCE 1:
2536     SEED1:    1832004151    SEED2:          0
2537 Elapsed simulation time in seconds:    0.12
2538 ESTIMATION STEP OMITTED:          YES
2539 Elapsed finaloutput time in seconds:    0.28
2540
2541 1
2542 PROBLEM NO.:          1          SUBPROBLEM NO.:          223
2543
2544 SIMULATION STEP PERFORMED
2545 SOURCE 1:
2546     SEED1:    1691857258    SEED2:    1053281952
2547 Elapsed simulation time in seconds:    0.13
2548 ESTIMATION STEP OMITTED:          YES
2549 Elapsed finaloutput time in seconds:    0.28
2550
2551 1
2552 PROBLEM NO.:          1          SUBPROBLEM NO.:          224
2553
2554 SIMULATION STEP PERFORMED
2555 SOURCE 1:
2556     SEED1:    2131241517    SEED2:          0
2557 Elapsed simulation time in seconds:    0.12
2558 ESTIMATION STEP OMITTED:          YES
2559 Elapsed finaloutput time in seconds:    0.28
2560
2561 1
2562 PROBLEM NO.:          1          SUBPROBLEM NO.:          225
2563
2564 SIMULATION STEP PERFORMED
2565 SOURCE 1:
2566     SEED1:    422748261    SEED2:    1056203946
2567 Elapsed simulation time in seconds:    0.12
2568 ESTIMATION STEP OMITTED:          YES
2569 Elapsed finaloutput time in seconds:    0.28
2570
2571 1
2572 PROBLEM NO.:          1          SUBPROBLEM NO.:          226
2573
2574 SIMULATION STEP PERFORMED
2575 SOURCE 1:
2576     SEED1:    567174232    SEED2:          0
2577 Elapsed simulation time in seconds:    0.13

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2578 ESTIMATION STEP OMITTED: YES
2579 Elapsed finaloutput time in seconds: 0.28
2580
2581 1
2582 PROBLEM NO.: 1 SUBPROBLEM NO.: 227
2583
2584 SIMULATION STEP PERFORMED
2585 SOURCE 1:
2586 SEED1: 1117801761 SEED2: -1075082068
2587 Elapsed simulation time in seconds: 0.12
2588 ESTIMATION STEP OMITTED: YES
2589 Elapsed finaloutput time in seconds: 0.28
2590
2591 1
2592 PROBLEM NO.: 1 SUBPROBLEM NO.: 228
2593
2594 SIMULATION STEP PERFORMED
2595 SOURCE 1:
2596 SEED1: 832360917 SEED2: 0
2597 Elapsed simulation time in seconds: 0.14
2598 ESTIMATION STEP OMITTED: YES
2599 Elapsed finaloutput time in seconds: 0.28
2600
2601 1
2602 PROBLEM NO.: 1 SUBPROBLEM NO.: 229
2603
2604 SIMULATION STEP PERFORMED
2605 SOURCE 1:
2606 SEED1: 849918117 SEED2: -1079285319
2607 Elapsed simulation time in seconds: 0.12
2608 ESTIMATION STEP OMITTED: YES
2609 Elapsed finaloutput time in seconds: 0.28
2610
2611 1
2612 PROBLEM NO.: 1 SUBPROBLEM NO.: 230
2613
2614 SIMULATION STEP PERFORMED
2615 SOURCE 1:
2616 SEED1: 802721516 SEED2: 0
2617 Elapsed simulation time in seconds: 0.13
2618 ESTIMATION STEP OMITTED: YES
2619 Elapsed finaloutput time in seconds: 0.28
2620
2621 1
2622 PROBLEM NO.: 1 SUBPROBLEM NO.: 231
2623
2624 SIMULATION STEP PERFORMED
2625 SOURCE 1:
2626 SEED1: 1565947238 SEED2: -1131318844
2627 Elapsed simulation time in seconds: 0.12
2628 ESTIMATION STEP OMITTED: YES
2629 Elapsed finaloutput time in seconds: 0.28
2630
2631 1
2632 PROBLEM NO.: 1 SUBPROBLEM NO.: 232
2633
2634 SIMULATION STEP PERFORMED
2635 SOURCE 1:
2636 SEED1: 1301802968 SEED2: 0
2637 Elapsed simulation time in seconds: 0.12
2638 ESTIMATION STEP OMITTED: YES
2639 Elapsed finaloutput time in seconds: 0.28
2640
2641 1
2642 PROBLEM NO.: 1 SUBPROBLEM NO.: 233
2643
2644 SIMULATION STEP PERFORMED
2645 SOURCE 1:

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2646     SEED1:      490743665     SEED2:      1048168907
2647 Elapsed simulation  time in seconds:      0.13
2648 ESTIMATION STEP OMITTED:      YES
2649 Elapsed finaloutput  time in seconds:      0.28
2650
2651 1
2652 PROBLEM NO.:      1      SUBPROBLEM NO.:      234
2653
2654 SIMULATION STEP PERFORMED
2655 SOURCE 1:
2656     SEED1:      316460572     SEED2:      0
2657 Elapsed simulation  time in seconds:      0.13
2658 ESTIMATION STEP OMITTED:      YES
2659 Elapsed finaloutput  time in seconds:      0.28
2660
2661 1
2662 PROBLEM NO.:      1      SUBPROBLEM NO.:      235
2663
2664 SIMULATION STEP PERFORMED
2665 SOURCE 1:
2666     SEED1:      1813787972     SEED2:      1055740950
2667 Elapsed simulation  time in seconds:      0.12
2668 ESTIMATION STEP OMITTED:      YES
2669 Elapsed finaloutput  time in seconds:      0.28
2670
2671 1
2672 PROBLEM NO.:      1      SUBPROBLEM NO.:      236
2673
2674 SIMULATION STEP PERFORMED
2675 SOURCE 1:
2676     SEED1:      2117136908     SEED2:      0
2677 Elapsed simulation  time in seconds:      0.12
2678 ESTIMATION STEP OMITTED:      YES
2679 Elapsed finaloutput  time in seconds:      0.28
2680
2681 1
2682 PROBLEM NO.:      1      SUBPROBLEM NO.:      237
2683
2684 SIMULATION STEP PERFORMED
2685 SOURCE 1:
2686     SEED1:      2093549232     SEED2:      1075079810
2687 Elapsed simulation  time in seconds:      0.13
2688 ESTIMATION STEP OMITTED:      YES
2689 Elapsed finaloutput  time in seconds:      0.28
2690
2691 1
2692 PROBLEM NO.:      1      SUBPROBLEM NO.:      238
2693
2694 SIMULATION STEP PERFORMED
2695 SOURCE 1:
2696     SEED1:      2110684532     SEED2:      0
2697 Elapsed simulation  time in seconds:      0.12
2698 ESTIMATION STEP OMITTED:      YES
2699 Elapsed finaloutput  time in seconds:      0.28
2700
2701 1
2702 PROBLEM NO.:      1      SUBPROBLEM NO.:      239
2703
2704 SIMULATION STEP PERFORMED
2705 SOURCE 1:
2706     SEED1:      69761161     SEED2:      1060489857
2707 Elapsed simulation  time in seconds:      0.12
2708 ESTIMATION STEP OMITTED:      YES
2709 Elapsed finaloutput  time in seconds:      0.28
2710
2711 1
2712 PROBLEM NO.:      1      SUBPROBLEM NO.:      240
2713

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2714 SIMULATION STEP PERFORMED
2715 SOURCE 1:
2716 SEED1: 1360874447 SEED2: 0
2717 Elapsed simulation time in seconds: 0.12
2718 ESTIMATION STEP OMITTED: YES
2719 Elapsed finaloutput time in seconds: 0.28
2720
2721 1
2722 PROBLEM NO.: 1 SUBPROBLEM NO.: 241
2723
2724 SIMULATION STEP PERFORMED
2725 SOURCE 1:
2726 SEED1: 206484441 SEED2: 1066831057
2727 Elapsed simulation time in seconds: 0.12
2728 ESTIMATION STEP OMITTED: YES
2729 Elapsed finaloutput time in seconds: 0.28
2730
2731 1
2732 PROBLEM NO.: 1 SUBPROBLEM NO.: 242
2733
2734 SIMULATION STEP PERFORMED
2735 SOURCE 1:
2736 SEED1: 285848624 SEED2: 0
2737 Elapsed simulation time in seconds: 0.13
2738 ESTIMATION STEP OMITTED: YES
2739 Elapsed finaloutput time in seconds: 0.29
2740
2741 1
2742 PROBLEM NO.: 1 SUBPROBLEM NO.: 243
2743
2744 SIMULATION STEP PERFORMED
2745 SOURCE 1:
2746 SEED1: 187551835 SEED2: 1070377117
2747 Elapsed simulation time in seconds: 0.13
2748 ESTIMATION STEP OMITTED: YES
2749 Elapsed finaloutput time in seconds: 0.28
2750
2751 1
2752 PROBLEM NO.: 1 SUBPROBLEM NO.: 244
2753
2754 SIMULATION STEP PERFORMED
2755 SOURCE 1:
2756 SEED1: 1922978643 SEED2: 0
2757 Elapsed simulation time in seconds: 0.13
2758 ESTIMATION STEP OMITTED: YES
2759 Elapsed finaloutput time in seconds: 0.28
2760
2761 1
2762 PROBLEM NO.: 1 SUBPROBLEM NO.: 245
2763
2764 SIMULATION STEP PERFORMED
2765 SOURCE 1:
2766 SEED1: 84125857 SEED2: 1058647553
2767 Elapsed simulation time in seconds: 0.13
2768 ESTIMATION STEP OMITTED: YES
2769 Elapsed finaloutput time in seconds: 0.28
2770
2771 1
2772 PROBLEM NO.: 1 SUBPROBLEM NO.: 246
2773
2774 SIMULATION STEP PERFORMED
2775 SOURCE 1:
2776 SEED1: 1882060359 SEED2: 0
2777 Elapsed simulation time in seconds: 0.13
2778 ESTIMATION STEP OMITTED: YES
2779 Elapsed finaloutput time in seconds: 0.29
2780
2781 1

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2782 PROBLEM NO.:          1          SUBPROBLEM NO.:          247
2783
2784 SIMULATION STEP PERFORMED
2785 SOURCE 1:
2786     SEED1:    1998522933    SEED2:    1074713357
2787 Elapsed simulation  time in seconds:    0.13
2788 ESTIMATION STEP OMITTED:          YES
2789 Elapsed finaloutput  time in seconds:    0.28
2790
2791 1
2792 PROBLEM NO.:          1          SUBPROBLEM NO.:          248
2793
2794 SIMULATION STEP PERFORMED
2795 SOURCE 1:
2796     SEED1:    1315508188    SEED2:          0
2797 Elapsed simulation  time in seconds:    0.12
2798 ESTIMATION STEP OMITTED:          YES
2799 Elapsed finaloutput  time in seconds:    0.28
2800
2801 1
2802 PROBLEM NO.:          1          SUBPROBLEM NO.:          249
2803
2804 SIMULATION STEP PERFORMED
2805 SOURCE 1:
2806     SEED1:    1870985311    SEED2:    1061024597
2807 Elapsed simulation  time in seconds:    0.13
2808 ESTIMATION STEP OMITTED:          YES
2809 Elapsed finaloutput  time in seconds:    0.28
2810
2811 1
2812 PROBLEM NO.:          1          SUBPROBLEM NO.:          250
2813
2814 SIMULATION STEP PERFORMED
2815 SOURCE 1:
2816     SEED1:    876703064    SEED2:          0
2817 Elapsed simulation  time in seconds:    0.13
2818 ESTIMATION STEP OMITTED:          YES
2819 Elapsed finaloutput  time in seconds:    0.29
2820
2821 1
2822 PROBLEM NO.:          1          SUBPROBLEM NO.:          251
2823
2824 SIMULATION STEP PERFORMED
2825 SOURCE 1:
2826     SEED1:    547712233    SEED2:   -1122401169
2827 Elapsed simulation  time in seconds:    0.13
2828 ESTIMATION STEP OMITTED:          YES
2829 Elapsed finaloutput  time in seconds:    0.29
2830
2831 1
2832 PROBLEM NO.:          1          SUBPROBLEM NO.:          252
2833
2834 SIMULATION STEP PERFORMED
2835 SOURCE 1:
2836     SEED1:    149259389    SEED2:          0
2837 Elapsed simulation  time in seconds:    0.12
2838 ESTIMATION STEP OMITTED:          YES
2839 Elapsed finaloutput  time in seconds:    0.28
2840
2841 1
2842 PROBLEM NO.:          1          SUBPROBLEM NO.:          253
2843
2844 SIMULATION STEP PERFORMED
2845 SOURCE 1:
2846     SEED1:    1214613865    SEED2:   -1083201542
2847 Elapsed simulation  time in seconds:    0.18
2848 ESTIMATION STEP OMITTED:          YES
2849 Elapsed finaloutput  time in seconds:    0.28

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2850
2851 1
2852 PROBLEM NO.:          1          SUBPROBLEM NO.:          254
2853
2854 SIMULATION STEP PERFORMED
2855 SOURCE 1:
2856     SEED1:      842920264    SEED2:          0
2857 Elapsed simulation  time in seconds:      0.13
2858 ESTIMATION STEP OMITTED:          YES
2859 Elapsed finaloutput  time in seconds:      0.28
2860
2861 1
2862 PROBLEM NO.:          1          SUBPROBLEM NO.:          255
2863
2864 SIMULATION STEP PERFORMED
2865 SOURCE 1:
2866     SEED1:      53359628    SEED2:    1063554011
2867 Elapsed simulation  time in seconds:      0.25
2868 ESTIMATION STEP OMITTED:          YES
2869 Elapsed finaloutput  time in seconds:      0.28
2870
2871 1
2872 PROBLEM NO.:          1          SUBPROBLEM NO.:          256
2873
2874 SIMULATION STEP PERFORMED
2875 SOURCE 1:
2876     SEED1:      1777966585   SEED2:          0
2877 Elapsed simulation  time in seconds:      0.12
2878 ESTIMATION STEP OMITTED:          YES
2879 Elapsed finaloutput  time in seconds:      0.28
2880
2881 1
2882 PROBLEM NO.:          1          SUBPROBLEM NO.:          257
2883
2884 SIMULATION STEP PERFORMED
2885 SOURCE 1:
2886     SEED1:      275588733    SEED2:    1071177357
2887 Elapsed simulation  time in seconds:      0.13
2888 ESTIMATION STEP OMITTED:          YES
2889 Elapsed finaloutput  time in seconds:      0.28
2890
2891 1
2892 PROBLEM NO.:          1          SUBPROBLEM NO.:          258
2893
2894 SIMULATION STEP PERFORMED
2895 SOURCE 1:
2896     SEED1:      445676568    SEED2:          0
2897 Elapsed simulation  time in seconds:      0.12
2898 ESTIMATION STEP OMITTED:          YES
2899 Elapsed finaloutput  time in seconds:      0.29
2900
2901 1
2902 PROBLEM NO.:          1          SUBPROBLEM NO.:          259
2903
2904 SIMULATION STEP PERFORMED
2905 SOURCE 1:
2906     SEED1:      294991609    SEED2:    1060607614
2907 Elapsed simulation  time in seconds:      0.12
2908 ESTIMATION STEP OMITTED:          YES
2909 Elapsed finaloutput  time in seconds:      0.28
2910
2911 1
2912 PROBLEM NO.:          1          SUBPROBLEM NO.:          260
2913
2914 SIMULATION STEP PERFORMED
2915 SOURCE 1:
2916     SEED1:      321827360    SEED2:          0
2917 Elapsed simulation  time in seconds:      0.13

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2918 ESTIMATION STEP OMITTED: YES
2919 Elapsed finaloutput time in seconds: 0.28
2920
2921 1
2922 PROBLEM NO.: 1 SUBPROBLEM NO.: 261
2923
2924 SIMULATION STEP PERFORMED
2925 SOURCE 1:
2926 SEED1: 1689451427 SEED2: 1050763703
2927 Elapsed simulation time in seconds: 0.14
2928 ESTIMATION STEP OMITTED: YES
2929 Elapsed finaloutput time in seconds: 0.28
2930
2931 1
2932 PROBLEM NO.: 1 SUBPROBLEM NO.: 262
2933
2934 SIMULATION STEP PERFORMED
2935 SOURCE 1:
2936 SEED1: 1484493687 SEED2: 0
2937 Elapsed simulation time in seconds: 0.13
2938 ESTIMATION STEP OMITTED: YES
2939 Elapsed finaloutput time in seconds: 0.29
2940
2941 1
2942 PROBLEM NO.: 1 SUBPROBLEM NO.: 263
2943
2944 SIMULATION STEP PERFORMED
2945 SOURCE 1:
2946 SEED1: 1231664398 SEED2: -1084756381
2947 Elapsed simulation time in seconds: 0.13
2948 ESTIMATION STEP OMITTED: YES
2949 Elapsed finaloutput time in seconds: 0.28
2950
2951 1
2952 PROBLEM NO.: 1 SUBPROBLEM NO.: 264
2953
2954 SIMULATION STEP PERFORMED
2955 SOURCE 1:
2956 SEED1: 2070380906 SEED2: 0
2957 Elapsed simulation time in seconds: 0.13
2958 ESTIMATION STEP OMITTED: YES
2959 Elapsed finaloutput time in seconds: 0.28
2960
2961 1
2962 PROBLEM NO.: 1 SUBPROBLEM NO.: 265
2963
2964 SIMULATION STEP PERFORMED
2965 SOURCE 1:
2966 SEED1: 2061317884 SEED2: 1068028510
2967 Elapsed simulation time in seconds: 0.13
2968 ESTIMATION STEP OMITTED: YES
2969 Elapsed finaloutput time in seconds: 0.28
2970
2971 1
2972 PROBLEM NO.: 1 SUBPROBLEM NO.: 266
2973
2974 SIMULATION STEP PERFORMED
2975 SOURCE 1:
2976 SEED1: 1795036094 SEED2: 0
2977 Elapsed simulation time in seconds: 0.12
2978 ESTIMATION STEP OMITTED: YES
2979 Elapsed finaloutput time in seconds: 0.28
2980
2981 1
2982 PROBLEM NO.: 1 SUBPROBLEM NO.: 267
2983
2984 SIMULATION STEP PERFORMED
2985 SOURCE 1:

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2986     SEED1:    1084361482    SEED2:   -1079370484
2987 Elapsed simulation  time in seconds:    0.13
2988 ESTIMATION STEP OMITTED:    YES
2989 Elapsed finaloutput  time in seconds:    0.28
2990
2991 1
2992 PROBLEM NO.:          1          SUBPROBLEM NO.:          268
2993
2994 SIMULATION STEP PERFORMED
2995 SOURCE 1:
2996     SEED1:    179650598    SEED2:           0
2997 Elapsed simulation  time in seconds:    0.12
2998 ESTIMATION STEP OMITTED:    YES
2999 Elapsed finaloutput  time in seconds:    0.28
3000
3001 1
3002 PROBLEM NO.:          1          SUBPROBLEM NO.:          269
3003
3004 SIMULATION STEP PERFORMED
3005 SOURCE 1:
3006     SEED1:    476485349    SEED2:   1049348654
3007 Elapsed simulation  time in seconds:    0.13
3008 ESTIMATION STEP OMITTED:    YES
3009 Elapsed finaloutput  time in seconds:    0.28
3010
3011 1
3012 PROBLEM NO.:          1          SUBPROBLEM NO.:          270
3013
3014 SIMULATION STEP PERFORMED
3015 SOURCE 1:
3016     SEED1:    1434067045    SEED2:           0
3017 Elapsed simulation  time in seconds:    0.12
3018 ESTIMATION STEP OMITTED:    YES
3019 Elapsed finaloutput  time in seconds:    0.28
3020
3021 1
3022 PROBLEM NO.:          1          SUBPROBLEM NO.:          271
3023
3024 SIMULATION STEP PERFORMED
3025 SOURCE 1:
3026     SEED1:    1245952633    SEED2:  -1081371320
3027 Elapsed simulation  time in seconds:    0.12
3028 ESTIMATION STEP OMITTED:    YES
3029 Elapsed finaloutput  time in seconds:    0.28
3030
3031 1
3032 PROBLEM NO.:          1          SUBPROBLEM NO.:          272
3033
3034 SIMULATION STEP PERFORMED
3035 SOURCE 1:
3036     SEED1:    2060770463    SEED2:           0
3037 Elapsed simulation  time in seconds:    0.13
3038 ESTIMATION STEP OMITTED:    YES
3039 Elapsed finaloutput  time in seconds:    0.28
3040
3041 1
3042 PROBLEM NO.:          1          SUBPROBLEM NO.:          273
3043
3044 SIMULATION STEP PERFORMED
3045 SOURCE 1:
3046     SEED1:    532434517    SEED2:   1019023313
3047 Elapsed simulation  time in seconds:    0.15
3048 ESTIMATION STEP OMITTED:    YES
3049 Elapsed finaloutput  time in seconds:    0.28
3050
3051 1
3052 PROBLEM NO.:          1          SUBPROBLEM NO.:          274
3053

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3054 SIMULATION STEP PERFORMED
3055 SOURCE 1:
3056 SEED1: 741870060 SEED2: 0
3057 Elapsed simulation time in seconds: 0.12
3058 ESTIMATION STEP OMITTED: YES
3059 Elapsed finaloutput time in seconds: 0.28
3060
3061 1
3062 PROBLEM NO.: 1 SUBPROBLEM NO.: 275
3063
3064 SIMULATION STEP PERFORMED
3065 SOURCE 1:
3066 SEED1: 1810286330 SEED2: 1037104986
3067 Elapsed simulation time in seconds: 0.13
3068 ESTIMATION STEP OMITTED: YES
3069 Elapsed finaloutput time in seconds: 0.28
3070
3071 1
3072 PROBLEM NO.: 1 SUBPROBLEM NO.: 276
3073
3074 SIMULATION STEP PERFORMED
3075 SOURCE 1:
3076 SEED1: 1109595062 SEED2: 0
3077 Elapsed simulation time in seconds: 0.13
3078 ESTIMATION STEP OMITTED: YES
3079 Elapsed finaloutput time in seconds: 0.28
3080
3081 1
3082 PROBLEM NO.: 1 SUBPROBLEM NO.: 277
3083
3084 SIMULATION STEP PERFORMED
3085 SOURCE 1:
3086 SEED1: 155563282 SEED2: 1058827436
3087 Elapsed simulation time in seconds: 0.13
3088 ESTIMATION STEP OMITTED: YES
3089 Elapsed finaloutput time in seconds: 0.28
3090
3091 1
3092 PROBLEM NO.: 1 SUBPROBLEM NO.: 278
3093
3094 SIMULATION STEP PERFORMED
3095 SOURCE 1:
3096 SEED1: 1248755097 SEED2: 0
3097 Elapsed simulation time in seconds: 0.13
3098 ESTIMATION STEP OMITTED: YES
3099 Elapsed finaloutput time in seconds: 0.28
3100
3101 1
3102 PROBLEM NO.: 1 SUBPROBLEM NO.: 279
3103
3104 SIMULATION STEP PERFORMED
3105 SOURCE 1:
3106 SEED1: 2058486499 SEED2: 1065210769
3107 Elapsed simulation time in seconds: 0.13
3108 ESTIMATION STEP OMITTED: YES
3109 Elapsed finaloutput time in seconds: 0.28
3110
3111 1
3112 PROBLEM NO.: 1 SUBPROBLEM NO.: 280
3113
3114 SIMULATION STEP PERFORMED
3115 SOURCE 1:
3116 SEED1: 648870275 SEED2: 0
3117 Elapsed simulation time in seconds: 0.15
3118 ESTIMATION STEP OMITTED: YES
3119 Elapsed finaloutput time in seconds: 0.28
3120
3121 1

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3122 PROBLEM NO.:          1          SUBPROBLEM NO.:          281
3123
3124 SIMULATION STEP PERFORMED
3125 SOURCE 1:
3126     SEED1:    1520485471    SEED2:    -1098680425
3127 Elapsed simulation  time in seconds:    0.13
3128 ESTIMATION STEP OMITTED:          YES
3129 Elapsed finaloutput  time in seconds:    0.28
3130
3131 1
3132 PROBLEM NO.:          1          SUBPROBLEM NO.:          282
3133
3134 SIMULATION STEP PERFORMED
3135 SOURCE 1:
3136     SEED1:      864203711    SEED2:           0
3137 Elapsed simulation  time in seconds:    0.13
3138 ESTIMATION STEP OMITTED:          YES
3139 Elapsed finaloutput  time in seconds:    0.28
3140
3141 1
3142 PROBLEM NO.:          1          SUBPROBLEM NO.:          283
3143
3144 SIMULATION STEP PERFORMED
3145 SOURCE 1:
3146     SEED1:    1902525628    SEED2:    1049408484
3147 Elapsed simulation  time in seconds:    0.14
3148 ESTIMATION STEP OMITTED:          YES
3149 Elapsed finaloutput  time in seconds:    0.28
3150
3151 1
3152 PROBLEM NO.:          1          SUBPROBLEM NO.:          284
3153
3154 SIMULATION STEP PERFORMED
3155 SOURCE 1:
3156     SEED1:    1280849355    SEED2:           0
3157 Elapsed simulation  time in seconds:    0.12
3158 ESTIMATION STEP OMITTED:          YES
3159 Elapsed finaloutput  time in seconds:    0.28
3160
3161 1
3162 PROBLEM NO.:          1          SUBPROBLEM NO.:          285
3163
3164 SIMULATION STEP PERFORMED
3165 SOURCE 1:
3166     SEED1:    1819019082    SEED2:    1049269372
3167 Elapsed simulation  time in seconds:    0.13
3168 ESTIMATION STEP OMITTED:          YES
3169 Elapsed finaloutput  time in seconds:    0.28
3170
3171 1
3172 PROBLEM NO.:          1          SUBPROBLEM NO.:          286
3173
3174 SIMULATION STEP PERFORMED
3175 SOURCE 1:
3176     SEED1:    1414350277    SEED2:           0
3177 Elapsed simulation  time in seconds:    0.13
3178 ESTIMATION STEP OMITTED:          YES
3179 Elapsed finaloutput  time in seconds:    0.28
3180
3181 1
3182 PROBLEM NO.:          1          SUBPROBLEM NO.:          287
3183
3184 SIMULATION STEP PERFORMED
3185 SOURCE 1:
3186     SEED1:      423638997    SEED2:    1054887686
3187 Elapsed simulation  time in seconds:    0.12
3188 ESTIMATION STEP OMITTED:          YES
3189 Elapsed finaloutput  time in seconds:    0.28

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3190
3191 1
3192 PROBLEM NO.:          1          SUBPROBLEM NO.:          288
3193
3194 SIMULATION STEP PERFORMED
3195 SOURCE 1:
3196     SEED1:    1177634329    SEED2:          0
3197 Elapsed simulation time in seconds:    0.13
3198 ESTIMATION STEP OMITTED:          YES
3199 Elapsed finaloutput time in seconds:    0.28
3200
3201 1
3202 PROBLEM NO.:          1          SUBPROBLEM NO.:          289
3203
3204 SIMULATION STEP PERFORMED
3205 SOURCE 1:
3206     SEED1:    1435796927    SEED2:   -1081206394
3207 Elapsed simulation time in seconds:    0.12
3208 ESTIMATION STEP OMITTED:          YES
3209 Elapsed finaloutput time in seconds:    0.28
3210
3211 1
3212 PROBLEM NO.:          1          SUBPROBLEM NO.:          290
3213
3214 SIMULATION STEP PERFORMED
3215 SOURCE 1:
3216     SEED1:    1409136478    SEED2:          0
3217 Elapsed simulation time in seconds:    0.13
3218 ESTIMATION STEP OMITTED:          YES
3219 Elapsed finaloutput time in seconds:    0.28
3220
3221 1
3222 PROBLEM NO.:          1          SUBPROBLEM NO.:          291
3223
3224 SIMULATION STEP PERFORMED
3225 SOURCE 1:
3226     SEED1:    1474653194    SEED2:   -1095920338
3227 Elapsed simulation time in seconds:    0.12
3228 ESTIMATION STEP OMITTED:          YES
3229 Elapsed finaloutput time in seconds:    0.28
3230
3231 1
3232 PROBLEM NO.:          1          SUBPROBLEM NO.:          292
3233
3234 SIMULATION STEP PERFORMED
3235 SOURCE 1:
3236     SEED1:    1305655710    SEED2:          0
3237 Elapsed simulation time in seconds:    0.12
3238 ESTIMATION STEP OMITTED:          YES
3239 Elapsed finaloutput time in seconds:    0.28
3240
3241 1
3242 PROBLEM NO.:          1          SUBPROBLEM NO.:          293
3243
3244 SIMULATION STEP PERFORMED
3245 SOURCE 1:
3246     SEED1:    979803943    SEED2:   -1072447264
3247 Elapsed simulation time in seconds:    0.13
3248 ESTIMATION STEP OMITTED:          YES
3249 Elapsed finaloutput time in seconds:    0.28
3250
3251 1
3252 PROBLEM NO.:          1          SUBPROBLEM NO.:          294
3253
3254 SIMULATION STEP PERFORMED
3255 SOURCE 1:
3256     SEED1:    1070473587    SEED2:          0
3257 Elapsed simulation time in seconds:    0.13

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3258 ESTIMATION STEP OMITTED: YES
3259 Elapsed finaloutput time in seconds: 0.28
3260
3261 1
3262 PROBLEM NO.: 1 SUBPROBLEM NO.: 295
3263
3264 SIMULATION STEP PERFORMED
3265 SOURCE 1:
3266 SEED1: 221128406 SEED2: 1065569616
3267 Elapsed simulation time in seconds: 0.14
3268 ESTIMATION STEP OMITTED: YES
3269 Elapsed finaloutput time in seconds: 0.28
3270
3271 1
3272 PROBLEM NO.: 1 SUBPROBLEM NO.: 296
3273
3274 SIMULATION STEP PERFORMED
3275 SOURCE 1:
3276 SEED1: 1832153475 SEED2: 0
3277 Elapsed simulation time in seconds: 0.16
3278 ESTIMATION STEP OMITTED: YES
3279 Elapsed finaloutput time in seconds: 0.28
3280
3281 1
3282 PROBLEM NO.: 1 SUBPROBLEM NO.: 297
3283
3284 SIMULATION STEP PERFORMED
3285 SOURCE 1:
3286 SEED1: 11168780 SEED2: 1052762681
3287 Elapsed simulation time in seconds: 0.12
3288 ESTIMATION STEP OMITTED: YES
3289 Elapsed finaloutput time in seconds: 0.28
3290
3291 1
3292 PROBLEM NO.: 1 SUBPROBLEM NO.: 298
3293
3294 SIMULATION STEP PERFORMED
3295 SOURCE 1:
3296 SEED1: 168432565 SEED2: 0
3297 Elapsed simulation time in seconds: 0.12
3298 ESTIMATION STEP OMITTED: YES
3299 Elapsed finaloutput time in seconds: 0.28
3300
3301 1
3302 PROBLEM NO.: 1 SUBPROBLEM NO.: 299
3303
3304 SIMULATION STEP PERFORMED
3305 SOURCE 1:
3306 SEED1: 1300432468 SEED2: -1085114643
3307 Elapsed simulation time in seconds: 0.13
3308 ESTIMATION STEP OMITTED: YES
3309 Elapsed finaloutput time in seconds: 0.28
3310
3311 1
3312 PROBLEM NO.: 1 SUBPROBLEM NO.: 300
3313
3314 SIMULATION STEP PERFORMED
3315 SOURCE 1:
3316 SEED1: 221036576 SEED2: 0
3317 Elapsed simulation time in seconds: 0.20
3318 ESTIMATION STEP OMITTED: YES
3319 Elapsed finaloutput time in seconds: 0.28
3320
3321 1
3322 PROBLEM NO.: 1 SUBPROBLEM NO.: 301
3323
3324 SIMULATION STEP PERFORMED
3325 SOURCE 1:

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3326     SEED1:      516457664     SEED2:      1039522572
3327 Elapsed simulation  time in seconds:      0.12
3328 ESTIMATION STEP OMITTED:      YES
3329 Elapsed finaloutput  time in seconds:      0.28
3330
3331 1
3332 PROBLEM NO.:      1      SUBPROBLEM NO.:      302
3333
3334 SIMULATION STEP PERFORMED
3335 SOURCE 1:
3336     SEED1:      1192123722     SEED2:      0
3337 Elapsed simulation  time in seconds:      0.13
3338 ESTIMATION STEP OMITTED:      YES
3339 Elapsed finaloutput  time in seconds:      0.28
3340
3341 1
3342 PROBLEM NO.:      1      SUBPROBLEM NO.:      303
3343
3344 SIMULATION STEP PERFORMED
3345 SOURCE 1:
3346     SEED1:      2076713372     SEED2:      1069464523
3347 Elapsed simulation  time in seconds:      0.13
3348 ESTIMATION STEP OMITTED:      YES
3349 Elapsed finaloutput  time in seconds:      0.28
3350
3351 1
3352 PROBLEM NO.:      1      SUBPROBLEM NO.:      304
3353
3354 SIMULATION STEP PERFORMED
3355 SOURCE 1:
3356     SEED1:      1159112879     SEED2:      0
3357 Elapsed simulation  time in seconds:      0.13
3358 ESTIMATION STEP OMITTED:      YES
3359 Elapsed finaloutput  time in seconds:      0.28
3360
3361 1
3362 PROBLEM NO.:      1      SUBPROBLEM NO.:      305
3363
3364 SIMULATION STEP PERFORMED
3365 SOURCE 1:
3366     SEED1:      633824419     SEED2:      -1093533916
3367 Elapsed simulation  time in seconds:      0.13
3368 ESTIMATION STEP OMITTED:      YES
3369 Elapsed finaloutput  time in seconds:      0.28
3370
3371 1
3372 PROBLEM NO.:      1      SUBPROBLEM NO.:      306
3373
3374 SIMULATION STEP PERFORMED
3375 SOURCE 1:
3376     SEED1:      144180658     SEED2:      0
3377 Elapsed simulation  time in seconds:      0.20
3378 ESTIMATION STEP OMITTED:      YES
3379 Elapsed finaloutput  time in seconds:      0.28
3380
3381 1
3382 PROBLEM NO.:      1      SUBPROBLEM NO.:      307
3383
3384 SIMULATION STEP PERFORMED
3385 SOURCE 1:
3386     SEED1:      2062153546     SEED2:      1067843825
3387 Elapsed simulation  time in seconds:      0.18
3388 ESTIMATION STEP OMITTED:      YES
3389 Elapsed finaloutput  time in seconds:      0.29
3390
3391 1
3392 PROBLEM NO.:      1      SUBPROBLEM NO.:      308
3393

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3394 SIMULATION STEP PERFORMED
3395 SOURCE 1:
3396 SEED1: 180531332 SEED2: 0
3397 Elapsed simulation time in seconds: 0.13
3398 ESTIMATION STEP OMITTED: YES
3399 Elapsed finaloutput time in seconds: 0.29
3400
3401 1
3402 PROBLEM NO.: 1 SUBPROBLEM NO.: 309
3403
3404 SIMULATION STEP PERFORMED
3405 SOURCE 1:
3406 SEED1: 281787132 SEED2: 1053838237
3407 Elapsed simulation time in seconds: 0.13
3408 ESTIMATION STEP OMITTED: YES
3409 Elapsed finaloutput time in seconds: 0.28
3410
3411 1
3412 PROBLEM NO.: 1 SUBPROBLEM NO.: 310
3413
3414 SIMULATION STEP PERFORMED
3415 SOURCE 1:
3416 SEED1: 1046251472 SEED2: 0
3417 Elapsed simulation time in seconds: 0.14
3418 ESTIMATION STEP OMITTED: YES
3419 Elapsed finaloutput time in seconds: 0.28
3420
3421 1
3422 PROBLEM NO.: 1 SUBPROBLEM NO.: 311
3423
3424 SIMULATION STEP PERFORMED
3425 SOURCE 1:
3426 SEED1: 1265239766 SEED2: -1080067787
3427 Elapsed simulation time in seconds: 0.13
3428 ESTIMATION STEP OMITTED: YES
3429 Elapsed finaloutput time in seconds: 0.36
3430
3431 1
3432 PROBLEM NO.: 1 SUBPROBLEM NO.: 312
3433
3434 SIMULATION STEP PERFORMED
3435 SOURCE 1:
3436 SEED1: 676833051 SEED2: 0
3437 Elapsed simulation time in seconds: 0.12
3438 ESTIMATION STEP OMITTED: YES
3439 Elapsed finaloutput time in seconds: 0.29
3440
3441 1
3442 PROBLEM NO.: 1 SUBPROBLEM NO.: 313
3443
3444 SIMULATION STEP PERFORMED
3445 SOURCE 1:
3446 SEED1: 365963215 SEED2: 1049729571
3447 Elapsed simulation time in seconds: 0.12
3448 ESTIMATION STEP OMITTED: YES
3449 Elapsed finaloutput time in seconds: 0.28
3450
3451 1
3452 PROBLEM NO.: 1 SUBPROBLEM NO.: 314
3453
3454 SIMULATION STEP PERFORMED
3455 SOURCE 1:
3456 SEED1: 1933068311 SEED2: 0
3457 Elapsed simulation time in seconds: 0.13
3458 ESTIMATION STEP OMITTED: YES
3459 Elapsed finaloutput time in seconds: 0.28
3460
3461 1

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3462 PROBLEM NO.:          1          SUBPROBLEM NO.:          315
3463
3464 SIMULATION STEP PERFORMED
3465 SOURCE 1:
3466     SEED1:    1926945757    SEED2:    1068906714
3467 Elapsed simulation  time in seconds:    0.13
3468 ESTIMATION STEP OMITTED:          YES
3469 Elapsed finaloutput  time in seconds:    0.28
3470
3471 1
3472 PROBLEM NO.:          1          SUBPROBLEM NO.:          316
3473
3474 SIMULATION STEP PERFORMED
3475 SOURCE 1:
3476     SEED1:    869175299    SEED2:          0
3477 Elapsed simulation  time in seconds:    0.13
3478 ESTIMATION STEP OMITTED:          YES
3479 Elapsed finaloutput  time in seconds:    0.28
3480
3481 1
3482 PROBLEM NO.:          1          SUBPROBLEM NO.:          317
3483
3484 SIMULATION STEP PERFORMED
3485 SOURCE 1:
3486     SEED1:    2064205659    SEED2:    1056359715
3487 Elapsed simulation  time in seconds:    0.12
3488 ESTIMATION STEP OMITTED:          YES
3489 Elapsed finaloutput  time in seconds:    0.28
3490
3491 1
3492 PROBLEM NO.:          1          SUBPROBLEM NO.:          318
3493
3494 SIMULATION STEP PERFORMED
3495 SOURCE 1:
3496     SEED1:    2069580719    SEED2:          0
3497 Elapsed simulation  time in seconds:    0.15
3498 ESTIMATION STEP OMITTED:          YES
3499 Elapsed finaloutput  time in seconds:    0.28
3500
3501 1
3502 PROBLEM NO.:          1          SUBPROBLEM NO.:          319
3503
3504 SIMULATION STEP PERFORMED
3505 SOURCE 1:
3506     SEED1:    1114068844    SEED2:   -1081146963
3507 Elapsed simulation  time in seconds:    0.13
3508 ESTIMATION STEP OMITTED:          YES
3509 Elapsed finaloutput  time in seconds:    0.28
3510
3511 1
3512 PROBLEM NO.:          1          SUBPROBLEM NO.:          320
3513
3514 SIMULATION STEP PERFORMED
3515 SOURCE 1:
3516     SEED1:    967679258    SEED2:          0
3517 Elapsed simulation  time in seconds:    0.14
3518 ESTIMATION STEP OMITTED:          YES
3519 Elapsed finaloutput  time in seconds:    0.28
3520
3521 1
3522 PROBLEM NO.:          1          SUBPROBLEM NO.:          321
3523
3524 SIMULATION STEP PERFORMED
3525 SOURCE 1:
3526     SEED1:    432076140    SEED2:    1053651937
3527 Elapsed simulation  time in seconds:    0.13
3528 ESTIMATION STEP OMITTED:          YES
3529 Elapsed finaloutput  time in seconds:    0.28

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3530
3531 1
3532 PROBLEM NO.:          1          SUBPROBLEM NO.:          322
3533
3534 SIMULATION STEP PERFORMED
3535 SOURCE 1:
3536     SEED1:    1824138167    SEED2:          0
3537 Elapsed simulation time in seconds:    0.14
3538 ESTIMATION STEP OMITTED:          YES
3539 Elapsed finaloutput time in seconds:    0.28
3540
3541 1
3542 PROBLEM NO.:          1          SUBPROBLEM NO.:          323
3543
3544 SIMULATION STEP PERFORMED
3545 SOURCE 1:
3546     SEED1:    1325467899    SEED2:   -1089068162
3547 Elapsed simulation time in seconds:    0.14
3548 ESTIMATION STEP OMITTED:          YES
3549 Elapsed finaloutput time in seconds:    0.28
3550
3551 1
3552 PROBLEM NO.:          1          SUBPROBLEM NO.:          324
3553
3554 SIMULATION STEP PERFORMED
3555 SOURCE 1:
3556     SEED1:    946705200    SEED2:          0
3557 Elapsed simulation time in seconds:    0.15
3558 ESTIMATION STEP OMITTED:          YES
3559 Elapsed finaloutput time in seconds:    0.28
3560
3561 1
3562 PROBLEM NO.:          1          SUBPROBLEM NO.:          325
3563
3564 SIMULATION STEP PERFORMED
3565 SOURCE 1:
3566     SEED1:    1213498569    SEED2:   -1078611918
3567 Elapsed simulation time in seconds:    0.15
3568 ESTIMATION STEP OMITTED:          YES
3569 Elapsed finaloutput time in seconds:    0.29
3570
3571 1
3572 PROBLEM NO.:          1          SUBPROBLEM NO.:          326
3573
3574 SIMULATION STEP PERFORMED
3575 SOURCE 1:
3576     SEED1:    439038587    SEED2:          0
3577 Elapsed simulation time in seconds:    0.14
3578 ESTIMATION STEP OMITTED:          YES
3579 Elapsed finaloutput time in seconds:    0.28
3580
3581 1
3582 PROBLEM NO.:          1          SUBPROBLEM NO.:          327
3583
3584 SIMULATION STEP PERFORMED
3585 SOURCE 1:
3586     SEED1:    1114663947    SEED2:   -1097158274
3587 Elapsed simulation time in seconds:    0.18
3588 ESTIMATION STEP OMITTED:          YES
3589 Elapsed finaloutput time in seconds:    0.28
3590
3591 1
3592 PROBLEM NO.:          1          SUBPROBLEM NO.:          328
3593
3594 SIMULATION STEP PERFORMED
3595 SOURCE 1:
3596     SEED1:    383698028    SEED2:          0
3597 Elapsed simulation time in seconds:    0.13

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3598 ESTIMATION STEP OMITTED: YES
3599 Elapsed finaloutput time in seconds: 0.28
3600
3601 1
3602 PROBLEM NO.: 1 SUBPROBLEM NO.: 329
3603
3604 SIMULATION STEP PERFORMED
3605 SOURCE 1:
3606 SEED1: 912318856 SEED2: -1079722490
3607 Elapsed simulation time in seconds: 0.13
3608 ESTIMATION STEP OMITTED: YES
3609 Elapsed finaloutput time in seconds: 0.28
3610
3611 1
3612 PROBLEM NO.: 1 SUBPROBLEM NO.: 330
3613
3614 SIMULATION STEP PERFORMED
3615 SOURCE 1:
3616 SEED1: 1527077947 SEED2: 0
3617 Elapsed simulation time in seconds: 0.14
3618 ESTIMATION STEP OMITTED: YES
3619 Elapsed finaloutput time in seconds: 0.28
3620
3621 1
3622 PROBLEM NO.: 1 SUBPROBLEM NO.: 331
3623
3624 SIMULATION STEP PERFORMED
3625 SOURCE 1:
3626 SEED1: 344939912 SEED2: 1061748265
3627 Elapsed simulation time in seconds: 0.12
3628 ESTIMATION STEP OMITTED: YES
3629 Elapsed finaloutput time in seconds: 0.28
3630
3631 1
3632 PROBLEM NO.: 1 SUBPROBLEM NO.: 332
3633
3634 SIMULATION STEP PERFORMED
3635 SOURCE 1:
3636 SEED1: 174310945 SEED2: 0
3637 Elapsed simulation time in seconds: 0.17
3638 ESTIMATION STEP OMITTED: YES
3639 Elapsed finaloutput time in seconds: 0.28
3640
3641 1
3642 PROBLEM NO.: 1 SUBPROBLEM NO.: 333
3643
3644 SIMULATION STEP PERFORMED
3645 SOURCE 1:
3646 SEED1: 449030745 SEED2: 1048924624
3647 Elapsed simulation time in seconds: 0.13
3648 ESTIMATION STEP OMITTED: YES
3649 Elapsed finaloutput time in seconds: 0.28
3650
3651 1
3652 PROBLEM NO.: 1 SUBPROBLEM NO.: 334
3653
3654 SIMULATION STEP PERFORMED
3655 SOURCE 1:
3656 SEED1: 408631785 SEED2: 0
3657 Elapsed simulation time in seconds: 0.14
3658 ESTIMATION STEP OMITTED: YES
3659 Elapsed finaloutput time in seconds: 0.28
3660
3661 1
3662 PROBLEM NO.: 1 SUBPROBLEM NO.: 335
3663
3664 SIMULATION STEP PERFORMED
3665 SOURCE 1:

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3666     SEED1:    1804608747    SEED2:    1060106281
3667 Elapsed simulation  time in seconds:    0.14
3668 ESTIMATION STEP OMITTED:    YES
3669 Elapsed finaloutput  time in seconds:    0.28
3670
3671 1
3672 PROBLEM NO.:          1          SUBPROBLEM NO.:          336
3673
3674 SIMULATION STEP PERFORMED
3675 SOURCE 1:
3676     SEED1:    750581528    SEED2:          0
3677 Elapsed simulation  time in seconds:    0.13
3678 ESTIMATION STEP OMITTED:    YES
3679 Elapsed finaloutput  time in seconds:    0.28
3680
3681 1
3682 PROBLEM NO.:          1          SUBPROBLEM NO.:          337
3683
3684 SIMULATION STEP PERFORMED
3685 SOURCE 1:
3686     SEED1:    520769371    SEED2:    1040579321
3687 Elapsed simulation  time in seconds:    0.13
3688 ESTIMATION STEP OMITTED:    YES
3689 Elapsed finaloutput  time in seconds:    0.28
3690
3691 1
3692 PROBLEM NO.:          1          SUBPROBLEM NO.:          338
3693
3694 SIMULATION STEP PERFORMED
3695 SOURCE 1:
3696     SEED1:    883550848    SEED2:          0
3697 Elapsed simulation  time in seconds:    0.13
3698 ESTIMATION STEP OMITTED:    YES
3699 Elapsed finaloutput  time in seconds:    0.28
3700
3701 1
3702 PROBLEM NO.:          1          SUBPROBLEM NO.:          339
3703
3704 SIMULATION STEP PERFORMED
3705 SOURCE 1:
3706     SEED1:    825044313    SEED2:   -1088300442
3707 Elapsed simulation  time in seconds:    0.15
3708 ESTIMATION STEP OMITTED:    YES
3709 Elapsed finaloutput  time in seconds:    0.29
3710
3711 1
3712 PROBLEM NO.:          1          SUBPROBLEM NO.:          340
3713
3714 SIMULATION STEP PERFORMED
3715 SOURCE 1:
3716     SEED1:    1234492624    SEED2:          0
3717 Elapsed simulation  time in seconds:    0.16
3718 ESTIMATION STEP OMITTED:    YES
3719 Elapsed finaloutput  time in seconds:    0.28
3720
3721 1
3722 PROBLEM NO.:          1          SUBPROBLEM NO.:          341
3723
3724 SIMULATION STEP PERFORMED
3725 SOURCE 1:
3726     SEED1:    658654336    SEED2:   -1106429124
3727 Elapsed simulation  time in seconds:    0.25
3728 ESTIMATION STEP OMITTED:    YES
3729 Elapsed finaloutput  time in seconds:    0.28
3730
3731 1
3732 PROBLEM NO.:          1          SUBPROBLEM NO.:          342
3733

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3734 SIMULATION STEP PERFORMED
3735 SOURCE 1:
3736 SEED1: 42543419 SEED2: 0
3737 Elapsed simulation time in seconds: 0.14
3738 ESTIMATION STEP OMITTED: YES
3739 Elapsed finaloutput time in seconds: 0.28
3740
3741 1
3742 PROBLEM NO.: 1 SUBPROBLEM NO.: 343
3743
3744 SIMULATION STEP PERFORMED
3745 SOURCE 1:
3746 SEED1: 1898219924 SEED2: 1074242589
3747 Elapsed simulation time in seconds: 0.14
3748 ESTIMATION STEP OMITTED: YES
3749 Elapsed finaloutput time in seconds: 0.28
3750
3751 1
3752 PROBLEM NO.: 1 SUBPROBLEM NO.: 344
3753
3754 SIMULATION STEP PERFORMED
3755 SOURCE 1:
3756 SEED1: 892489748 SEED2: 0
3757 Elapsed simulation time in seconds: 0.13
3758 ESTIMATION STEP OMITTED: YES
3759 Elapsed finaloutput time in seconds: 0.28
3760
3761 1
3762 PROBLEM NO.: 1 SUBPROBLEM NO.: 345
3763
3764 SIMULATION STEP PERFORMED
3765 SOURCE 1:
3766 SEED1: 1789325836 SEED2: 1050612083
3767 Elapsed simulation time in seconds: 0.13
3768 ESTIMATION STEP OMITTED: YES
3769 Elapsed finaloutput time in seconds: 0.28
3770
3771 1
3772 PROBLEM NO.: 1 SUBPROBLEM NO.: 346
3773
3774 SIMULATION STEP PERFORMED
3775 SOURCE 1:
3776 SEED1: 1503084253 SEED2: 0
3777 Elapsed simulation time in seconds: 0.16
3778 ESTIMATION STEP OMITTED: YES
3779 Elapsed finaloutput time in seconds: 0.28
3780
3781 1
3782 PROBLEM NO.: 1 SUBPROBLEM NO.: 347
3783
3784 SIMULATION STEP PERFORMED
3785 SOURCE 1:
3786 SEED1: 1375712786 SEED2: -1087073313
3787 Elapsed simulation time in seconds: 0.14
3788 ESTIMATION STEP OMITTED: YES
3789 Elapsed finaloutput time in seconds: 0.28
3790
3791 1
3792 PROBLEM NO.: 1 SUBPROBLEM NO.: 348
3793
3794 SIMULATION STEP PERFORMED
3795 SOURCE 1:
3796 SEED1: 51260206 SEED2: 0
3797 Elapsed simulation time in seconds: 0.17
3798 ESTIMATION STEP OMITTED: YES
3799 Elapsed finaloutput time in seconds: 0.28
3800
3801 1

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3802  PROBLEM NO.:          1          SUBPROBLEM NO.:          349
3803
3804  SIMULATION STEP PERFORMED
3805  SOURCE 1:
3806      SEED1:    1741367888    SEED2:    1062153977
3807  Elapsed simulation  time  in seconds:    0.15
3808  ESTIMATION STEP OMITTED:          YES
3809  Elapsed finaloutput  time  in seconds:    0.28
3810
3811  1
3812  PROBLEM NO.:          1          SUBPROBLEM NO.:          350
3813
3814  SIMULATION STEP PERFORMED
3815  SOURCE 1:
3816      SEED1:    835029874    SEED2:          0
3817  Elapsed simulation  time  in seconds:    0.15
3818  ESTIMATION STEP OMITTED:          YES
3819  Elapsed finaloutput  time  in seconds:    0.28
3820
3821  1
3822  PROBLEM NO.:          1          SUBPROBLEM NO.:          351
3823
3824  SIMULATION STEP PERFORMED
3825  SOURCE 1:
3826      SEED1:    1501912151    SEED2:   -1097504313
3827  Elapsed simulation  time  in seconds:    0.14
3828  ESTIMATION STEP OMITTED:          YES
3829  Elapsed finaloutput  time  in seconds:    0.28
3830
3831  1
3832  PROBLEM NO.:          1          SUBPROBLEM NO.:          352
3833
3834  SIMULATION STEP PERFORMED
3835  SOURCE 1:
3836      SEED1:    1172815171    SEED2:          0
3837  Elapsed simulation  time  in seconds:    0.14
3838  ESTIMATION STEP OMITTED:          YES
3839  Elapsed finaloutput  time  in seconds:    0.28
3840
3841  1
3842  PROBLEM NO.:          1          SUBPROBLEM NO.:          353
3843
3844  SIMULATION STEP PERFORMED
3845  SOURCE 1:
3846      SEED1:    1428104998    SEED2:   -1086597518
3847  Elapsed simulation  time  in seconds:    0.12
3848  ESTIMATION STEP OMITTED:          YES
3849  Elapsed finaloutput  time  in seconds:    0.28
3850
3851  1
3852  PROBLEM NO.:          1          SUBPROBLEM NO.:          354
3853
3854  SIMULATION STEP PERFORMED
3855  SOURCE 1:
3856      SEED1:    92009839    SEED2:          0
3857  Elapsed simulation  time  in seconds:    0.14
3858  ESTIMATION STEP OMITTED:          YES
3859  Elapsed finaloutput  time  in seconds:    0.28
3860
3861  1
3862  PROBLEM NO.:          1          SUBPROBLEM NO.:          355
3863
3864  SIMULATION STEP PERFORMED
3865  SOURCE 1:
3866      SEED1:    358701755    SEED2:    1050050408
3867  Elapsed simulation  time  in seconds:    0.16
3868  ESTIMATION STEP OMITTED:          YES
3869  Elapsed finaloutput  time  in seconds:    0.28

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3870
3871 1
3872 PROBLEM NO.:          1          SUBPROBLEM NO.:          356
3873
3874 SIMULATION STEP PERFORMED
3875 SOURCE 1:
3876     SEED1:      928948582    SEED2:          0
3877 Elapsed simulation  time in seconds:      0.14
3878 ESTIMATION STEP OMITTED:          YES
3879 Elapsed finaloutput  time in seconds:      0.28
3880
3881 1
3882 PROBLEM NO.:          1          SUBPROBLEM NO.:          357
3883
3884 SIMULATION STEP PERFORMED
3885 SOURCE 1:
3886     SEED1:      789674660    SEED2:    -1102113907
3887 Elapsed simulation  time in seconds:      0.14
3888 ESTIMATION STEP OMITTED:          YES
3889 Elapsed finaloutput  time in seconds:      0.28
3890
3891 1
3892 PROBLEM NO.:          1          SUBPROBLEM NO.:          358
3893
3894 SIMULATION STEP PERFORMED
3895 SOURCE 1:
3896     SEED1:     1075592971    SEED2:          0
3897 Elapsed simulation  time in seconds:      0.14
3898 ESTIMATION STEP OMITTED:          YES
3899 Elapsed finaloutput  time in seconds:      0.28
3900
3901 1
3902 PROBLEM NO.:          1          SUBPROBLEM NO.:          359
3903
3904 SIMULATION STEP PERFORMED
3905 SOURCE 1:
3906     SEED1:     1253775621    SEED2:    -1081321251
3907 Elapsed simulation  time in seconds:      0.12
3908 ESTIMATION STEP OMITTED:          YES
3909 Elapsed finaloutput  time in seconds:      0.28
3910
3911 1
3912 PROBLEM NO.:          1          SUBPROBLEM NO.:          360
3913
3914 SIMULATION STEP PERFORMED
3915 SOURCE 1:
3916     SEED1:      719866856    SEED2:          0
3917 Elapsed simulation  time in seconds:      0.12
3918 ESTIMATION STEP OMITTED:          YES
3919 Elapsed finaloutput  time in seconds:      0.28
3920
3921 1
3922 PROBLEM NO.:          1          SUBPROBLEM NO.:          361
3923
3924 SIMULATION STEP PERFORMED
3925 SOURCE 1:
3926     SEED1:      706687123    SEED2:    -1092960919
3927 Elapsed simulation  time in seconds:      0.12
3928 ESTIMATION STEP OMITTED:          YES
3929 Elapsed finaloutput  time in seconds:      0.28
3930
3931 1
3932 PROBLEM NO.:          1          SUBPROBLEM NO.:          362
3933
3934 SIMULATION STEP PERFORMED
3935 SOURCE 1:
3936     SEED1:      857685696    SEED2:          0
3937 Elapsed simulation  time in seconds:      0.13

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3938 ESTIMATION STEP OMITTED: YES
3939 Elapsed finaloutput time in seconds: 0.28
3940
3941 1
3942 PROBLEM NO.: 1 SUBPROBLEM NO.: 363
3943
3944 SIMULATION STEP PERFORMED
3945 SOURCE 1:
3946 SEED1: 1366708172 SEED2: -1097249729
3947 Elapsed simulation time in seconds: 0.12
3948 ESTIMATION STEP OMITTED: YES
3949 Elapsed finaloutput time in seconds: 0.28
3950
3951 1
3952 PROBLEM NO.: 1 SUBPROBLEM NO.: 364
3953
3954 SIMULATION STEP PERFORMED
3955 SOURCE 1:
3956 SEED1: 1992219766 SEED2: 0
3957 Elapsed simulation time in seconds: 0.12
3958 ESTIMATION STEP OMITTED: YES
3959 Elapsed finaloutput time in seconds: 0.28
3960
3961 1
3962 PROBLEM NO.: 1 SUBPROBLEM NO.: 365
3963
3964 SIMULATION STEP PERFORMED
3965 SOURCE 1:
3966 SEED1: 1670705156 SEED2: 1033048018
3967 Elapsed simulation time in seconds: 0.14
3968 ESTIMATION STEP OMITTED: YES
3969 Elapsed finaloutput time in seconds: 0.28
3970
3971 1
3972 PROBLEM NO.: 1 SUBPROBLEM NO.: 366
3973
3974 SIMULATION STEP PERFORMED
3975 SOURCE 1:
3976 SEED1: 943685477 SEED2: 0
3977 Elapsed simulation time in seconds: 0.14
3978 ESTIMATION STEP OMITTED: YES
3979 Elapsed finaloutput time in seconds: 0.28
3980
3981 1
3982 PROBLEM NO.: 1 SUBPROBLEM NO.: 367
3983
3984 SIMULATION STEP PERFORMED
3985 SOURCE 1:
3986 SEED1: 1588457176 SEED2: -1119331375
3987 Elapsed simulation time in seconds: 0.15
3988 ESTIMATION STEP OMITTED: YES
3989 Elapsed finaloutput time in seconds: 0.28
3990
3991 1
3992 PROBLEM NO.: 1 SUBPROBLEM NO.: 368
3993
3994 SIMULATION STEP PERFORMED
3995 SOURCE 1:
3996 SEED1: 1781903799 SEED2: 0
3997 Elapsed simulation time in seconds: 0.12
3998 ESTIMATION STEP OMITTED: YES
3999 Elapsed finaloutput time in seconds: 0.28
4000
4001 1
4002 PROBLEM NO.: 1 SUBPROBLEM NO.: 369
4003
4004 SIMULATION STEP PERFORMED
4005 SOURCE 1:

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4006     SEED1:      941389527     SEED2:    -1073479663
4007 Elapsed simulation  time in seconds:      0.16
4008 ESTIMATION STEP OMITTED:      YES
4009 Elapsed finaloutput  time in seconds:      0.28
4010
4011 1
4012 PROBLEM NO.:      1      SUBPROBLEM NO.:      370
4013
4014 SIMULATION STEP PERFORMED
4015 SOURCE 1:
4016     SEED1:      954346896     SEED2:      0
4017 Elapsed simulation  time in seconds:      0.15
4018 ESTIMATION STEP OMITTED:      YES
4019 Elapsed finaloutput  time in seconds:      0.28
4020
4021 1
4022 PROBLEM NO.:      1      SUBPROBLEM NO.:      371
4023
4024 SIMULATION STEP PERFORMED
4025 SOURCE 1:
4026     SEED1:      1451474772     SEED2:    -1085420014
4027 Elapsed simulation  time in seconds:      0.13
4028 ESTIMATION STEP OMITTED:      YES
4029 Elapsed finaloutput  time in seconds:      0.28
4030
4031 1
4032 PROBLEM NO.:      1      SUBPROBLEM NO.:      372
4033
4034 SIMULATION STEP PERFORMED
4035 SOURCE 1:
4036     SEED1:      1170449029     SEED2:      0
4037 Elapsed simulation  time in seconds:      0.13
4038 ESTIMATION STEP OMITTED:      YES
4039 Elapsed finaloutput  time in seconds:      0.28
4040
4041 1
4042 PROBLEM NO.:      1      SUBPROBLEM NO.:      373
4043
4044 SIMULATION STEP PERFORMED
4045 SOURCE 1:
4046     SEED1:      358726569     SEED2:    1059368217
4047 Elapsed simulation  time in seconds:      0.14
4048 ESTIMATION STEP OMITTED:      YES
4049 Elapsed finaloutput  time in seconds:      0.28
4050
4051 1
4052 PROBLEM NO.:      1      SUBPROBLEM NO.:      374
4053
4054 SIMULATION STEP PERFORMED
4055 SOURCE 1:
4056     SEED1:      441356214     SEED2:      0
4057 Elapsed simulation  time in seconds:      0.12
4058 ESTIMATION STEP OMITTED:      YES
4059 Elapsed finaloutput  time in seconds:      0.28
4060
4061 1
4062 PROBLEM NO.:      1      SUBPROBLEM NO.:      375
4063
4064 SIMULATION STEP PERFORMED
4065 SOURCE 1:
4066     SEED1:      1756619011     SEED2:    1052923629
4067 Elapsed simulation  time in seconds:      0.13
4068 ESTIMATION STEP OMITTED:      YES
4069 Elapsed finaloutput  time in seconds:      0.28
4070
4071 1
4072 PROBLEM NO.:      1      SUBPROBLEM NO.:      376
4073

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4074 SIMULATION STEP PERFORMED
4075 SOURCE 1:
4076 SEED1: 1213435730 SEED2: 0
4077 Elapsed simulation time in seconds: 0.14
4078 ESTIMATION STEP OMITTED: YES
4079 Elapsed finaloutput time in seconds: 0.28
4080
4081 1
4082 PROBLEM NO.: 1 SUBPROBLEM NO.: 377
4083
4084 SIMULATION STEP PERFORMED
4085 SOURCE 1:
4086 SEED1: 555134540 SEED2: -1123279184
4087 Elapsed simulation time in seconds: 0.14
4088 ESTIMATION STEP OMITTED: YES
4089 Elapsed finaloutput time in seconds: 0.28
4090
4091 1
4092 PROBLEM NO.: 1 SUBPROBLEM NO.: 378
4093
4094 SIMULATION STEP PERFORMED
4095 SOURCE 1:
4096 SEED1: 1776769356 SEED2: 0
4097 Elapsed simulation time in seconds: 0.14
4098 ESTIMATION STEP OMITTED: YES
4099 Elapsed finaloutput time in seconds: 0.28
4100
4101 1
4102 PROBLEM NO.: 1 SUBPROBLEM NO.: 379
4103
4104 SIMULATION STEP PERFORMED
4105 SOURCE 1:
4106 SEED1: 1459221488 SEED2: -1098799966
4107 Elapsed simulation time in seconds: 0.13
4108 ESTIMATION STEP OMITTED: YES
4109 Elapsed finaloutput time in seconds: 0.28
4110
4111 1
4112 PROBLEM NO.: 1 SUBPROBLEM NO.: 380
4113
4114 SIMULATION STEP PERFORMED
4115 SOURCE 1:
4116 SEED1: 1195697600 SEED2: 0
4117 Elapsed simulation time in seconds: 0.12
4118 ESTIMATION STEP OMITTED: YES
4119 Elapsed finaloutput time in seconds: 0.28
4120
4121 1
4122 PROBLEM NO.: 1 SUBPROBLEM NO.: 381
4123
4124 SIMULATION STEP PERFORMED
4125 SOURCE 1:
4126 SEED1: 739048729 SEED2: -1088603910
4127 Elapsed simulation time in seconds: 0.13
4128 ESTIMATION STEP OMITTED: YES
4129 Elapsed finaloutput time in seconds: 0.28
4130
4131 1
4132 PROBLEM NO.: 1 SUBPROBLEM NO.: 382
4133
4134 SIMULATION STEP PERFORMED
4135 SOURCE 1:
4136 SEED1: 395184570 SEED2: 0
4137 Elapsed simulation time in seconds: 0.13
4138 ESTIMATION STEP OMITTED: YES
4139 Elapsed finaloutput time in seconds: 0.29
4140
4141 1
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4142 PROBLEM NO.:          1          SUBPROBLEM NO.:          383
4143
4144 SIMULATION STEP PERFORMED
4145 SOURCE 1:
4146     SEED1:          6374665    SEED2:          1070550527
4147 Elapsed simulation  time in seconds:          0.13
4148 ESTIMATION STEP OMITTED:          YES
4149 Elapsed finaloutput  time in seconds:          0.29
4150
4151 1
4152 PROBLEM NO.:          1          SUBPROBLEM NO.:          384
4153
4154 SIMULATION STEP PERFORMED
4155 SOURCE 1:
4156     SEED1:          498479453    SEED2:              0
4157 Elapsed simulation  time in seconds:          0.13
4158 ESTIMATION STEP OMITTED:          YES
4159 Elapsed finaloutput  time in seconds:          0.29
4160
4161 1
4162 PROBLEM NO.:          1          SUBPROBLEM NO.:          385
4163
4164 SIMULATION STEP PERFORMED
4165 SOURCE 1:
4166     SEED1:          1428670791    SEED2:         -1080179365
4167 Elapsed simulation  time in seconds:          0.12
4168 ESTIMATION STEP OMITTED:          YES
4169 Elapsed finaloutput  time in seconds:          0.28
4170
4171 1
4172 PROBLEM NO.:          1          SUBPROBLEM NO.:          386
4173
4174 SIMULATION STEP PERFORMED
4175 SOURCE 1:
4176     SEED1:          1410501473    SEED2:              0
4177 Elapsed simulation  time in seconds:          0.12
4178 ESTIMATION STEP OMITTED:          YES
4179 Elapsed finaloutput  time in seconds:          0.28
4180
4181 1
4182 PROBLEM NO.:          1          SUBPROBLEM NO.:          387
4183
4184 SIMULATION STEP PERFORMED
4185 SOURCE 1:
4186     SEED1:          222464933    SEED2:          1057476790
4187 Elapsed simulation  time in seconds:          0.13
4188 ESTIMATION STEP OMITTED:          YES
4189 Elapsed finaloutput  time in seconds:          0.28
4190
4191 1
4192 PROBLEM NO.:          1          SUBPROBLEM NO.:          388
4193
4194 SIMULATION STEP PERFORMED
4195 SOURCE 1:
4196     SEED1:          295291343    SEED2:              0
4197 Elapsed simulation  time in seconds:          0.13
4198 ESTIMATION STEP OMITTED:          YES
4199 Elapsed finaloutput  time in seconds:          0.28
4200
4201 1
4202 PROBLEM NO.:          1          SUBPROBLEM NO.:          389
4203
4204 SIMULATION STEP PERFORMED
4205 SOURCE 1:
4206     SEED1:          1428147644    SEED2:         -1097074379
4207 Elapsed simulation  time in seconds:          0.14
4208 ESTIMATION STEP OMITTED:          YES
4209 Elapsed finaloutput  time in seconds:          0.29

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4210
4211 1
4212 PROBLEM NO.:          1          SUBPROBLEM NO.:          390
4213
4214 SIMULATION STEP PERFORMED
4215 SOURCE 1:
4216     SEED1:      679733764    SEED2:          0
4217 Elapsed simulation time in seconds:      0.12
4218 ESTIMATION STEP OMITTED:          YES
4219 Elapsed finaloutput time in seconds:      0.29
4220
4221 1
4222 PROBLEM NO.:          1          SUBPROBLEM NO.:          391
4223
4224 SIMULATION STEP PERFORMED
4225 SOURCE 1:
4226     SEED1:     1200434396    SEED2:   -1098557449
4227 Elapsed simulation time in seconds:      0.14
4228 ESTIMATION STEP OMITTED:          YES
4229 Elapsed finaloutput time in seconds:      0.28
4230
4231 1
4232 PROBLEM NO.:          1          SUBPROBLEM NO.:          392
4233
4234 SIMULATION STEP PERFORMED
4235 SOURCE 1:
4236     SEED1:      953298645    SEED2:          0
4237 Elapsed simulation time in seconds:      0.13
4238 ESTIMATION STEP OMITTED:          YES
4239 Elapsed finaloutput time in seconds:      0.29
4240
4241 1
4242 PROBLEM NO.:          1          SUBPROBLEM NO.:          393
4243
4244 SIMULATION STEP PERFORMED
4245 SOURCE 1:
4246     SEED1:     1133075792    SEED2:   -1096748647
4247 Elapsed simulation time in seconds:      0.13
4248 ESTIMATION STEP OMITTED:          YES
4249 Elapsed finaloutput time in seconds:      0.28
4250
4251 1
4252 PROBLEM NO.:          1          SUBPROBLEM NO.:          394
4253
4254 SIMULATION STEP PERFORMED
4255 SOURCE 1:
4256     SEED1:      772743147    SEED2:          0
4257 Elapsed simulation time in seconds:      0.13
4258 ESTIMATION STEP OMITTED:          YES
4259 Elapsed finaloutput time in seconds:      0.28
4260
4261 1
4262 PROBLEM NO.:          1          SUBPROBLEM NO.:          395
4263
4264 SIMULATION STEP PERFORMED
4265 SOURCE 1:
4266     SEED1:      320343941    SEED2:   1059980486
4267 Elapsed simulation time in seconds:      0.12
4268 ESTIMATION STEP OMITTED:          YES
4269 Elapsed finaloutput time in seconds:      0.28
4270
4271 1
4272 PROBLEM NO.:          1          SUBPROBLEM NO.:          396
4273
4274 SIMULATION STEP PERFORMED
4275 SOURCE 1:
4276     SEED1:     1341804589    SEED2:          0
4277 Elapsed simulation time in seconds:      0.13

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4278 ESTIMATION STEP OMITTED: YES
4279 Elapsed finaloutput time in seconds: 0.28
4280
4281 1
4282 PROBLEM NO.: 1 SUBPROBLEM NO.: 397
4283
4284 SIMULATION STEP PERFORMED
4285 SOURCE 1:
4286 SEED1: 931315926 SEED2: -1086880574
4287 Elapsed simulation time in seconds: 0.12
4288 ESTIMATION STEP OMITTED: YES
4289 Elapsed finaloutput time in seconds: 0.28
4290
4291 1
4292 PROBLEM NO.: 1 SUBPROBLEM NO.: 398
4293
4294 SIMULATION STEP PERFORMED
4295 SOURCE 1:
4296 SEED1: 780067741 SEED2: 0
4297 Elapsed simulation time in seconds: 0.12
4298 ESTIMATION STEP OMITTED: YES
4299 Elapsed finaloutput time in seconds: 0.28
4300
4301 1
4302 PROBLEM NO.: 1 SUBPROBLEM NO.: 399
4303
4304 SIMULATION STEP PERFORMED
4305 SOURCE 1:
4306 SEED1: 2102735911 SEED2: 1067712433
4307 Elapsed simulation time in seconds: 0.13
4308 ESTIMATION STEP OMITTED: YES
4309 Elapsed finaloutput time in seconds: 0.29
4310
4311 1
4312 PROBLEM NO.: 1 SUBPROBLEM NO.: 400
4313
4314 SIMULATION STEP PERFORMED
4315 SOURCE 1:
4316 SEED1: 1345467994 SEED2: 0
4317 Elapsed simulation time in seconds: 0.13
4318 ESTIMATION STEP OMITTED: YES
4319 Elapsed finaloutput time in seconds: 0.28
4320
4321 1
4322 PROBLEM NO.: 1 SUBPROBLEM NO.: 401
4323
4324 SIMULATION STEP PERFORMED
4325 SOURCE 1:
4326 SEED1: 691803242 SEED2: -1090126242
4327 Elapsed simulation time in seconds: 0.14
4328 ESTIMATION STEP OMITTED: YES
4329 Elapsed finaloutput time in seconds: 0.28
4330
4331 1
4332 PROBLEM NO.: 1 SUBPROBLEM NO.: 402
4333
4334 SIMULATION STEP PERFORMED
4335 SOURCE 1:
4336 SEED1: 1591589014 SEED2: 0
4337 Elapsed simulation time in seconds: 0.13
4338 ESTIMATION STEP OMITTED: YES
4339 Elapsed finaloutput time in seconds: 0.28
4340
4341 1
4342 PROBLEM NO.: 1 SUBPROBLEM NO.: 403
4343
4344 SIMULATION STEP PERFORMED
4345 SOURCE 1:

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4346     SEED1:    2031140526    SEED2:    1065134223
4347 Elapsed simulation  time in seconds:    0.12
4348 ESTIMATION STEP OMITTED:    YES
4349 Elapsed finaloutput  time in seconds:    0.28
4350
4351 1
4352 PROBLEM NO.:          1          SUBPROBLEM NO.:          404
4353
4354 SIMULATION STEP PERFORMED
4355 SOURCE 1:
4356     SEED1:    209939984    SEED2:          0
4357 Elapsed simulation  time in seconds:    0.13
4358 ESTIMATION STEP OMITTED:    YES
4359 Elapsed finaloutput  time in seconds:    0.29
4360
4361 1
4362 PROBLEM NO.:          1          SUBPROBLEM NO.:          405
4363
4364 SIMULATION STEP PERFORMED
4365 SOURCE 1:
4366     SEED1:    644611692    SEED2:   -1089184683
4367 Elapsed simulation  time in seconds:    0.13
4368 ESTIMATION STEP OMITTED:    YES
4369 Elapsed finaloutput  time in seconds:    0.28
4370
4371 1
4372 PROBLEM NO.:          1          SUBPROBLEM NO.:          406
4373
4374 SIMULATION STEP PERFORMED
4375 SOURCE 1:
4376     SEED1:    418565228    SEED2:          0
4377 Elapsed simulation  time in seconds:    0.12
4378 ESTIMATION STEP OMITTED:    YES
4379 Elapsed finaloutput  time in seconds:    0.28
4380
4381 1
4382 PROBLEM NO.:          1          SUBPROBLEM NO.:          407
4383
4384 SIMULATION STEP PERFORMED
4385 SOURCE 1:
4386     SEED1:    456671770    SEED2:    1044778263
4387 Elapsed simulation  time in seconds:    0.13
4388 ESTIMATION STEP OMITTED:    YES
4389 Elapsed finaloutput  time in seconds:    0.28
4390
4391 1
4392 PROBLEM NO.:          1          SUBPROBLEM NO.:          408
4393
4394 SIMULATION STEP PERFORMED
4395 SOURCE 1:
4396     SEED1:    1199566973    SEED2:          0
4397 Elapsed simulation  time in seconds:    0.12
4398 ESTIMATION STEP OMITTED:    YES
4399 Elapsed finaloutput  time in seconds:    0.28
4400
4401 1
4402 PROBLEM NO.:          1          SUBPROBLEM NO.:          409
4403
4404 SIMULATION STEP PERFORMED
4405 SOURCE 1:
4406     SEED1:    740322494    SEED2:   -1085719590
4407 Elapsed simulation  time in seconds:    0.14
4408 ESTIMATION STEP OMITTED:    YES
4409 Elapsed finaloutput  time in seconds:    0.28
4410
4411 1
4412 PROBLEM NO.:          1          SUBPROBLEM NO.:          410
4413

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4414 SIMULATION STEP PERFORMED
4415 SOURCE 1:
4416 SEED1: 2040888484 SEED2: 0
4417 Elapsed simulation time in seconds: 0.13
4418 ESTIMATION STEP OMITTED: YES
4419 Elapsed finaloutput time in seconds: 0.28
4420
4421 1
4422 PROBLEM NO.: 1 SUBPROBLEM NO.: 411
4423
4424 SIMULATION STEP PERFORMED
4425 SOURCE 1:
4426 SEED1: 1693043444 SEED2: 1025022121
4427 Elapsed simulation time in seconds: 0.13
4428 ESTIMATION STEP OMITTED: YES
4429 Elapsed finaloutput time in seconds: 0.28
4430
4431 1
4432 PROBLEM NO.: 1 SUBPROBLEM NO.: 412
4433
4434 SIMULATION STEP PERFORMED
4435 SOURCE 1:
4436 SEED1: 1349500072 SEED2: 0
4437 Elapsed simulation time in seconds: 0.16
4438 ESTIMATION STEP OMITTED: YES
4439 Elapsed finaloutput time in seconds: 0.28
4440
4441 1
4442 PROBLEM NO.: 1 SUBPROBLEM NO.: 413
4443
4444 SIMULATION STEP PERFORMED
4445 SOURCE 1:
4446 SEED1: 674437773 SEED2: -1095707546
4447 Elapsed simulation time in seconds: 0.14
4448 ESTIMATION STEP OMITTED: YES
4449 Elapsed finaloutput time in seconds: 0.28
4450
4451 1
4452 PROBLEM NO.: 1 SUBPROBLEM NO.: 414
4453
4454 SIMULATION STEP PERFORMED
4455 SOURCE 1:
4456 SEED1: 1828191309 SEED2: 0
4457 Elapsed simulation time in seconds: 0.13
4458 ESTIMATION STEP OMITTED: YES
4459 Elapsed finaloutput time in seconds: 0.28
4460
4461 1
4462 PROBLEM NO.: 1 SUBPROBLEM NO.: 415
4463
4464 SIMULATION STEP PERFORMED
4465 SOURCE 1:
4466 SEED1: 1504302406 SEED2: -1094045356
4467 Elapsed simulation time in seconds: 0.12
4468 ESTIMATION STEP OMITTED: YES
4469 Elapsed finaloutput time in seconds: 0.28
4470
4471 1
4472 PROBLEM NO.: 1 SUBPROBLEM NO.: 416
4473
4474 SIMULATION STEP PERFORMED
4475 SOURCE 1:
4476 SEED1: 1264697659 SEED2: 0
4477 Elapsed simulation time in seconds: 0.14
4478 ESTIMATION STEP OMITTED: YES
4479 Elapsed finaloutput time in seconds: 0.28
4480
4481 1

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4482 PROBLEM NO.:          1          SUBPROBLEM NO.:          417
4483
4484 SIMULATION STEP PERFORMED
4485 SOURCE 1:
4486     SEED1:    1462692557    SEED2:    -1106165417
4487 Elapsed simulation  time in seconds:    0.13
4488 ESTIMATION STEP OMITTED:          YES
4489 Elapsed finaloutput  time in seconds:    0.28
4490
4491 1
4492 PROBLEM NO.:          1          SUBPROBLEM NO.:          418
4493
4494 SIMULATION STEP PERFORMED
4495 SOURCE 1:
4496     SEED1:    1109998395    SEED2:          0
4497 Elapsed simulation  time in seconds:    0.12
4498 ESTIMATION STEP OMITTED:          YES
4499 Elapsed finaloutput  time in seconds:    0.28
4500
4501 1
4502 PROBLEM NO.:          1          SUBPROBLEM NO.:          419
4503
4504 SIMULATION STEP PERFORMED
4505 SOURCE 1:
4506     SEED1:    716046458    SEED2:    -1082985145
4507 Elapsed simulation  time in seconds:    0.14
4508 ESTIMATION STEP OMITTED:          YES
4509 Elapsed finaloutput  time in seconds:    0.28
4510
4511 1
4512 PROBLEM NO.:          1          SUBPROBLEM NO.:          420
4513
4514 SIMULATION STEP PERFORMED
4515 SOURCE 1:
4516     SEED1:    492121996    SEED2:          0
4517 Elapsed simulation  time in seconds:    0.14
4518 ESTIMATION STEP OMITTED:          YES
4519 Elapsed finaloutput  time in seconds:    0.28
4520
4521 1
4522 PROBLEM NO.:          1          SUBPROBLEM NO.:          421
4523
4524 SIMULATION STEP PERFORMED
4525 SOURCE 1:
4526     SEED1:    1629039128    SEED2:    1040490148
4527 Elapsed simulation  time in seconds:    0.13
4528 ESTIMATION STEP OMITTED:          YES
4529 Elapsed finaloutput  time in seconds:    0.28
4530
4531 1
4532 PROBLEM NO.:          1          SUBPROBLEM NO.:          422
4533
4534 SIMULATION STEP PERFORMED
4535 SOURCE 1:
4536     SEED1:    1028676708    SEED2:          0
4537 Elapsed simulation  time in seconds:    0.14
4538 ESTIMATION STEP OMITTED:          YES
4539 Elapsed finaloutput  time in seconds:    0.28
4540
4541 1
4542 PROBLEM NO.:          1          SUBPROBLEM NO.:          423
4543
4544 SIMULATION STEP PERFORMED
4545 SOURCE 1:
4546     SEED1:    723018645    SEED2:    -1088891734
4547 Elapsed simulation  time in seconds:    0.14
4548 ESTIMATION STEP OMITTED:          YES
4549 Elapsed finaloutput  time in seconds:    0.29

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4550
4551 1
4552 PROBLEM NO.:          1          SUBPROBLEM NO.:          424
4553
4554 SIMULATION STEP PERFORMED
4555 SOURCE 1:
4556     SEED1:    1517727865    SEED2:          0
4557 Elapsed simulation time in seconds:    0.14
4558 ESTIMATION STEP OMITTED:          YES
4559 Elapsed finaloutput time in seconds:    0.28
4560
4561 1
4562 PROBLEM NO.:          1          SUBPROBLEM NO.:          425
4563
4564 SIMULATION STEP PERFORMED
4565 SOURCE 1:
4566     SEED1:    1389620832    SEED2:   -1081568523
4567 Elapsed simulation time in seconds:    0.13
4568 ESTIMATION STEP OMITTED:          YES
4569 Elapsed finaloutput time in seconds:    0.28
4570
4571 1
4572 PROBLEM NO.:          1          SUBPROBLEM NO.:          426
4573
4574 SIMULATION STEP PERFORMED
4575 SOURCE 1:
4576     SEED1:    1116084897    SEED2:          0
4577 Elapsed simulation time in seconds:    0.13
4578 ESTIMATION STEP OMITTED:          YES
4579 Elapsed finaloutput time in seconds:    0.28
4580
4581 1
4582 PROBLEM NO.:          1          SUBPROBLEM NO.:          427
4583
4584 SIMULATION STEP PERFORMED
4585 SOURCE 1:
4586     SEED1:    1438615960    SEED2:   -1082768315
4587 Elapsed simulation time in seconds:    0.13
4588 ESTIMATION STEP OMITTED:          YES
4589 Elapsed finaloutput time in seconds:    0.28
4590
4591 1
4592 PROBLEM NO.:          1          SUBPROBLEM NO.:          428
4593
4594 SIMULATION STEP PERFORMED
4595 SOURCE 1:
4596     SEED1:    771867695    SEED2:          0
4597 Elapsed simulation time in seconds:    0.12
4598 ESTIMATION STEP OMITTED:          YES
4599 Elapsed finaloutput time in seconds:    0.28
4600
4601 1
4602 PROBLEM NO.:          1          SUBPROBLEM NO.:          429
4603
4604 SIMULATION STEP PERFORMED
4605 SOURCE 1:
4606     SEED1:    121368559    SEED2:   1066635588
4607 Elapsed simulation time in seconds:    0.13
4608 ESTIMATION STEP OMITTED:          YES
4609 Elapsed finaloutput time in seconds:    0.28
4610
4611 1
4612 PROBLEM NO.:          1          SUBPROBLEM NO.:          430
4613
4614 SIMULATION STEP PERFORMED
4615 SOURCE 1:
4616     SEED1:    1389532841    SEED2:          0
4617 Elapsed simulation time in seconds:    0.14

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4618 ESTIMATION STEP OMITTED: YES
4619 Elapsed finaloutput time in seconds: 0.28
4620
4621 1
4622 PROBLEM NO.: 1 SUBPROBLEM NO.: 431
4623
4624 SIMULATION STEP PERFORMED
4625 SOURCE 1:
4626 SEED1: 920668720 SEED2: -1094721688
4627 Elapsed simulation time in seconds: 0.12
4628 ESTIMATION STEP OMITTED: YES
4629 Elapsed finaloutput time in seconds: 0.28
4630
4631 1
4632 PROBLEM NO.: 1 SUBPROBLEM NO.: 432
4633
4634 SIMULATION STEP PERFORMED
4635 SOURCE 1:
4636 SEED1: 1768641625 SEED2: 0
4637 Elapsed simulation time in seconds: 0.13
4638 ESTIMATION STEP OMITTED: YES
4639 Elapsed finaloutput time in seconds: 0.29
4640
4641 1
4642 PROBLEM NO.: 1 SUBPROBLEM NO.: 433
4643
4644 SIMULATION STEP PERFORMED
4645 SOURCE 1:
4646 SEED1: 1705154366 SEED2: 1048758898
4647 Elapsed simulation time in seconds: 0.13
4648 ESTIMATION STEP OMITTED: YES
4649 Elapsed finaloutput time in seconds: 0.28
4650
4651 1
4652 PROBLEM NO.: 1 SUBPROBLEM NO.: 434
4653
4654 SIMULATION STEP PERFORMED
4655 SOURCE 1:
4656 SEED1: 784732895 SEED2: 0
4657 Elapsed simulation time in seconds: 0.13
4658 ESTIMATION STEP OMITTED: YES
4659 Elapsed finaloutput time in seconds: 0.28
4660
4661 1
4662 PROBLEM NO.: 1 SUBPROBLEM NO.: 435
4663
4664 SIMULATION STEP PERFORMED
4665 SOURCE 1:
4666 SEED1: 1217522980 SEED2: -1081061590
4667 Elapsed simulation time in seconds: 0.13
4668 ESTIMATION STEP OMITTED: YES
4669 Elapsed finaloutput time in seconds: 0.28
4670
4671 1
4672 PROBLEM NO.: 1 SUBPROBLEM NO.: 436
4673
4674 SIMULATION STEP PERFORMED
4675 SOURCE 1:
4676 SEED1: 530934723 SEED2: 0
4677 Elapsed simulation time in seconds: 0.14
4678 ESTIMATION STEP OMITTED: YES
4679 Elapsed finaloutput time in seconds: 0.28
4680
4681 1
4682 PROBLEM NO.: 1 SUBPROBLEM NO.: 437
4683
4684 SIMULATION STEP PERFORMED
4685 SOURCE 1:

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```

4686     SEED1:    1463148549    SEED2:    -1080125761
4687 Elapsed simulation  time in seconds:    0.12
4688 ESTIMATION STEP OMITTED:    YES
4689 Elapsed finaloutput  time in seconds:    0.28
4690
4691 1
4692 PROBLEM NO.:          1          SUBPROBLEM NO.:          438
4693
4694 SIMULATION STEP PERFORMED
4695 SOURCE 1:
4696     SEED1:    1040910819    SEED2:          0
4697 Elapsed simulation  time in seconds:    0.14
4698 ESTIMATION STEP OMITTED:    YES
4699 Elapsed finaloutput  time in seconds:    0.28
4700
4701 1
4702 PROBLEM NO.:          1          SUBPROBLEM NO.:          439
4703
4704 SIMULATION STEP PERFORMED
4705 SOURCE 1:
4706     SEED1:    2064464137    SEED2:    1068140895
4707 Elapsed simulation  time in seconds:    0.13
4708 ESTIMATION STEP OMITTED:    YES
4709 Elapsed finaloutput  time in seconds:    0.28
4710
4711 1
4712 PROBLEM NO.:          1          SUBPROBLEM NO.:          440
4713
4714 SIMULATION STEP PERFORMED
4715 SOURCE 1:
4716     SEED1:    703740196    SEED2:          0
4717 Elapsed simulation  time in seconds:    0.14
4718 ESTIMATION STEP OMITTED:    YES
4719 Elapsed finaloutput  time in seconds:    0.29
4720
4721 1
4722 PROBLEM NO.:          1          SUBPROBLEM NO.:          441
4723
4724 SIMULATION STEP PERFORMED
4725 SOURCE 1:
4726     SEED1:    1772707344    SEED2:    1041909529
4727 Elapsed simulation  time in seconds:    0.13
4728 ESTIMATION STEP OMITTED:    YES
4729 Elapsed finaloutput  time in seconds:    0.28
4730
4731 1
4732 PROBLEM NO.:          1          SUBPROBLEM NO.:          442
4733
4734 SIMULATION STEP PERFORMED
4735 SOURCE 1:
4736     SEED1:    277340837    SEED2:          0
4737 Elapsed simulation  time in seconds:    0.14
4738 ESTIMATION STEP OMITTED:    YES
4739 Elapsed finaloutput  time in seconds:    0.28
4740
4741 1
4742 PROBLEM NO.:          1          SUBPROBLEM NO.:          443
4743
4744 SIMULATION STEP PERFORMED
4745 SOURCE 1:
4746     SEED1:    1514673503    SEED2:    -1098127174
4747 Elapsed simulation  time in seconds:    0.14
4748 ESTIMATION STEP OMITTED:    YES
4749 Elapsed finaloutput  time in seconds:    0.28
4750
4751 1
4752 PROBLEM NO.:          1          SUBPROBLEM NO.:          444
4753

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4754 SIMULATION STEP PERFORMED
4755 SOURCE 1:
4756 SEED1: 1084207866 SEED2: 0
4757 Elapsed simulation time in seconds: 0.13
4758 ESTIMATION STEP OMITTED: YES
4759 Elapsed finaloutput time in seconds: 0.28
4760
4761 1
4762 PROBLEM NO.: 1 SUBPROBLEM NO.: 445
4763
4764 SIMULATION STEP PERFORMED
4765 SOURCE 1:
4766 SEED1: 1362287108 SEED2: -1084299947
4767 Elapsed simulation time in seconds: 0.13
4768 ESTIMATION STEP OMITTED: YES
4769 Elapsed finaloutput time in seconds: 0.28
4770
4771 1
4772 PROBLEM NO.: 1 SUBPROBLEM NO.: 446
4773
4774 SIMULATION STEP PERFORMED
4775 SOURCE 1:
4776 SEED1: 1415440094 SEED2: 0
4777 Elapsed simulation time in seconds: 0.14
4778 ESTIMATION STEP OMITTED: YES
4779 Elapsed finaloutput time in seconds: 0.28
4780
4781 1
4782 PROBLEM NO.: 1 SUBPROBLEM NO.: 447
4783
4784 SIMULATION STEP PERFORMED
4785 SOURCE 1:
4786 SEED1: 1921154060 SEED2: 1054831250
4787 Elapsed simulation time in seconds: 0.13
4788 ESTIMATION STEP OMITTED: YES
4789 Elapsed finaloutput time in seconds: 0.28
4790
4791 1
4792 PROBLEM NO.: 1 SUBPROBLEM NO.: 448
4793
4794 SIMULATION STEP PERFORMED
4795 SOURCE 1:
4796 SEED1: 976622273 SEED2: 0
4797 Elapsed simulation time in seconds: 0.16
4798 ESTIMATION STEP OMITTED: YES
4799 Elapsed finaloutput time in seconds: 0.28
4800
4801 1
4802 PROBLEM NO.: 1 SUBPROBLEM NO.: 449
4803
4804 SIMULATION STEP PERFORMED
4805 SOURCE 1:
4806 SEED1: 2021105519 SEED2: 1063789545
4807 Elapsed simulation time in seconds: 0.14
4808 ESTIMATION STEP OMITTED: YES
4809 Elapsed finaloutput time in seconds: 0.28
4810
4811 1
4812 PROBLEM NO.: 1 SUBPROBLEM NO.: 450
4813
4814 SIMULATION STEP PERFORMED
4815 SOURCE 1:
4816 SEED1: 393008267 SEED2: 0
4817 Elapsed simulation time in seconds: 0.14
4818 ESTIMATION STEP OMITTED: YES
4819 Elapsed finaloutput time in seconds: 0.28
4820
4821 1

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4822  PROBLEM NO.:          1          SUBPROBLEM NO.:          451
4823
4824  SIMULATION STEP PERFORMED
4825  SOURCE 1:
4826      SEED1:          2195629    SEED2:          1069770553
4827  Elapsed simulation  time  in seconds:          0.14
4828  ESTIMATION STEP OMITTED:          YES
4829  Elapsed finaloutput  time  in seconds:          0.29
4830
4831  1
4832  PROBLEM NO.:          1          SUBPROBLEM NO.:          452
4833
4834  SIMULATION STEP PERFORMED
4835  SOURCE 1:
4836      SEED1:          1829704745    SEED2:              0
4837  Elapsed simulation  time  in seconds:          0.13
4838  ESTIMATION STEP OMITTED:          YES
4839  Elapsed finaloutput  time  in seconds:          0.35
4840
4841  1
4842  PROBLEM NO.:          1          SUBPROBLEM NO.:          453
4843
4844  SIMULATION STEP PERFORMED
4845  SOURCE 1:
4846      SEED1:          858308846    SEED2:         -1091353011
4847  Elapsed simulation  time  in seconds:          0.12
4848  ESTIMATION STEP OMITTED:          YES
4849  Elapsed finaloutput  time  in seconds:          0.28
4850
4851  1
4852  PROBLEM NO.:          1          SUBPROBLEM NO.:          454
4853
4854  SIMULATION STEP PERFORMED
4855  SOURCE 1:
4856      SEED1:          197847743    SEED2:              0
4857  Elapsed simulation  time  in seconds:          0.12
4858  ESTIMATION STEP OMITTED:          YES
4859  Elapsed finaloutput  time  in seconds:          0.28
4860
4861  1
4862  PROBLEM NO.:          1          SUBPROBLEM NO.:          455
4863
4864  SIMULATION STEP PERFORMED
4865  SOURCE 1:
4866      SEED1:          1744433337    SEED2:          1066453177
4867  Elapsed simulation  time  in seconds:          0.14
4868  ESTIMATION STEP OMITTED:          YES
4869  Elapsed finaloutput  time  in seconds:          0.28
4870
4871  1
4872  PROBLEM NO.:          1          SUBPROBLEM NO.:          456
4873
4874  SIMULATION STEP PERFORMED
4875  SOURCE 1:
4876      SEED1:          220481725    SEED2:              0
4877  Elapsed simulation  time  in seconds:          0.14
4878  ESTIMATION STEP OMITTED:          YES
4879  Elapsed finaloutput  time  in seconds:          0.29
4880
4881  1
4882  PROBLEM NO.:          1          SUBPROBLEM NO.:          457
4883
4884  SIMULATION STEP PERFORMED
4885  SOURCE 1:
4886      SEED1:          336545349    SEED2:          1058771819
4887  Elapsed simulation  time  in seconds:          0.14
4888  ESTIMATION STEP OMITTED:          YES
4889  Elapsed finaloutput  time  in seconds:          0.29

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4890
4891 1
4892 PROBLEM NO.:          1          SUBPROBLEM NO.:          458
4893
4894 SIMULATION STEP PERFORMED
4895 SOURCE 1:
4896     SEED1:    1259717787    SEED2:          0
4897 Elapsed simulation time in seconds:    0.13
4898 ESTIMATION STEP OMITTED:          YES
4899 Elapsed finaloutput time in seconds:    0.28
4900
4901 1
4902 PROBLEM NO.:          1          SUBPROBLEM NO.:          459
4903
4904 SIMULATION STEP PERFORMED
4905 SOURCE 1:
4906     SEED1:    203531661    SEED2:    1073859799
4907 Elapsed simulation time in seconds:    0.12
4908 ESTIMATION STEP OMITTED:          YES
4909 Elapsed finaloutput time in seconds:    0.28
4910
4911 1
4912 PROBLEM NO.:          1          SUBPROBLEM NO.:          460
4913
4914 SIMULATION STEP PERFORMED
4915 SOURCE 1:
4916     SEED1:    1179081366    SEED2:          0
4917 Elapsed simulation time in seconds:    0.13
4918 ESTIMATION STEP OMITTED:          YES
4919 Elapsed finaloutput time in seconds:    0.28
4920
4921 1
4922 PROBLEM NO.:          1          SUBPROBLEM NO.:          461
4923
4924 SIMULATION STEP PERFORMED
4925 SOURCE 1:
4926     SEED1:    758566356    SEED2:    -1085158932
4927 Elapsed simulation time in seconds:    0.14
4928 ESTIMATION STEP OMITTED:          YES
4929 Elapsed finaloutput time in seconds:    0.28
4930
4931 1
4932 PROBLEM NO.:          1          SUBPROBLEM NO.:          462
4933
4934 SIMULATION STEP PERFORMED
4935 SOURCE 1:
4936     SEED1:    1744253827    SEED2:          0
4937 Elapsed simulation time in seconds:    0.13
4938 ESTIMATION STEP OMITTED:          YES
4939 Elapsed finaloutput time in seconds:    0.28
4940
4941 1
4942 PROBLEM NO.:          1          SUBPROBLEM NO.:          463
4943
4944 SIMULATION STEP PERFORMED
4945 SOURCE 1:
4946     SEED1:    1686406930    SEED2:    1048628166
4947 Elapsed simulation time in seconds:    0.13
4948 ESTIMATION STEP OMITTED:          YES
4949 Elapsed finaloutput time in seconds:    0.28
4950
4951 1
4952 PROBLEM NO.:          1          SUBPROBLEM NO.:          464
4953
4954 SIMULATION STEP PERFORMED
4955 SOURCE 1:
4956     SEED1:    1015588811    SEED2:          0
4957 Elapsed simulation time in seconds:    0.14

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4958 ESTIMATION STEP OMITTED: YES
4959 Elapsed finaloutput time in seconds: 0.28
4960
4961 1
4962 PROBLEM NO.: 1 SUBPROBLEM NO.: 465
4963
4964 SIMULATION STEP PERFORMED
4965 SOURCE 1:
4966 SEED1: 706498104 SEED2: -1090760792
4967 Elapsed simulation time in seconds: 0.13
4968 ESTIMATION STEP OMITTED: YES
4969 Elapsed finaloutput time in seconds: 0.28
4970
4971 1
4972 PROBLEM NO.: 1 SUBPROBLEM NO.: 466
4973
4974 SIMULATION STEP PERFORMED
4975 SOURCE 1:
4976 SEED1: 173761414 SEED2: 0
4977 Elapsed simulation time in seconds: 0.13
4978 ESTIMATION STEP OMITTED: YES
4979 Elapsed finaloutput time in seconds: 0.29
4980
4981 1
4982 PROBLEM NO.: 1 SUBPROBLEM NO.: 467
4983
4984 SIMULATION STEP PERFORMED
4985 SOURCE 1:
4986 SEED1: 166153577 SEED2: 1066838693
4987 Elapsed simulation time in seconds: 0.13
4988 ESTIMATION STEP OMITTED: YES
4989 Elapsed finaloutput time in seconds: 0.29
4990
4991 1
4992 PROBLEM NO.: 1 SUBPROBLEM NO.: 468
4993
4994 SIMULATION STEP PERFORMED
4995 SOURCE 1:
4996 SEED1: 890718467 SEED2: 0
4997 Elapsed simulation time in seconds: 0.14
4998 ESTIMATION STEP OMITTED: YES
4999 Elapsed finaloutput time in seconds: 0.28
5000
5001 1
5002 PROBLEM NO.: 1 SUBPROBLEM NO.: 469
5003
5004 SIMULATION STEP PERFORMED
5005 SOURCE 1:
5006 SEED1: 573559549 SEED2: -1115046464
5007 Elapsed simulation time in seconds: 0.13
5008 ESTIMATION STEP OMITTED: YES
5009 Elapsed finaloutput time in seconds: 0.29
5010
5011 1
5012 PROBLEM NO.: 1 SUBPROBLEM NO.: 470
5013
5014 SIMULATION STEP PERFORMED
5015 SOURCE 1:
5016 SEED1: 804928779 SEED2: 0
5017 Elapsed simulation time in seconds: 0.12
5018 ESTIMATION STEP OMITTED: YES
5019 Elapsed finaloutput time in seconds: 0.28
5020
5021 1
5022 PROBLEM NO.: 1 SUBPROBLEM NO.: 471
5023
5024 SIMULATION STEP PERFORMED
5025 SOURCE 1:

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5026     SEED1:    1745948972    SEED2:    1049027787
5027 Elapsed simulation  time in seconds:    0.12
5028 ESTIMATION STEP OMITTED:    YES
5029 Elapsed finaloutput  time in seconds:    0.28
5030
5031 1
5032 PROBLEM NO.:          1          SUBPROBLEM NO.:          472
5033
5034 SIMULATION STEP PERFORMED
5035 SOURCE 1:
5036     SEED1:    461304981    SEED2:          0
5037 Elapsed simulation  time in seconds:    0.12
5038 ESTIMATION STEP OMITTED:    YES
5039 Elapsed finaloutput  time in seconds:    0.28
5040
5041 1
5042 PROBLEM NO.:          1          SUBPROBLEM NO.:          473
5043
5044 SIMULATION STEP PERFORMED
5045 SOURCE 1:
5046     SEED1:    1003601159    SEED2:   -1079809305
5047 Elapsed simulation  time in seconds:    0.12
5048 ESTIMATION STEP OMITTED:    YES
5049 Elapsed finaloutput  time in seconds:    0.29
5050
5051 1
5052 PROBLEM NO.:          1          SUBPROBLEM NO.:          474
5053
5054 SIMULATION STEP PERFORMED
5055 SOURCE 1:
5056     SEED1:    372877738    SEED2:          0
5057 Elapsed simulation  time in seconds:    0.18
5058 ESTIMATION STEP OMITTED:    YES
5059 Elapsed finaloutput  time in seconds:    0.28
5060
5061 1
5062 PROBLEM NO.:          1          SUBPROBLEM NO.:          475
5063
5064 SIMULATION STEP PERFORMED
5065 SOURCE 1:
5066     SEED1:    1012304592    SEED2:   -1085358927
5067 Elapsed simulation  time in seconds:    0.12
5068 ESTIMATION STEP OMITTED:    YES
5069 Elapsed finaloutput  time in seconds:    0.28
5070
5071 1
5072 PROBLEM NO.:          1          SUBPROBLEM NO.:          476
5073
5074 SIMULATION STEP PERFORMED
5075 SOURCE 1:
5076     SEED1:    1467163674    SEED2:          0
5077 Elapsed simulation  time in seconds:    0.13
5078 ESTIMATION STEP OMITTED:    YES
5079 Elapsed finaloutput  time in seconds:    0.28
5080
5081 1
5082 PROBLEM NO.:          1          SUBPROBLEM NO.:          477
5083
5084 SIMULATION STEP PERFORMED
5085 SOURCE 1:
5086     SEED1:    598209923    SEED2:   -1110163655
5087 Elapsed simulation  time in seconds:    0.13
5088 ESTIMATION STEP OMITTED:    YES
5089 Elapsed finaloutput  time in seconds:    0.29
5090
5091 1
5092 PROBLEM NO.:          1          SUBPROBLEM NO.:          478
5093

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5094 SIMULATION STEP PERFORMED
5095 SOURCE 1:
5096 SEED1: 1683805278 SEED2: 0
5097 Elapsed simulation time in seconds: 0.16
5098 ESTIMATION STEP OMITTED: YES
5099 Elapsed finaloutput time in seconds: 0.29
5100
5101 1
5102 PROBLEM NO.: 1 SUBPROBLEM NO.: 479
5103
5104 SIMULATION STEP PERFORMED
5105 SOURCE 1:
5106 SEED1: 588536612 SEED2: -1113211886
5107 Elapsed simulation time in seconds: 0.20
5108 ESTIMATION STEP OMITTED: YES
5109 Elapsed finaloutput time in seconds: 0.29
5110
5111 1
5112 PROBLEM NO.: 1 SUBPROBLEM NO.: 480
5113
5114 SIMULATION STEP PERFORMED
5115 SOURCE 1:
5116 SEED1: 536520505 SEED2: 0
5117 Elapsed simulation time in seconds: 0.14
5118 ESTIMATION STEP OMITTED: YES
5119 Elapsed finaloutput time in seconds: 0.29
5120
5121 1
5122 PROBLEM NO.: 1 SUBPROBLEM NO.: 481
5123
5124 SIMULATION STEP PERFORMED
5125 SOURCE 1:
5126 SEED1: 1656070542 SEED2: 1043382898
5127 Elapsed simulation time in seconds: 0.27
5128 ESTIMATION STEP OMITTED: YES
5129 Elapsed finaloutput time in seconds: 0.29
5130
5131 1
5132 PROBLEM NO.: 1 SUBPROBLEM NO.: 482
5133
5134 SIMULATION STEP PERFORMED
5135 SOURCE 1:
5136 SEED1: 398065117 SEED2: 0
5137 Elapsed simulation time in seconds: 0.14
5138 ESTIMATION STEP OMITTED: YES
5139 Elapsed finaloutput time in seconds: 0.29
5140
5141 1
5142 PROBLEM NO.: 1 SUBPROBLEM NO.: 483
5143
5144 SIMULATION STEP PERFORMED
5145 SOURCE 1:
5146 SEED1: 1298152521 SEED2: -1089103609
5147 Elapsed simulation time in seconds: 0.12
5148 ESTIMATION STEP OMITTED: YES
5149 Elapsed finaloutput time in seconds: 0.28
5150
5151 1
5152 PROBLEM NO.: 1 SUBPROBLEM NO.: 484
5153
5154 SIMULATION STEP PERFORMED
5155 SOURCE 1:
5156 SEED1: 1219620375 SEED2: 0
5157 Elapsed simulation time in seconds: 0.12
5158 ESTIMATION STEP OMITTED: YES
5159 Elapsed finaloutput time in seconds: 0.28
5160
5161 1

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5162 PROBLEM NO.:          1          SUBPROBLEM NO.:          485
5163
5164 SIMULATION STEP PERFORMED
5165 SOURCE 1:
5166     SEED1:    1266144164    SEED2:    -1090936376
5167 Elapsed simulation  time in seconds:    0.13
5168 ESTIMATION STEP OMITTED:          YES
5169 Elapsed finaloutput  time in seconds:    0.29
5170
5171 1
5172 PROBLEM NO.:          1          SUBPROBLEM NO.:          486
5173
5174 SIMULATION STEP PERFORMED
5175 SOURCE 1:
5176     SEED1:    663836033    SEED2:          0
5177 Elapsed simulation  time in seconds:    0.14
5178 ESTIMATION STEP OMITTED:          YES
5179 Elapsed finaloutput  time in seconds:    0.28
5180
5181 1
5182 PROBLEM NO.:          1          SUBPROBLEM NO.:          487
5183
5184 SIMULATION STEP PERFORMED
5185 SOURCE 1:
5186     SEED1:    1618414847    SEED2:    1019208715
5187 Elapsed simulation  time in seconds:    0.15
5188 ESTIMATION STEP OMITTED:          YES
5189 Elapsed finaloutput  time in seconds:    0.29
5190
5191 1
5192 PROBLEM NO.:          1          SUBPROBLEM NO.:          488
5193
5194 SIMULATION STEP PERFORMED
5195 SOURCE 1:
5196     SEED1:    1772576661    SEED2:          0
5197 Elapsed simulation  time in seconds:    0.16
5198 ESTIMATION STEP OMITTED:          YES
5199 Elapsed finaloutput  time in seconds:    0.29
5200
5201 1
5202 PROBLEM NO.:          1          SUBPROBLEM NO.:          489
5203
5204 SIMULATION STEP PERFORMED
5205 SOURCE 1:
5206     SEED1:    628113950    SEED2:    -1084471884
5207 Elapsed simulation  time in seconds:    0.13
5208 ESTIMATION STEP OMITTED:          YES
5209 Elapsed finaloutput  time in seconds:    0.29
5210
5211 1
5212 PROBLEM NO.:          1          SUBPROBLEM NO.:          490
5213
5214 SIMULATION STEP PERFORMED
5215 SOURCE 1:
5216     SEED1:    428604020    SEED2:          0
5217 Elapsed simulation  time in seconds:    0.15
5218 ESTIMATION STEP OMITTED:          YES
5219 Elapsed finaloutput  time in seconds:    0.29
5220
5221 1
5222 PROBLEM NO.:          1          SUBPROBLEM NO.:          491
5223
5224 SIMULATION STEP PERFORMED
5225 SOURCE 1:
5226     SEED1:    763693168    SEED2:    -1080830765
5227 Elapsed simulation  time in seconds:    0.13
5228 ESTIMATION STEP OMITTED:          YES
5229 Elapsed finaloutput  time in seconds:    0.29

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5230
5231 1
5232 PROBLEM NO.:          1          SUBPROBLEM NO.:          492
5233
5234 SIMULATION STEP PERFORMED
5235 SOURCE 1:
5236     SEED1:      596908683    SEED2:          0
5237 Elapsed simulation time in seconds:      0.13
5238 ESTIMATION STEP OMITTED:          YES
5239 Elapsed finaloutput time in seconds:      0.29
5240
5241 1
5242 PROBLEM NO.:          1          SUBPROBLEM NO.:          493
5243
5244 SIMULATION STEP PERFORMED
5245 SOURCE 1:
5246     SEED1:      1819701917    SEED2:      1056331450
5247 Elapsed simulation time in seconds:      0.14
5248 ESTIMATION STEP OMITTED:          YES
5249 Elapsed finaloutput time in seconds:      0.29
5250
5251 1
5252 PROBLEM NO.:          1          SUBPROBLEM NO.:          494
5253
5254 SIMULATION STEP PERFORMED
5255 SOURCE 1:
5256     SEED1:      702994367    SEED2:          0
5257 Elapsed simulation time in seconds:      0.14
5258 ESTIMATION STEP OMITTED:          YES
5259 Elapsed finaloutput time in seconds:      0.28
5260
5261 1
5262 PROBLEM NO.:          1          SUBPROBLEM NO.:          495
5263
5264 SIMULATION STEP PERFORMED
5265 SOURCE 1:
5266     SEED1:      1308121715    SEED2:      -1079709486
5267 Elapsed simulation time in seconds:      0.17
5268 ESTIMATION STEP OMITTED:          YES
5269 Elapsed finaloutput time in seconds:      0.29
5270
5271 1
5272 PROBLEM NO.:          1          SUBPROBLEM NO.:          496
5273
5274 SIMULATION STEP PERFORMED
5275 SOURCE 1:
5276     SEED1:      593886239    SEED2:          0
5277 Elapsed simulation time in seconds:      0.16
5278 ESTIMATION STEP OMITTED:          YES
5279 Elapsed finaloutput time in seconds:      0.29
5280
5281 1
5282 PROBLEM NO.:          1          SUBPROBLEM NO.:          497
5283
5284 SIMULATION STEP PERFORMED
5285 SOURCE 1:
5286     SEED1:      1383889818    SEED2:      -1088636329
5287 Elapsed simulation time in seconds:      0.14
5288 ESTIMATION STEP OMITTED:          YES
5289 Elapsed finaloutput time in seconds:      0.29
5290
5291 1
5292 PROBLEM NO.:          1          SUBPROBLEM NO.:          498
5293
5294 SIMULATION STEP PERFORMED
5295 SOURCE 1:
5296     SEED1:      796852079    SEED2:          0
5297 Elapsed simulation time in seconds:      0.17

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5298 ESTIMATION STEP OMITTED: YES
5299 Elapsed finaloutput time in seconds: 0.29
5300
5301 1
5302 PROBLEM NO.: 1 SUBPROBLEM NO.: 499
5303
5304 SIMULATION STEP PERFORMED
5305 SOURCE 1:
5306 SEED1: 983626008 SEED2: -1077578941
5307 Elapsed simulation time in seconds: 0.16
5308 ESTIMATION STEP OMITTED: YES
5309 Elapsed finaloutput time in seconds: 0.29
5310
5311 1
5312 PROBLEM NO.: 1 SUBPROBLEM NO.: 500
5313
5314 SIMULATION STEP PERFORMED
5315 SOURCE 1:
5316 SEED1: 1248674442 SEED2: 0
5317 Elapsed simulation time in seconds: 0.15
5318 ESTIMATION STEP OMITTED: YES
5319 Elapsed finaloutput time in seconds: 0.29
5320 #CPUT: Total CPU Time in Seconds, 494.698
5321 Stop Time:
5322 Mon Feb 24 12:33:03 EST 2020
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Repository artifact ID FI-519368.

```
1 # The purpose of this is to plot VPC of the final TGI model
2
3 rm(list=ls())
4
5 library(tidyverse)
6 library(vpc)
7 library(ggplot2)
8 library(lattice)
9 library(gridExtra)
10 library(dplyr)
11 library(GGally)
12 file.type <- "png"
13 library(survival)
14
15 asc<-function(x){as.numeric(as.character(x))}
16 asf<-function(x){as.numeric(as.factor(x))}
17
18
19
20 # ----- Load in the simulation of survival probability
21
22 sim2 <- read.table("simul6",na=".",header=F)
23 names<-c("REP", "ID", "PROT", "TIME",
24         "KL", "KD", "LAM", "TTG", "TR6", "TR8",
25         "BSLD", "DV", "TRT")
26 names(sim2)<-names
27 summary(sim2)
28
29 # create new ID combining REP and ID
30 sim2$NEWID<-paste0(sim2$REP,"-",sim2$ID)
31
32 # calculate change in tumor size from baseline
33 sim2$DSLD<-ifelse(sim2$TIME==0,0,sim2$DV-sim2$BSLD) # ensures we don't calculate it for time0
34 sim2$PSLD<-sim2$DSLD*100/sim2$BSLD
35
36
37 # Flag progressive disease per RECIST 1.1 (20% increase and absolute 5 mm increase)
38 sim2$FLAGPD<-ifelse(sim2$DSLD>=5 & sim2$PSLD>=20,1,0)
39
40
```

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```
41
42 # Get one progressive disease marking per patient per REP (use NEWID)
43 simpd<-aggregate(sim2$FLAGPD,by=list(sim2$NEWID),sum)
44 names(simpd)<-c("NEWID","SUMPD")
45 simpd$PD<-ifelse(simpd$SUMPD>0,1,simpd$SUMPD)
46 simpd2<-simpd %>% select(NEWID,PD)
47
48 # Merge back
49 sim3<-merge(sim2,simpd2,by=c("NEWID"),all.x = T)
50 sim3<-sim3 %>% arrange(REP,ID,TIME)
51
52
53 write.csv(sim3,file="simFlagPD.csv",quote=F,na=".",row.names = F)
54
55
56
57 # Filter out
58 sim4<-sim3 %>% filter(PD==0)
59
60 # Check how many
61 length(unique(sim3$NEWID))
62 # [1] 919500
63 length(unique(sim4$NEWID))
64 # [1] 621488
65 length(unique(sim4$NEWID))*100/length(unique(sim3$NEWID))
66 # [1] 67.58978
67 # About 32% of the simulation was omitted for the progressers
68
69 write.csv(sim4,file="simRemovePD.csv",quote=F,na=".",row.names = F)
70
71
72
73 # Alternatively, include PD before week 12 and remove those after
74 sim5<-sim3 %>% filter(FLAGPD==0 | FLAGPD==1 & TIME<=12)
75 length(unique(sim5$NEWID))*100/length(unique(sim3$NEWID))
76 # [1] 100
77 # Now we keep everyone
78
79 write.csv(sim5,file="simRemovePD2.csv",quote=F,na=".",row.names = F)
```

Repository artifact ID FI-1038459.

```
1 # The purpose of this is to plot VPC of the final TGI model
2
3 rm(list=ls())
4
5
6 library(vpc)
7 library(ggplot2)
8 library(lattice)
9 library(gridExtra)
10 library(dplyr)
11 library(GGally)
12 file.type <- "png"
13 library(survival)
14
15 asc<-function(x){as.numeric(as.character(x))}
16 asf<-function(x){as.numeric(as.factor(x))}
17
18 #####
19 #
20 # Load in data
21 #
22 #####
23
24 # ----- Load in the observed data from the model
25 obs<-read.table("tgi13.fit",na=".",header=T,skip=1)
26
```

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```
27
28 colnames(obs) <- tolower(colnames(obs))
29
30
31 # ----- Load in the simulation of survival probability
32 sim2<-read.csv("simFlagPD.csv",na.strings=".",stringsAsFactors=F, header=T)
33
34
35 # read in the one where we remove PD but still includes all patients
36 simpd1 <- read.csv("simRemovePD2.csv",na.strings=".",stringsAsFactors=F, header=T)
37
38
39
40
41
42 colnames(sim2) <- tolower(colnames(sim2))
43 colnames(simpd1)<-tolower(colnames(simpd1))
44
45
46
47 sim2 <- sim2 %>% dplyr::mutate(id = asc(id))
48 simpd1<-simpd1 %>% dplyr::mutate(id=asc(id))
49
50
51 #####
52 #
53 # Plotting aesthetics
54 #
55 #####
56
57 # make sizes for figures in Latex
58 size<- theme(axis.title.x=element_text(size=20),
59             axis.text.x=element_text(size=20),
60             axis.title.y=element_text(size=20),
61             axis.text.y=element_text(size=20),
62             legend.text=element_text(size=20),
63             legend.title=element_text(size=20),
64             plot.title=element_text(size=20),
65             strip.text.x=element_text(size=20),
66             strip.text.y=element_text(size=20))
67
68 size1<- theme(axis.title.x=element_text(size=28),
69             axis.text.x=element_text(size=24),
70             axis.title.y=element_text(size=28),
71             axis.text.y=element_text(size=24),
72             legend.text=element_text(size=20),
73             legend.title=element_text(size=24),
74             plot.title=element_text(size=28),
75             strip.text.x=element_text(size=24),
76             strip.text.y=element_text(size=24))
77
78 size2<- theme(axis.title.x=element_text(size=18),
79             axis.text.x=element_text(size=14),
80             axis.title.y=element_text(size=18),
81             axis.text.y=element_text(size=14),
82             legend.text=element_text(size=14),
83             legend.title=element_text(size=14),
84             plot.title=element_text(size=18),
85             strip.text.x=element_text(size=14),
86             strip.text.y=element_text(size=14))
87
88 themel <- new_vpc_theme(update = list(
89   obs_color = "grey55",
90   obs_ci_color = "#cc8833" ,
91   obs_alpha = .3,
92   sim_pi_fill = "#aa0000",
93   sim_pi_size = 2
94 ))
```

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```
95
96
97 #####
98 #
99 # Plot full and PD removed vpc
100 #
101 #####
102
103 # -- Plot by treatment group (trt)
104 # rename trt
105 sim2$Treatment<-ifelse(sim2$trt==1,"IFNa",
106                       ifelse(sim2$trt==2,"Sunitinib",
107                             ifelse(sim2$trt==3,"Sorafenib",
108                                   ifelse(sim2$trt==4,"Axitinib","Ave+Axi"))))
109
110 obs$Treatment<-ifelse(obs$trt==1,"IFNa",
111                      ifelse(obs$trt==2,"Sunitinib",
112                            ifelse(obs$trt==3,"Sorafenib",
113                                  ifelse(obs$trt==4,"Axitinib","Ave+Axi"))))
114
115 simpd1$Treatment<-ifelse(simpd1$trt==1,"IFNa",
116                          ifelse(simpd1$trt==2,"Sunitinib",
117                                ifelse(simpd1$trt==3,"Sorafenib",
119                                      ifelse(simpd1$trt==4,"Axitinib","Ave+Axi"))))
118
119
120 # obspdl$Treatment<-ifelse(obspdl$trt==1,"IFNa",
121 #                           ifelse(obspdl$trt==2,"Sunitinib",
122 #                                   ifelse(obspdl$trt==3,"Sorafenib",
123 #                                           ifelse(obspdl$trt==4,"Axitinib","Ave+Axi"))))
124
125
126 ##### Plotting
127
128
129 # Plot together
130 vpc1<-vpc(sim = sim2,
131           obs = obs,                                # supply simulation and observation
132           dataframes
133           obs_cols = list(
134             dv = "dv",                                # these column names are the default,
135             idv = "time"),                            # update these if different.
136           sim_cols = list(
137             dv = "dv",
138             idv = "time"),
139           n_bins = "auto",
140           # bins="density",
141           # bins = # specify bin separators manually
142           #stratify = c("Treatment"),                  # multiple stratifications possible,
143           just supply as vector
144           # bin_sep = FALSE,
145           pi = c(0.05, 0.95),                        # prediction interval simulated data to
146           show
147           ci = c(0.05, 0.95),                        # confidence intervals to show
148           pred_corr = F,                             # perform prediction-correction?
149           show = list(obs_dv = TRUE),                 # plot observations?
150           #facet = "rows",                            # wrap stratifications, or as "row" or "column"
151           #log_y = TRUE,
152           #log_y_min = 0.000001,
153           # ylim = c(0.2,5000),
154           ylab = "SLD (mm)",
155           xlab = "Time (weeks)",
156           vpc_theme = theme1)+
157           scale_x_continuous(limits = c(0,60),breaks = c(0,12,24,36,48,60))+
158           ylim(0,500)+
159           theme_bw()+
160           size
161
162 grid.arrange(vpc1,ncol=1)
```

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```
160
161 dev.print(file="VPCall.png", device=png, width=1000,height=600)
162
163
164 #PD removed
165
166 vpc1pd<-vpc(sim = simpd1,
167             obs = obs,                                # supply simulation and observation
168             dataframes
169             obs_cols = list(
170               dv = "dv",                                # these column names are the default,
171               idv = "time"),                             # update these if different.
172             sim_cols = list(
173               dv = "dv",
174               idv = "time"),
175             n_bins = "auto",
176             # bins="density",
177             # bins = # specify bin separators manually
178             #stratify = c("Treatment"),                  # multiple stratifications possible,
179             just supply as vector
180             # bin_sep = FALSE,
181             pi = c(0.05, 0.95),                          # prediction interval simulated data to
182             show
183             ci = c(0.05, 0.95),                          # confidence intervals to show
184             pred_corr = F,                               # perform prediction-correction?
185             show = list(obs_dv = TRUE),                  # plot observations?
186             #facet = "rows",                             # wrap stratifications, or as "row" or "column"
187             #log_y = TRUE,
188             #log_y_min = 0.000001,
189             # ylim = c(0.2,5000),
190             ylab = "SLD (mm)",
191             xlab = "Time (weeks)",
192             vpc_theme = theme1)+
193             scale_x_continuous(limits = c(0,60),breaks = c(0,12,24,36,48,60))+
194             ylim(0,500)+
195             theme_bw()+
196             size
197
198 grid.arrange(vpc1pd,ncol=1)
199
200 dev.print(file="vpcPDremovedall.png", device=png, width=1000,height=600)
201
202 # Truncate to 24 weeks
203 vpc1a<-vpc(sim = sim2,
204            obs = obs,                                # supply simulation and observation
205            dataframes
206            obs_cols = list(
207              dv = "dv",                                # these column names are the default,
208              idv = "time"),                             # update these if different.
209            sim_cols = list(
210              dv = "dv",
211              idv = "time"),
212            n_bins = "auto",
213            # bins="density",
214            # bins = # specify bin separators manually
215            #stratify = c("Treatment"),                  # multiple stratifications possible,
216            just supply as vector
217            # bin_sep = FALSE,
218            pi = c(0.05, 0.95),                          # prediction interval simulated data to
219            show
220            ci = c(0.05, 0.95),                          # confidence intervals to show
221            pred_corr = F,                               # perform prediction-correction?
222            show = list(obs_dv = TRUE),                  # plot observations?
223            #facet = "rows",                             # wrap stratifications, or as "row" or "column"
224            #log_y = TRUE,
225            #log_y_min = 0.000001,
226            # ylim = c(0.2,5000),
227            ylab = "SLD (mm)",
```

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```

222     xlab = "Time (weeks)",
223     vpc_theme = themel)+
224     scale_x_continuous(limits = c(0,24),breaks = c(0,6,12,18,24))+
225     ylim(0,500)+
226     theme_bw()+
227     size
228
229 grid.arrange(vpc1a,ncol=1)
230
231 dev.print(file="VPCall24weeks.png", device=png, width=1000,height=600)
232
233 # PD remove Truncate to 24 weeks
234 vpc1apd<-vpc(sim = simpd1,
235             obs = obs,                               # supply simulation and observation
236             dataframes
237             obs_cols = list(
238                 dv = "dv",                             # these column names are the default,
239                 idv = "time"),                         # update these if different.
240             sim_cols = list(
241                 dv = "dv",
242                 idv = "time"),
243             n_bins = "auto",
244             # bins="density",
245             # bins = # specify bin separators manually
246             #stratify = c("Treatment"),                 # multiple stratifications possible
247             , just supply as vector
248             # bin_sep = FALSE,
249             pi = c(0.05, 0.95),                         # prediction interval simulated data to
250             show
251             ci = c(0.05, 0.95),                         # confidence intervals to show
252             pred_corr = F,                             # perform prediction-correction?
253             show = list(obs_dv = TRUE),                 # plot observations?
254             #facet = "rows",                           # wrap stratifications, or as "row" or "column"
255             #log_y = TRUE,
256             #log_y_min = 0.000001,
257             # ylim = c(0.2,5000),
258             ylab = "SLD (mm)",
259             xlab = "Time (weeks)",
260             vpc_theme = themel)+
261     scale_x_continuous(limits = c(0,24),breaks = c(0,6,12,18,24))+
262     ylim(0,500)+
263     theme_bw()+
264     size
265
266 grid.arrange(vpc1apd,ncol=1)
267
268 dev.print(file="vpcPDremoveAll124weeks.png", device=png, width=1000,height=600)
269
270 ##### By treatment (in appendix only)
271
272 # Remove PD individual treatments to 24 weeks
273 vpc2t1pd<-vpc(sim = simpd1 %>% filter(trt==1),
274             obs = obs %>% filter(trt==1),             # supply simulation
275             and observation dataframes
276             obs_cols = list(
277                 dv = "dv",                             # these column names are the default,
278                 idv = "time"),                         # update these if different.
279             sim_cols = list(
280                 dv = "dv",
281                 idv = "time"),
282             n_bins = "auto",
283             # bins="density",
284             # bins = # specify bin separators manually
285             #stratify = c("Treatment"),                 # multiple stratifications
286             possible, just supply as vector
287             # bin_sep = FALSE,

```


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```

285         pi = c(0.05, 0.95),                                # prediction interval simulated data to
                show                                           # confidence intervals to show
286         ci = c(0.05, 0.95),                                # perform prediction-correction?
287         pred_corr = F,                                       # plot observations?
288         show = list(obs_dv = TRUE),                           # wrap stratifications, or as "row" or "column"
289         #facet = "rows",
                "
290         #log_y = TRUE,
291         #log_y_min = 0.000001,
292         # ylim = c(0.2,5000),
293         ylab = "SLD (mm)",
294         xlab = "Time (weeks)",
295         vpc_theme = theme1)+
296     scale_x_continuous(limits = c(0,24),breaks = c(0,6,12,18,24))+
297     ylim(0,500)+
298     theme_bw()+
299     labs(title = "IFNa")+
300     size
301
302 vpc2t2pd<-vpc(sim = simpd1 %>% filter(trt==2),
303               obs = obs %>% filter(trt==2),                  # supply simulation
                and observation dataframes
304               obs_cols = list(
305                 dv = "dv",                                     # these column names are the default,
306                 idv = "time"),                                # update these if different.
307               sim_cols = list(
308                 dv = "dv",
309                 idv = "time"),
310               n_bins = "auto",
311               # bins="density",
312               # bins = # specify bin separators manually
313               #stratify = c("Treatment"),                      # multiple stratifications
                possible, just supply as vector
314               # bin_sep = FALSE,
315               pi = c(0.05, 0.95),                             # prediction interval simulated data to
                show
316               ci = c(0.05, 0.95),                             # confidence intervals to show
317               pred_corr = F,                                   # perform prediction-correction?
318               show = list(obs_dv = TRUE),                      # plot observations?
319               #facet = "rows",                                  # wrap stratifications, or as "row" or "column"
                "
320               #log_y = TRUE,
321               #log_y_min = 0.000001,
322               # ylim = c(0.2,5000),
323               ylab = "SLD (mm)",
324               xlab = "Time (weeks)",
325               vpc_theme = theme1)+
326     scale_x_continuous(limits = c(0,24),breaks = c(0,6,12,18,24))+
327     ylim(0,500)+
328     theme_bw()+
329     labs(title = "Sunitinib")+
330     size
331
332 vpc2t3pd<-vpc(sim = simpd1 %>% filter(trt==3),
333               obs = obs %>% filter(trt==3),                  # supply simulation
                and observation dataframes
334               obs_cols = list(
335                 dv = "dv",                                     # these column names are the default,
336                 idv = "time"),                                # update these if different.
337               sim_cols = list(
338                 dv = "dv",
339                 idv = "time"),
340               n_bins = "auto",
341               # bins="density",
342               # bins = # specify bin separators manually
343               #stratify = c("Treatment"),                      # multiple stratifications
                possible, just supply as vector
344               # bin_sep = FALSE,

```

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```

345     pi = c(0.05, 0.95),                                # prediction interval simulated data to
        show                                              # confidence intervals to show
346     ci = c(0.05, 0.95),                                # perform prediction-correction?
347     pred_corr = F,                                     # plot observations?
348     show = list(obs_dv = TRUE),                         # wrap stratifications, or as "row" or "column"
349     #facet = "rows",
        "
350     #log_y = TRUE,
351     #log_y_min = 0.000001,
352     # ylim = c(0.2,5000),
353     ylab = "SLD (mm)",
354     xlab = "Time (weeks)",
355     vpc_theme = theme1)+
356     scale_x_continuous(limits = c(0,24),breaks = c(0,6,12,18,24))+
357     ylim(0,500)+
358     theme_bw()+
359     labs(title = "Sorafenib")+
360     size
361
362 vpc2t4pd<-vpc(sim = simpd1 %>% filter(trt==4),
363     obs = obs %>% filter(trt==4),                        # supply simulation
        and observation dataframes
364     obs_cols = list(
365         dv = "dv",                                       # these column names are the default,
366         idv = "time"),                                  # update these if different.
367     sim_cols = list(
368         dv = "dv",
369         idv = "time"),
370     n_bins = "auto",
371     # bins="density",
372     # bins = # specify bin separators manually
373     #stratify = c("Treatment"),                          # multiple stratifications
        possible, just supply as vector
374     # bin_sep = FALSE,
375     pi = c(0.05, 0.95),                                # prediction interval simulated data to
        show
376     ci = c(0.05, 0.95),                                # confidence intervals to show
377     pred_corr = F,                                     # perform prediction-correction?
378     show = list(obs_dv = TRUE),                         # plot observations?
379     #facet = "rows",
        " # wrap stratifications, or as "row" or "column"
380     #log_y = TRUE,
381     #log_y_min = 0.000001,
382     # ylim = c(0.2,5000),
383     ylab = "SLD (mm)",
384     xlab = "Time (weeks)",
385     vpc_theme = theme1)+
386     scale_x_continuous(limits = c(0,24),breaks = c(0,6,12,18,24))+
387     ylim(0,500)+
388     theme_bw()+
389     labs(title = "Axitinib")+
390     size
391
392 vpc2t5pd<-vpc(sim = simpd1 %>% filter(trt==5),
393     obs = obs %>% filter(trt==5),                        # supply simulation
        and observation dataframes
394     obs_cols = list(
395         dv = "dv",                                       # these column names are the default,
396         idv = "time"),                                  # update these if different.
397     sim_cols = list(
398         dv = "dv",
399         idv = "time"),
400     n_bins = "auto",
401     # bins="density",
402     # bins = # specify bin separators manually
403     #stratify = c("Treatment"),                          # multiple stratifications
        possible, just supply as vector
404     # bin_sep = FALSE,

```

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```

405     pi = c(0.05, 0.95),           # prediction interval simulated data to
        show                        # confidence intervals to show
406     ci = c(0.05, 0.95),           # perform prediction-correction?
407     pred_corr = F,                # plot observations?
408     show = list(obs_dv = TRUE),    # wrap stratifications, or as "row" or "column"
409     #facet = "rows",
        "
410     #log_y = TRUE,
411     #log_y_min = 0.000001,
412     # ylim = c(0.2,5000),
413     ylab = "SLD (mm)",
414     xlab = "Time (weeks)",
415     vpc_theme = theme1)+
416     scale_x_continuous(limits = c(0,24),breaks = c(0,6,12,18,24))+
417     ylim(0,500)+
418     theme_bw()+
419     labs(title = "Avelumab+Axitinib")+
420     size
421
422 grid.arrange(vpc2t1pd,vpc2t2pd,vpc2t3pd,vpc2t4pd,vpc2t5pd,ncol=3)
423
424 dev.print(file="vpcRemovePDtrt24weeks.png", device=png, width=1000,height=600)
425
426
427
428
429 # Remove PD individual treatments
430 vpc2t1pd<-vpc(sim = simpd1 %>% filter(trt==1),
431     obs = obs %>% filter(trt==1),           # supply simulation and
        observation dataframes
432     obs_cols = list(
433         dv = "dv",                         # these column names are the default,
434         idv = "time"),                     # update these if different.
435     sim_cols = list(
436         dv = "dv",
437         idv = "time"),
438     n_bins = "auto",
439     # bins="density",
440     # bins = # specify bin separators manually
441     #stratify = c("Treatment"),             # multiple stratifications possible
        , just supply as vector
442     # bin_sep = FALSE,
443     pi = c(0.05, 0.95),                   # prediction interval simulated data to
        show
444     ci = c(0.05, 0.95),                   # confidence intervals to show
445     pred_corr = F,                         # perform prediction-correction?
446     show = list(obs_dv = TRUE),           # plot observations?
447     #facet = "rows",                       # wrap stratifications, or as "row" or "column"
448     #log_y = TRUE,
449     #log_y_min = 0.000001,
450     # ylim = c(0.2,5000),
451     ylab = "SLD (mm)",
452     xlab = "Time (weeks)",
453     vpc_theme = theme1)+
454     scale_x_continuous(limits = c(0,60),breaks = c(0,12,24,36,48,60))+
455     ylim(0,500)+
456     theme_bw()+
457     labs(title = "IFNa")+
458     size
459
460 vpc2t2pd<-vpc(sim = simpd1 %>% filter(trt==2),
461     obs = obs %>% filter(trt==2),           # supply simulation and
        observation dataframes
462     obs_cols = list(
463         dv = "dv",                         # these column names are the default,
464         idv = "time"),                     # update these if different.
465     sim_cols = list(
466         dv = "dv",

```

```

467     idv = "time"),
468     n_bins = "auto",
469     # bins="density",
470     # bins = # specify bin separators manually
471     #stratify = c("Treatment"), # multiple stratifications possible
472     , just supply as vector
473     # bin_sep = FALSE,
474     pi = c(0.05, 0.95), # prediction interval simulated data to
475     show
476     ci = c(0.05, 0.95), # confidence intervals to show
477     pred_corr = F, # perform prediction-correction?
478     show = list(obs_dv = TRUE), # plot observations?
479     #facet = "rows", # wrap stratifications, or as "row" or "column"
480     #log_y = TRUE,
481     #log_y_min = 0.000001,
482     # ylim = c(0.2,5000),
483     ylab = "SLD (mm)",
484     xlab = "Time (weeks)",
485     vpc_theme = themel)+
486     scale_x_continuous(limits = c(0,60),breaks = c(0,12,24,36,48,60))+
487     ylim(0,500)+
488     theme_bw()+
489     labs(title = "Sunitinib")+
490     size
491
492 vpct3pd<-vpc(sim = simpd1 %>% filter(trt==3),
493     obs = obs %>% filter(trt==3), # supply simulation and
494     observation dataframes
495     obs_cols = list(
496     dv = "dv", # these column names are the default,
497     idv = "time", # update these if different.
498     sim_cols = list(
499     dv = "dv",
500     idv = "time",
501     n_bins = "auto",
502     # bins="density",
503     # bins = # specify bin separators manually
504     #stratify = c("Treatment"), # multiple stratifications possible
505     , just supply as vector
506     # bin_sep = FALSE,
507     pi = c(0.05, 0.95), # prediction interval simulated data to
508     show
509     ci = c(0.05, 0.95), # confidence intervals to show
510     pred_corr = F, # perform prediction-correction?
511     show = list(obs_dv = TRUE), # plot observations?
512     #facet = "rows", # wrap stratifications, or as "row" or "column"
513     #log_y = TRUE,
514     #log_y_min = 0.000001,
515     # ylim = c(0.2,5000),
516     ylab = "SLD (mm)",
517     xlab = "Time (weeks)",
518     vpc_theme = themel)+
519     scale_x_continuous(limits = c(0,60),breaks = c(0,12,24,36,48,60))+
520     ylim(0,500)+
521     theme_bw()+
522     labs(title = "Sorafenib")+
523     size
524
525 vpct4pd<-vpc(sim = simpd1 %>% filter(trt==4),
526     obs = obs %>% filter(trt==4), # supply simulation and
527     observation dataframes
528     obs_cols = list(
529     dv = "dv", # these column names are the default,
530     idv = "time", # update these if different.
531     sim_cols = list(
532     dv = "dv",
533     idv = "time",
534     n_bins = "auto",

```

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```

529         # bins="density",
530         # bins =      # specify bin separators manually
531         #stratify = c("Treatment"),           # multiple stratifications possible
532         , just supply as vector
533         # bin_sep = FALSE,
534         pi = c(0.05, 0.95),                  # prediction interval simulated data to
535         show
536         ci = c(0.05, 0.95),                  # confidence intervals to show
537         pred_corr = F,                       # perform prediction-correction?
538         show = list(obs_dv = TRUE),          # plot observations?
539         #facet = "rows",                    # wrap stratifications, or as "row" or "column"
540         #log_y = TRUE,
541         #log_y_min = 0.000001,
542         # ylim = c(0.2,5000),
543         ylab = "SLD (mm)",
544         xlab = "Time (weeks)",
545         vpc_theme = themel)+
546     scale_x_continuous(limits = c(0,60),breaks = c(0,12,24,36,48,60))+
547     ylim(0,500)+
548     theme_bw()+
549     labs(title = "Axitinib")+
550     size
551 vpct5pd<-vpc(sim = simpd1 %>% filter(trt==5),
552             obs = obs %>% filter(trt==5),          # supply simulation and
553             observation dataframes
554             obs_cols = list(
555                 dv = "dv",                        # these column names are the default,
556                 idv = "time"),                    # update these if different.
557             sim_cols = list(
558                 dv = "dv",
559                 idv = "time"),
560             n_bins = "auto",
561             # bins="density",
562             # bins =      # specify bin separators manually
563             #stratify = c("Treatment"),           # multiple stratifications possible
564             , just supply as vector
565             # bin_sep = FALSE,
566             pi = c(0.05, 0.95),                  # prediction interval simulated data to
567             show
568             ci = c(0.05, 0.95),                  # confidence intervals to show
569             pred_corr = F,                       # perform prediction-correction?
570             show = list(obs_dv = TRUE),          # plot observations?
571             #facet = "rows",                    # wrap stratifications, or as "row" or "column"
572             #log_y = TRUE,
573             #log_y_min = 0.000001,
574             # ylim = c(0.2,5000),
575             ylab = "SLD (mm)",
576             xlab = "Time (weeks)",
577             vpc_theme = themel)+
578     scale_x_continuous(limits = c(0,60),breaks = c(0,12,24,36,48,60))+
579     ylim(0,500)+
580     theme_bw()+
581     labs(title = "Avelumab+Axitinib")+
582     size
583 grid.arrange(vpctl1pd, vpct2pd, vpct3pd, vpct4pd, vpct5pd, ncol=3)
584
585 dev.print(file="vpcRemovePDtrt.png", device=png, width=1000,height=600)
586
587 # ##### These plots below are not used.
588 #
589 # # individual treatments
590 # vpctl1<-vpc(sim = sim2 %>% filter(trt==1),
591             obs = obs %>% filter(trt==1),          # supply simulation
592             and observation dataframes

```

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```

591 #           obs_cols = list(
592 #               dv = "dv",                               # these column names are the default,
593 #               idv = "time"),                             # update these if different.
594 #           sim_cols = list(
595 #               dv = "dv",
596 #               idv = "time"),
597 #           n_bins = "auto",
598 #           # bins="density",
599 #           # bins = # specify bin separators manually
600 #           #stratify = c("Treatment"),                    # multiple stratifications
possible, just supply as vector
601 #           # bin_sep = FALSE,
602 #           pi = c(0.05, 0.95),                            # prediction interval simulated data to
show
603 #           ci = c(0.05, 0.95),                            # confidence intervals to show
604 #           pred_corr = F,                                  # perform prediction-correction?
605 #           show = list(obs_dv = TRUE),                     # plot observations?
606 #           #facet = "rows",                               # wrap stratifications, or as "row" or "
column"
607 #           #log_y = TRUE,
608 #           #log_y_min = 0.000001,
609 #           # ylim = c(0.2, 5000),
610 #           ylab = "SLD (mm)",
611 #           xlab = "Time (weeks)",
612 #           vpc_theme = theme1)+
613 #   scale_x_continuous(limits = c(0, 60), breaks = c(0, 12, 24, 36, 48, 60))+
614 #   ylim(0, 500)+
615 #   theme_bw()+
616 #   labs(title = "IFNa")+
617 #   size
618 #
619 # vpct2<-vpc(sim = sim2 %>% filter(trt==2),
620 #           obs = obs %>% filter(trt==2),                    # supply simulation
and observation dataframes
621 #           obs_cols = list(
622 #               dv = "dv",                               # these column names are the default,
623 #               idv = "time"),                             # update these if different.
624 #           sim_cols = list(
625 #               dv = "dv",
626 #               idv = "time"),
627 #           n_bins = "auto",
628 #           # bins="density",
629 #           # bins = # specify bin separators manually
630 #           #stratify = c("Treatment"),                    # multiple stratifications
possible, just supply as vector
631 #           # bin_sep = FALSE,
632 #           pi = c(0.05, 0.95),                            # prediction interval simulated data to
show
633 #           ci = c(0.05, 0.95),                            # confidence intervals to show
634 #           pred_corr = F,                                  # perform prediction-correction?
635 #           show = list(obs_dv = TRUE),                     # plot observations?
636 #           #facet = "rows",                               # wrap stratifications, or as "row" or "
column"
637 #           #log_y = TRUE,
638 #           #log_y_min = 0.000001,
639 #           # ylim = c(0.2, 5000),
640 #           ylab = "SLD (mm)",
641 #           xlab = "Time (weeks)",
642 #           vpc_theme = theme1)+
643 #   scale_x_continuous(limits = c(0, 60), breaks = c(0, 12, 24, 36, 48, 60))+
644 #   ylim(0, 500)+
645 #   theme_bw()+
646 #   labs(title = "Sunitinib")+
647 #   size
648 #
649 # vpct3<-vpc(sim = sim2 %>% filter(trt==3),
650 #           obs = obs %>% filter(trt==3),                    # supply simulation
and observation dataframes

```

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```

651 #           obs_cols = list(
652 #               dv = "dv",                               # these column names are the default,
653 #               idv = "time"),                             # update these if different.
654 #           sim_cols = list(
655 #               dv = "dv",
656 #               idv = "time"),
657 #           n_bins = "auto",
658 #           # bins="density",
659 #           # bins = # specify bin separators manually
660 #           #stratify = c("Treatment"),                    # multiple stratifications
possible, just supply as vector
661 #           # bin_sep = FALSE,
662 #           pi = c(0.05, 0.95),                            # prediction interval simulated data to
show
663 #           ci = c(0.05, 0.95),                            # confidence intervals to show
664 #           pred_corr = F,                                # perform prediction-correction?
665 #           show = list(obs_dv = TRUE),                    # plot observations?
666 #           #facet = "rows",                              # wrap stratifications, or as "row" or "
column"
667 #           #log_y = TRUE,
668 #           #log_y_min = 0.000001,
669 #           # ylim = c(0.2, 5000),
670 #           ylab = "SLD (mm)",
671 #           xlab = "Time (weeks)",
672 #           vpc_theme = theme1)+
673 #   scale_x_continuous(limits = c(0, 60), breaks = c(0, 12, 24, 36, 48, 60))+
674 #   ylim(0, 500)+
675 #   theme_bw()+
676 #   labs(title = "Sorafenib")+
677 #   size
678 #
679 # vpct4<-vpc(sim = sim2 %>% filter(trt==4),
680 #           obs = obs %>% filter(trt==4),                    # supply simulation
and observation dataframes
681 #           obs_cols = list(
682 #               dv = "dv",                               # these column names are the default,
683 #               idv = "time"),                             # update these if different.
684 #           sim_cols = list(
685 #               dv = "dv",
686 #               idv = "time"),
687 #           n_bins = "auto",
688 #           # bins="density",
689 #           # bins = # specify bin separators manually
690 #           #stratify = c("Treatment"),                    # multiple stratifications
possible, just supply as vector
691 #           # bin_sep = FALSE,
692 #           pi = c(0.05, 0.95),                            # prediction interval simulated data to
show
693 #           ci = c(0.05, 0.95),                            # confidence intervals to show
694 #           pred_corr = F,                                # perform prediction-correction?
695 #           show = list(obs_dv = TRUE),                    # plot observations?
696 #           #facet = "rows",                              # wrap stratifications, or as "row" or "
column"
697 #           #log_y = TRUE,
698 #           #log_y_min = 0.000001,
699 #           # ylim = c(0.2, 5000),
700 #           ylab = "SLD (mm)",
701 #           xlab = "Time (weeks)",
702 #           vpc_theme = theme1)+
703 #   scale_x_continuous(limits = c(0, 60), breaks = c(0, 12, 24, 36, 48, 60))+
704 #   ylim(0, 500)+
705 #   theme_bw()+
706 #   labs(title = "Axitinib")+
707 #   size
708 #
709 # vpct5<-vpc(sim = sim2 %>% filter(trt==5),
710 #           obs = obs %>% filter(trt==5),                    # supply simulation
and observation dataframes

```

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```

711 #           obs_cols = list(
712 #               dv = "dv",                      # these column names are the default,
713 #               idv = "time"),                  # update these if different.
714 #           sim_cols = list(
715 #               dv = "dv",
716 #               idv = "time"),
717 #           n_bins = "auto",
718 #           # bins="density",
719 #           # bins =    # specify bin separators manually
720 #           #stratify = c("Treatment"),          # multiple stratifications
possible, just supply as vector
721 #           # bin_sep = FALSE,
722 #           pi = c(0.05, 0.95),                # prediction interval simulated data to
show
723 #           ci = c(0.05, 0.95),                # confidence intervals to show
724 #           pred_corr = F,                     # perform prediction-correction?
725 #           show = list(obs_dv = TRUE),        # plot observations?
726 #           #facet = "rows",                  # wrap stratifications, or as "row" or "
column"
727 #           #log_y = TRUE,
728 #           #log_y_min = 0.000001,
729 #           # ylim = c(0.2,5000),
730 #           ylab = "SLD (mm)",
731 #           xlab = "Time (weeks)",
732 #           vpc_theme = themel)+
733 #   scale_x_continuous(limits = c(0,60),breaks = c(0,12,24,36,48,60))+
734 #   ylim(0,500)+
735 #   theme_bw()+
736 #   labs(title = "Avelumab+Axitinib")+
737 #   size
738 #
739 # grid.arrange(vpct1, vpct2, vpct3, vpct4, vpct5, ncol=3)
740 #
741 # dev.print(file="VPCtrt.png", device=png, width=1000,height=600)
742 #
743 #
744 # # individual treatments to 24 weeks
745 # vpc2t1<-vpc(sim = sim2 %>% filter(trt==1),
746 #             obs = obs %>% filter(trt==1),          # supply simulation
and observation dataframes
747 #             obs_cols = list(
748 #                 dv = "dv",                      # these column names are the default,
749 #                 idv = "time"),                  # update these if different.
750 #             sim_cols = list(
751 #                 dv = "dv",
752 #                 idv = "time"),
753 #             n_bins = "auto",
754 #             # bins="density",
755 #             # bins =    # specify bin separators manually
756 #             #stratify = c("Treatment"),          # multiple stratifications
possible, just supply as vector
757 #             # bin_sep = FALSE,
758 #             pi = c(0.05, 0.95),                # prediction interval simulated data to
show
759 #             ci = c(0.05, 0.95),                # confidence intervals to show
760 #             pred_corr = F,                     # perform prediction-correction?
761 #             show = list(obs_dv = TRUE),        # plot observations?
762 #             #facet = "rows",                  # wrap stratifications, or as "row" or "
column"
763 #             #log_y = TRUE,
764 #             #log_y_min = 0.000001,
765 #             # ylim = c(0.2,5000),
766 #             ylab = "SLD (mm)",
767 #             xlab = "Time (weeks)",
768 #             vpc_theme = themel)+
769 #   scale_x_continuous(limits = c(0,24),breaks = c(0,6,12,18,24))+
770 #   ylim(0,500)+
771 #   theme_bw()+

```


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```

772 #   geom_line(data=curv1, aes(x=time, y=pr), linetype='dashed')+
773 #   labs(title = "IFNa")+
774 #   size
775 #
776 # vpc2t2<-vpc(sim = sim2 %>% filter(trt==2),
777 #             obs = obs %>% filter(trt==2),           # supply simulation
778 #             and observation dataframes
779 #             obs_cols = list(
780 #               dv = "dv",                               # these column names are the default,
781 #               idv = "time"),                           # update these if different.
782 #             sim_cols = list(
783 #               dv = "dv",
784 #               idv = "time"),
785 #             n_bins = "auto",
786 #             # bins="density",
787 #             # bins =    # specify bin separators manually
788 #             #stratify = c("Treatment"),                # multiple stratifications
789 #             possible, just supply as vector
790 #             # bin_sep = FALSE,
791 #             pi = c(0.05, 0.95),                        # prediction interval simulated data to
792 #             show
793 #             ci = c(0.05, 0.95),                        # confidence intervals to show
794 #             pred_corr = F,                             # perform prediction-correction?
795 #             show = list(obs_dv = TRUE),                # plot observations?
796 #             #facet = "rows",                          # wrap stratifications, or as "row" or "
797 #             column"
798 #             #log_y = TRUE,
799 #             #log_y_min = 0.000001,
800 #             # ylim = c(0.2,5000),
801 #             ylab = "SLD (mm)",
802 #             xlab = "Time (weeks)",
803 #             vpc_theme = themel)+
804 #   scale_x_continuous(limits = c(0,24),breaks = c(0,6,12,18,24))+
805 #   ylim(0,500)+
806 #   theme_bw()+
807 #   geom_line(data=curv2, aes(x=time, y=pr), linetype='dashed')+
808 #   labs(title = "Sunitinib")+
809 #   size
810 #
811 # vpc2t3<-vpc(sim = sim2 %>% filter(trt==3),
812 #             obs = obs %>% filter(trt==3),           # supply simulation
813 #             and observation dataframes
814 #             obs_cols = list(
815 #               dv = "dv",                               # these column names are the default,
816 #               idv = "time"),                           # update these if different.
817 #             sim_cols = list(
818 #               dv = "dv",
819 #               idv = "time"),
820 #             n_bins = "auto",
821 #             # bins="density",
822 #             # bins =    # specify bin separators manually
823 #             #stratify = c("Treatment"),                # multiple stratifications
824 #             possible, just supply as vector
825 #             # bin_sep = FALSE,
826 #             pi = c(0.05, 0.95),                        # prediction interval simulated data to
827 #             show
828 #             ci = c(0.05, 0.95),                        # confidence intervals to show
829 #             pred_corr = F,                             # perform prediction-correction?
830 #             show = list(obs_dv = TRUE),                # plot observations?
831 #             #facet = "rows",                          # wrap stratifications, or as "row" or "
832 #             column"
833 #             #log_y = TRUE,
834 #             #log_y_min = 0.000001,
835 #             # ylim = c(0.2,5000),
836 #             ylab = "SLD (mm)",
837 #             xlab = "Time (weeks)",
838 #             vpc_theme = themel)+
839 #   scale_x_continuous(limits = c(0,24),breaks = c(0,6,12,18,24))+

```

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```

832 #   ylim(0,500)+
833 #   theme_bw()+
834 #   geom_line(data=curv3, aes(x=time, y=pr), linetype='dashed')+
835 #   labs(title = "Sorafenib")+
836 #   size
837 #
838 # vpc2t4<-vpc(sim = sim2 %>% filter(trt==4),
839 #             obs = obs %>% filter(trt==4),           # supply simulation
840 #             and observation dataframes
841 #             obs_cols = list(
842 #               dv = "dv",           # these column names are the default,
843 #               idv = "time"),       # update these if different.
844 #             sim_cols = list(
845 #               dv = "dv",
846 #               idv = "time"),
847 #             n_bins = "auto",
848 #             # bins="density",
849 #             # bins = # specify bin separators manually
850 #             #stratify = c("Treatment"),           # multiple stratifications
851 #             possible, just supply as vector
852 #             # bin_sep = FALSE,
853 #             pi = c(0.05, 0.95),           # prediction interval simulated data to
854 #             show
855 #             ci = c(0.05, 0.95),           # confidence intervals to show
856 #             pred_corr = F,               # perform prediction-correction?
857 #             show = list(obs_dv = TRUE),   # plot observations?
858 #             #facet = "rows",             # wrap stratifications, or as "row" or "
859 #             column"
860 #             #log_y = TRUE,
861 #             #log_y_min = 0.000001,
862 #             # ylim = c(0.2,5000),
863 #             ylab = "SLD (mm)",
864 #             xlab = "Time (weeks)",
865 #             vpc_theme = theme1)+
866 #   scale_x_continuous(limits = c(0,24),breaks = c(0,6,12,18,24))+
867 #   ylim(0,500)+
868 #   theme_bw()+
869 #   geom_line(data=curv4, aes(x=time, y=pr), linetype='dashed')+
870 #   labs(title = "Axitinib")+
871 #   size
872 #
873 # vpc2t5<-vpc(sim = sim2 %>% filter(trt==5),
874 #             obs = obs %>% filter(trt==5),           # supply simulation
875 #             and observation dataframes
876 #             obs_cols = list(
877 #               dv = "dv",           # these column names are the default,
878 #               idv = "time"),       # update these if different.
879 #             sim_cols = list(
880 #               dv = "dv",
881 #               idv = "time"),
882 #             n_bins = "auto",
883 #             # bins="density",
884 #             # bins = # specify bin separators manually
885 #             #stratify = c("Treatment"),           # multiple stratifications
886 #             possible, just supply as vector
887 #             # bin_sep = FALSE,
888 #             pi = c(0.05, 0.95),           # prediction interval simulated data to
889 #             show
890 #             ci = c(0.05, 0.95),           # confidence intervals to show
891 #             pred_corr = F,               # perform prediction-correction?
892 #             show = list(obs_dv = TRUE),   # plot observations?
893 #             #facet = "rows",             # wrap stratifications, or as "row" or "
894 #             column"
895 #             #log_y = TRUE,
896 #             #log_y_min = 0.000001,
897 #             # ylim = c(0.2,5000),
898 #             ylab = "SLD (mm)",
899 #             xlab = "Time (weeks)",

```

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```
892 #         vpc_theme = theme1)+  
893 #   scale_x_continuous(limits = c(0,24),breaks = c(0,6,12,18,24))+  
894 #   ylim(0,500)+  
895 #   theme_bw()+  
896 #   geom_line(data=curv5, aes(x=time, y=pr), linetype='dashed')+  
897 #   labs(title = "Avelumab+Axitinib")+  
898 #   size  
899 #  
900 # grid.arrange(vpc2t1,vpc2t2,vpc2t3,vpc2t4,vpc2t5,ncol=3)  
901 #  
902 # dev.print(file="VPCtrt24weeks.png", device=png, width=1000,height=600)  
903 #  
904 #  
905 #
```

Repository artifact ID FI-519241.

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Appendix 9. Additional Documentation

LIST OF ARTIFACTS

ARTIFACT	VERSION ID	FILENAME	UPDATE (GMT)
CP1:FI-432749	CP1:FI-432749-4	Run2.R	2019-Nov-07 10:23:24
CP1:FI-640386	CP1:FI-640386-7	PMARSLDchangesbyStudy.png	2020-Jul-17 15:45:32
CP1:FI-3035962	CP1:FI-3035962-2	TGImetricsCompare.csv	2020-Feb-24 17:12:27
CP1:FI-2009063	CP1:FI-2009063-5	finalmodel.csv	2020-Jan-29 16:38:17
CP1:FI-3035963	CP1:FI-3035963-2	TGIpametersCompare.csv	2020-Feb-24 17:12:27
CP1:FI-2191381	CP1:FI-2191381-7	Metrics_byBSLDQ.png	2020-Aug-18 10:49:57
eph:RA10962791	eph:RAV20482232	runlatex.sh	2016-Mar-25 08:35:54
CP1:FI-2128549	CP1:FI-2128549-6	ttpsum.csv	2020-Aug-18 10:49:57
CP1:FI-651640	CP1:FI-651640-5	BaseModelresults.csv	2020-Feb-24 15:58:10
CP1:FI-637819	CP1:FI-637819-1	B9991003_PD_2_Programming_Plan.pdf	2019-Nov-13 13:18:30
CP1:FI-637818	CP1:FI-637818-1	B9991002_PD_2_Programming_Plan.pdf	2019-Nov-13 13:18:30
CP1:FI-637817	CP1:FI-637817-1	A6181034_PD_2_Programming_Plan.pdf	2019-Nov-13 13:18:30
CP1:FI-10120735	CP1:FI-10120735-1	SummaryTumorMetrics.csv	2020-Aug-13 13:45:46
CP1:FI-482733	CP1:FI-482733-4	BSLD_ETA.png	2020-Aug-13 13:45:46
CP1:FI-482734	CP1:FI-482734-4	DV_Pop-Predictions.png	2020-Aug-13 13:45:46
CP1:FI-2128550	CP1:FI-2128550-6	ttrsum.csv	2020-Aug-18 10:49:57
CP1:FI-482536	CP1:FI-482536-2	run13.lst	2020-Feb-24 13:19:46
CP1:FI-637816	CP1:FI-637816-1	A4061051_PD_2_Programming_Plan.pdf	2019-Nov-13 13:18:30
CP1:FI-482257	CP1:FI-482257-1	scm.conf	2019-Nov-07 16:43:25
eph:RA16910626	eph:RA16910626-8	PfizerReport.cls	2020-May-02 20:49:20
eph:RA10686674	eph:RAV19937070	pmx.bst	2016-Jan-21 05:27:12
eph:RA10686675	eph:RAV23314076	global-glossary.tex	2017-Feb-02 15:27:53
CP1:FI-482736	CP1:FI-482736-4	ETA_Histogram.png	2020-Aug-13 13:45:46
eph:RA10686673	eph:RAV19526015	logo.png	2015-Nov-09 13:20:29
CP1:FI-482738	CP1:FI-482738-4	individual plots.pdf	2020-Aug-13 13:45:46
CP1:FI-2009670	CP1:FI-2009670-5	HistogramTimeNumSLD.png	2020-Jul-17 15:45:32
CP1:FI-481251	CP1:FI-481251-5	RunPPR	2020-Aug-13 13:45:46
CP1:FI-651697	CP1:FI-651697-6	BSLDhistogram.png	2020-Jul-17 15:45:32
CP1:FI-2097928	CP1:FI-2097928-3	summarySLDObsTime.csv	2020-Jul-17 15:45:32
CP1:FI-482743	CP1:FI-482743-4	RES_pred.png	2020-Aug-13 13:45:46
CP1:FI-482746	CP1:FI-482746-4	TTG_byTRT.png	2020-Aug-13 13:45:46
CP1:FI-482745	CP1:FI-482745-4	TRT_ETA.png	2020-Aug-13 13:45:46
CP1:FI-482742	CP1:FI-482742-4	RES_logtime.png	2020-Aug-13 13:45:46
CP1:FI-1038459	CP1:FI-1038459-5	rmvpd.R	2019-Nov-20 18:14:13
CP1:FI-482747	CP1:FI-482747-4	TumorRatio_byTRT.png	2020-Aug-13 13:45:46
CP1:FI-2129857	CP1:FI-2129857-2	FinModelComparison.csv	2020-Feb-24 17:07:00
CP1:FI-9442131	CP1:FI-9442131-2	summaryPSLD.csv	2020-Jul-17 15:45:32
CP1:FI-434982	CP1:FI-434982-2	run8.lst	2020-Feb-24 13:14:21
CP1:FI-766606	CP1:FI-766606-3	ETAHistogram.png	2020-Jul-17 15:59:06
CP1:FI-482270	CP1:FI-482270-1	scmlog.txt	2019-Nov-07 16:43:25
CP1:FI-766609	CP1:FI-766609-3	RESlogtime.png	2020-Jul-17 15:59:06
CP1:FI-9451084	CP1:FI-9451084-1	PROTETA.png	2020-Jul-17 15:59:06
CP1:FI-766604	CP1:FI-766604-3	DVPopPredictions.png	2020-Jul-17 15:59:06
CP1:FI-766603	CP1:FI-766603-3	BSLDETA.png	2020-Jul-17 15:59:06
CP1:FI-639243	CP1:FI-639243-9	summaryBSLD.csv	2020-Jul-17 15:45:32
CP1:FI-1137284	CP1:FI-1137284-3	VPCall.png	2020-Jul-27 17:49:20
CP1:FI-432756	CP1:FI-432756-3	Run3.R	2019-Nov-07 10:27:21
CP1:FI-1137288	CP1:FI-1137288-2	vpcRemovePDtrt.png	2020-Jul-27 17:49:20
CP1:FI-1137287	CP1:FI-1137287-3	vpcPDremovedall.png	2020-Jul-27 17:49:20
CP1:FI-519368	CP1:FI-519368-5	run18.lst	2020-Feb-24 12:49:54
CP1:FI-766610	CP1:FI-766610-3	RESpred.png	2020-Jul-17 15:59:06
CP1:FI-519241	CP1:FI-519241-6	vpc.R	2020-Jul-27 17:49:20
CP1:FI-766612	CP1:FI-766612-3	TRTETA.png	2020-Jul-17 15:59:06

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Avelumab, Axitinib, Sunitinib
ASR-EQDD-B999e-Other-994

ARTIFACT	VERSION ID	FILENAME	UPDATE (GMT)
eph:RA16374921	eph:RAV30687466	PMAP-EQDD-B999e-Other-994.pdf	2019-Oct-02 18:47:56