Summary of TMB runs

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24/05/2021

```
source("../2_inference_TMB/helper_TMB.R")
source("../../../CDA_in_Cancer/code/functions/meretricious/pretty_plots/prettySignatures.R")
```

```
## Loading required package: coda
```

```
## Loading required package: MASS
```

```
## Warning in .recacheSubclasses(def@className, def, env): undefined subclass
## "numericVector" of class "Mnumeric"; definition not updated
```

```
## ##
## ## Markov Chain Monte Carlo Package (MCMCpack)
```

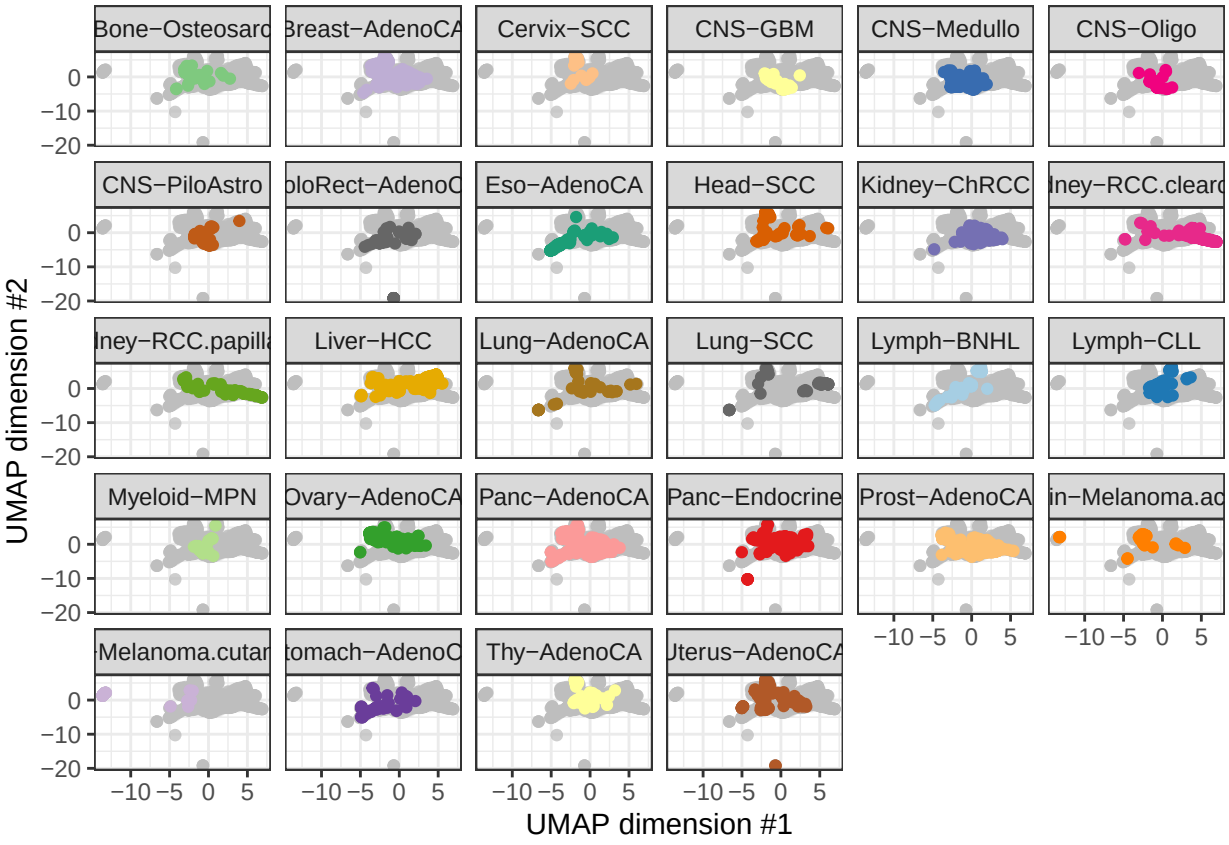
```
## ## Copyright (C) 2003-2021 Andrew D. Martin, Kevin M. Quinn, and Jong Hee Park
```

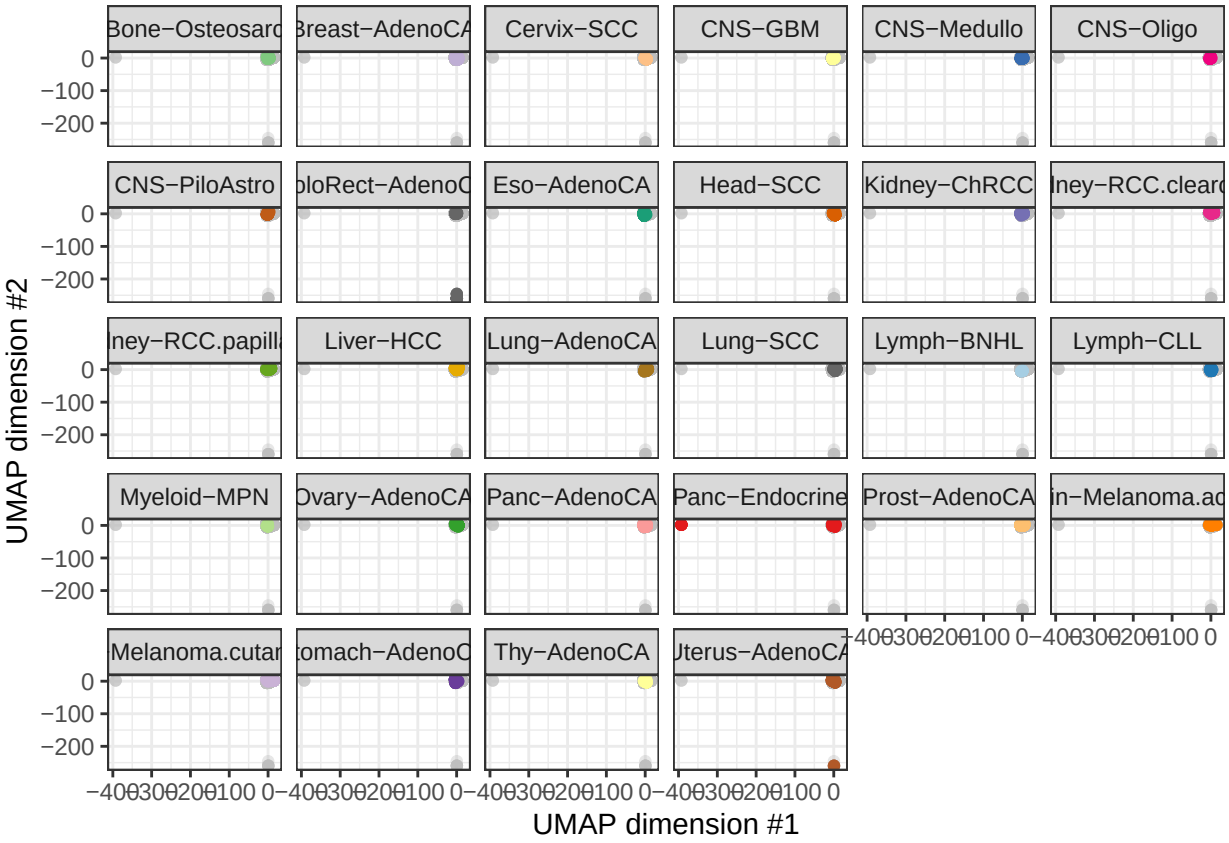
```
## ##
## ## Support provided by the U.S. National Science Foundation
```

```
## ## (Grants SES-0350646 and SES-0350613)
## ##
```

```
## Error in slot(i, "count_matrices_all") :
##   cannot get a slot ("count_matrices_all") from an object of type "logical"
```

```
## Error in slot(i, "count_matrices_all") :
##   cannot get a slot ("count_matrices_all") from an object of type "logical"
```


Bone−Osteosarc
Breast−AdenoCA
Cervix−SCC
CNS−GBM
CNS−Medullo
CNS−Oligo
CNS−PiloAstro
oloRect−AdenoC
Eso−AdenoCA
Head−SCC
Kidney−ChRCC
ney−RCC.clearc
ney−RCC.papill
Liver−HCC
Lung−AdenoCA
Lung−SCC
Lymph−BNHL
Lymph−CLL
Myeloid−MPN
Ovary−AdenoCA
Panc−AdenoCA
Panc−Endocrine
Prost−AdenoCA
in−Melanoma.ac
Melanoma.cutar
tomach−AdenoC
Thy−AdenoCA
Uterus−AdenoCA
UMAP dimension #2
UMAP dimension #1
0
−10
−20
−10 −5 0 5



Contents

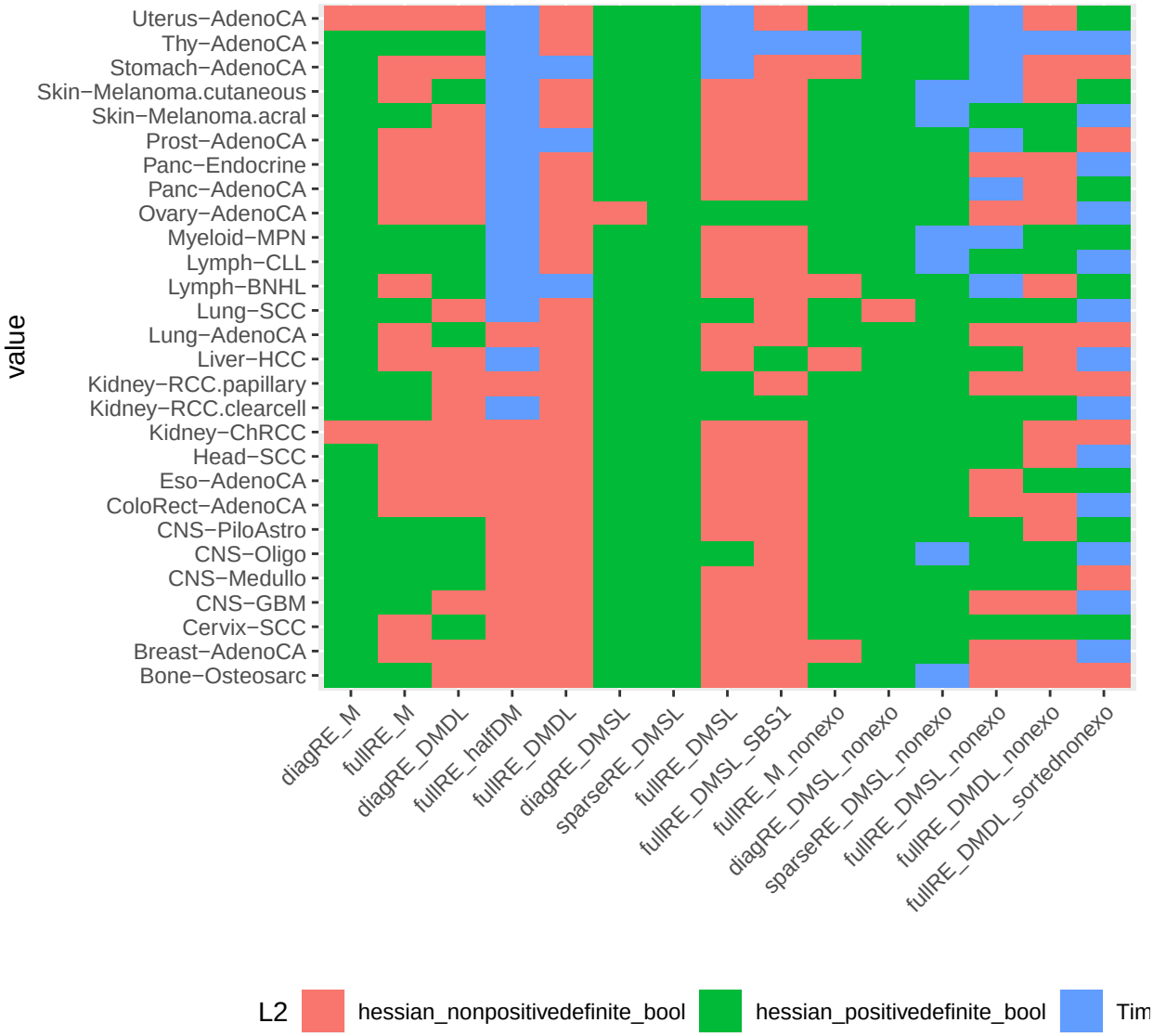
Information about models

Default order of categories for each model

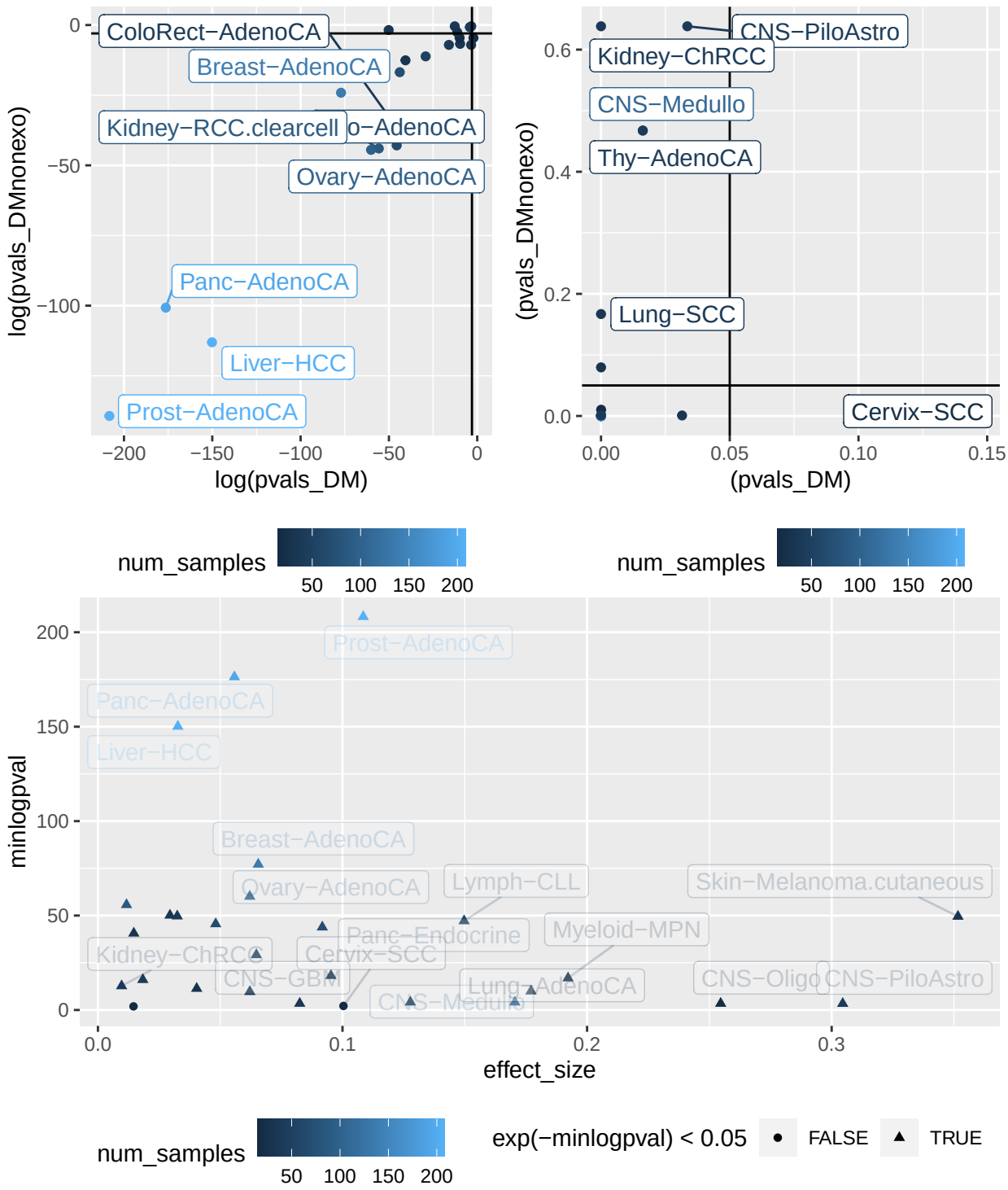
Name model	Extension	Sorted	File in which they were created
fullREDMsinglelambda	fullRE_DMSL_	Not sorted	run_TMB_PCAWG.R
fullREDMsinglelambda2	fullRE_DMSL2_	Sorted	run_TMB_PCAWG.R
diagREDMsinglelambda	diagRE_DMSL_	Unknown	run_TMB_PCAWG.R
fullRE_M	fullRE_M_	Sorted in previous version of wrapper_run_TMB	run_TMB_PCAWG.R
diagRE_DM	diagRE_DM_	Sorted in previous version of wrapper_run_TMB	run_TMB_PCAWG.R
fullRE_DM	fullRE_DM_	Sorted in previous version of wrapper_run_TMB	run_TMB_PCAWG.R
sparseRE_DMSL2	sparseRE_nonexo_DMSL_	Sorted	find_subset_signatures.R
fullREDMsinglelambda	fullRE_nonexo_DMSL_	Not sorted	find_subset_signatures.R
fullRE_M	fullRE_nonexo_M_	Not sorted	find_subset_signatures.R
diagREDMsinglelambda	diagRE_nonexo_DMSL_	Not sorted	find_subset_signatures.R
fullRE_DM	fullLRE_nonexo_DM_	Not sorted	find_subset_signatures.R
diagREDMsinglelambda	diagRE_DMSL_	Not sorted	find_subset_signatures.R

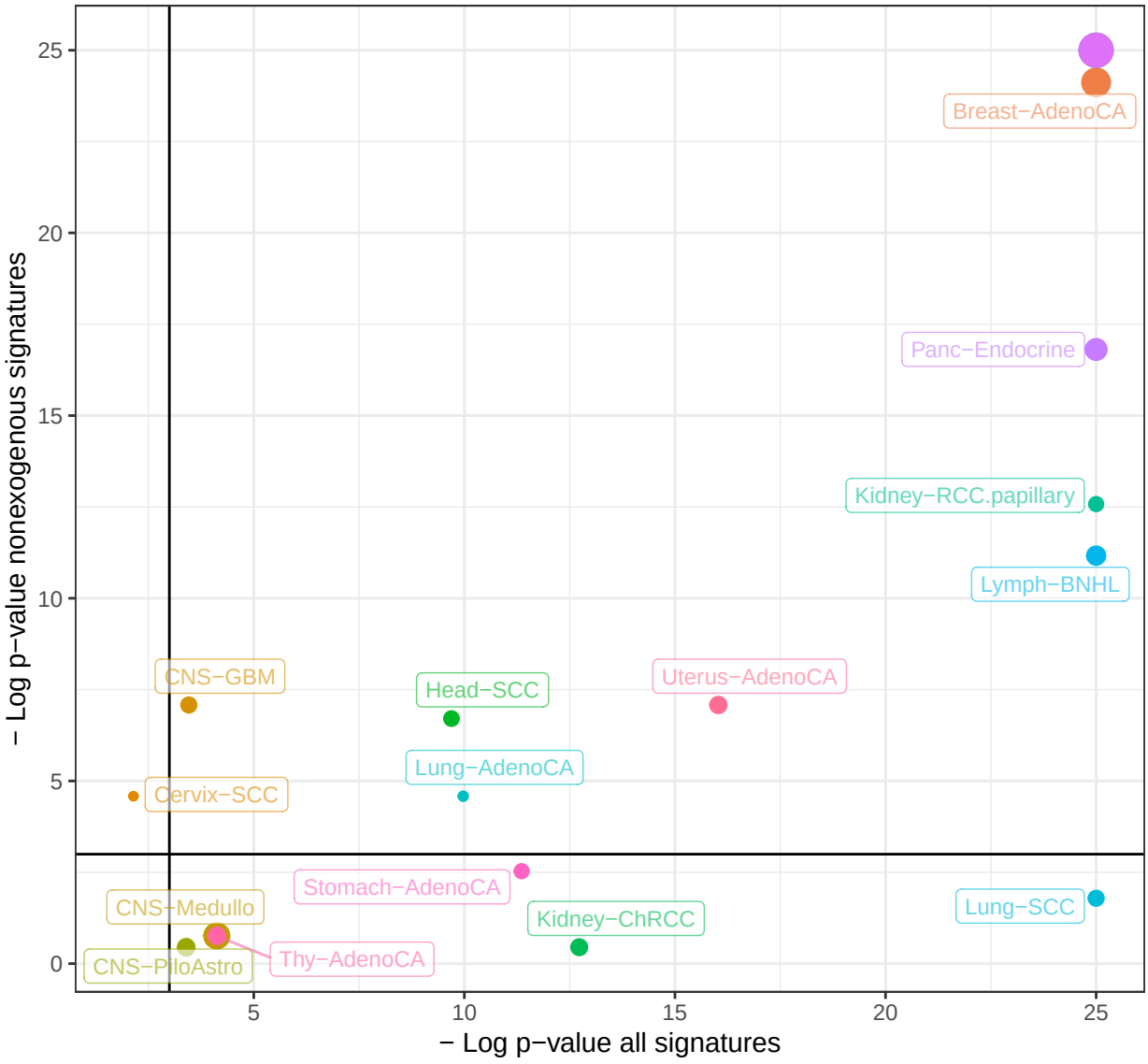
General results of all models

Check the results of all of the models



P-values for all cancer types

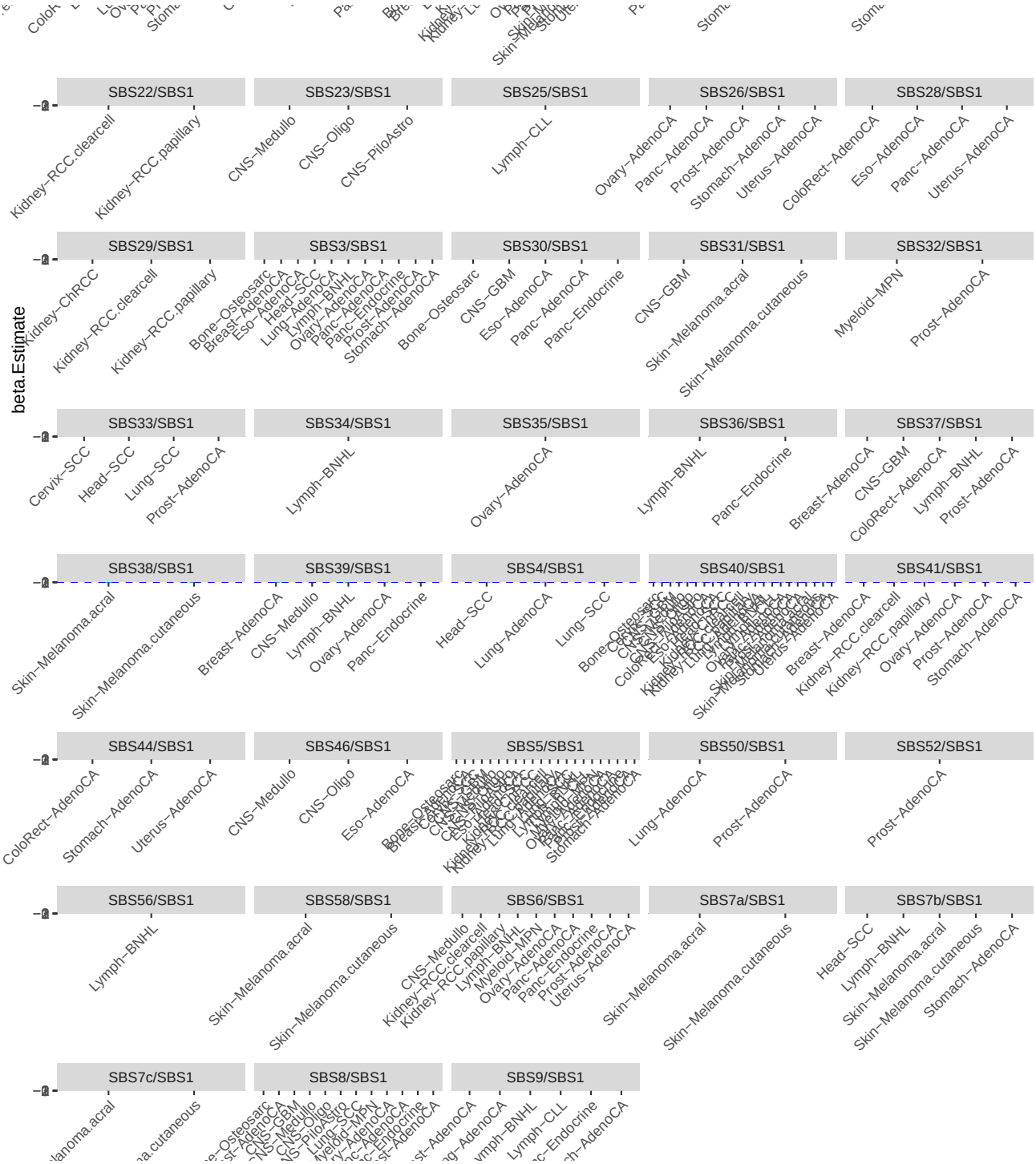


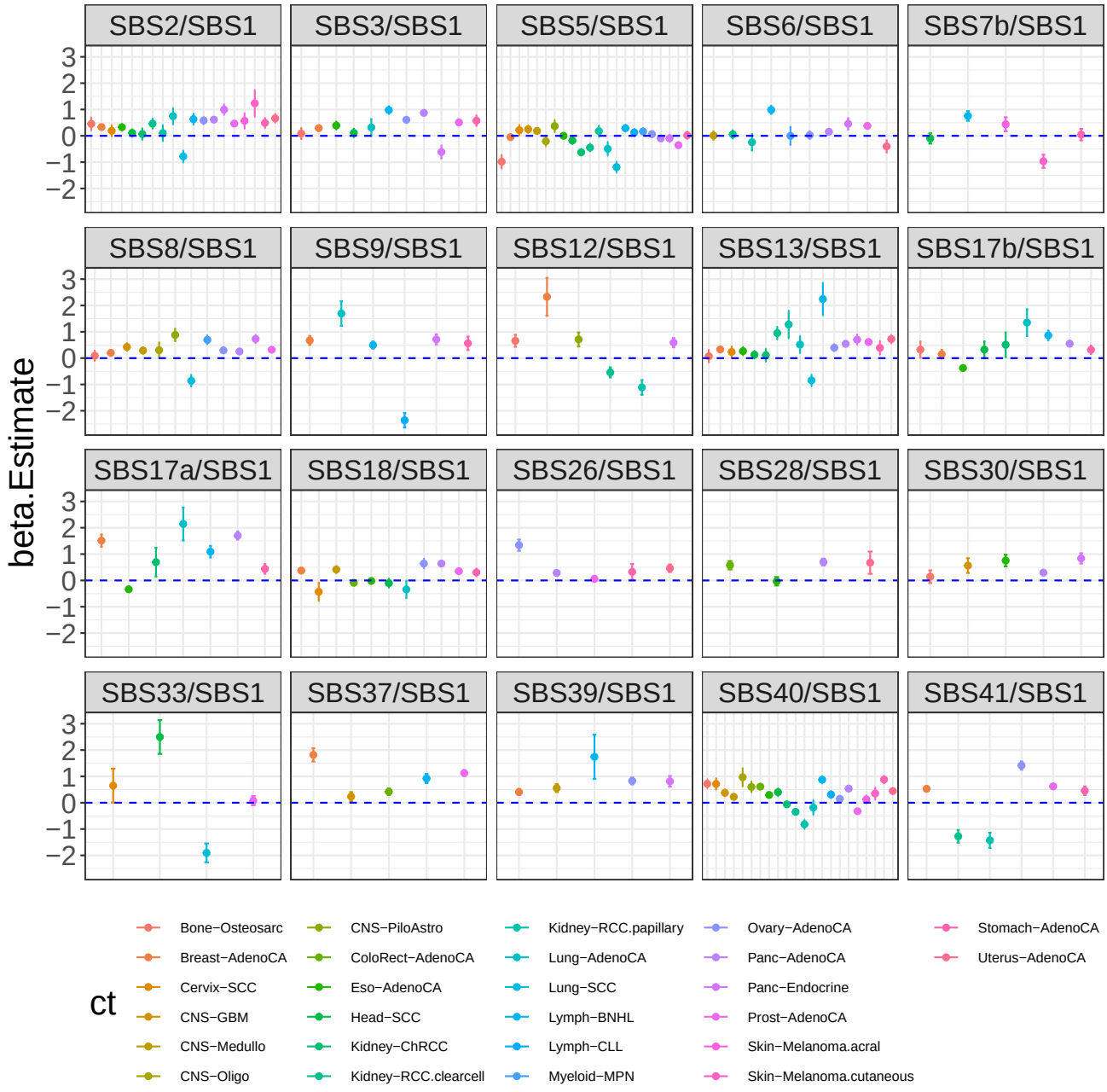


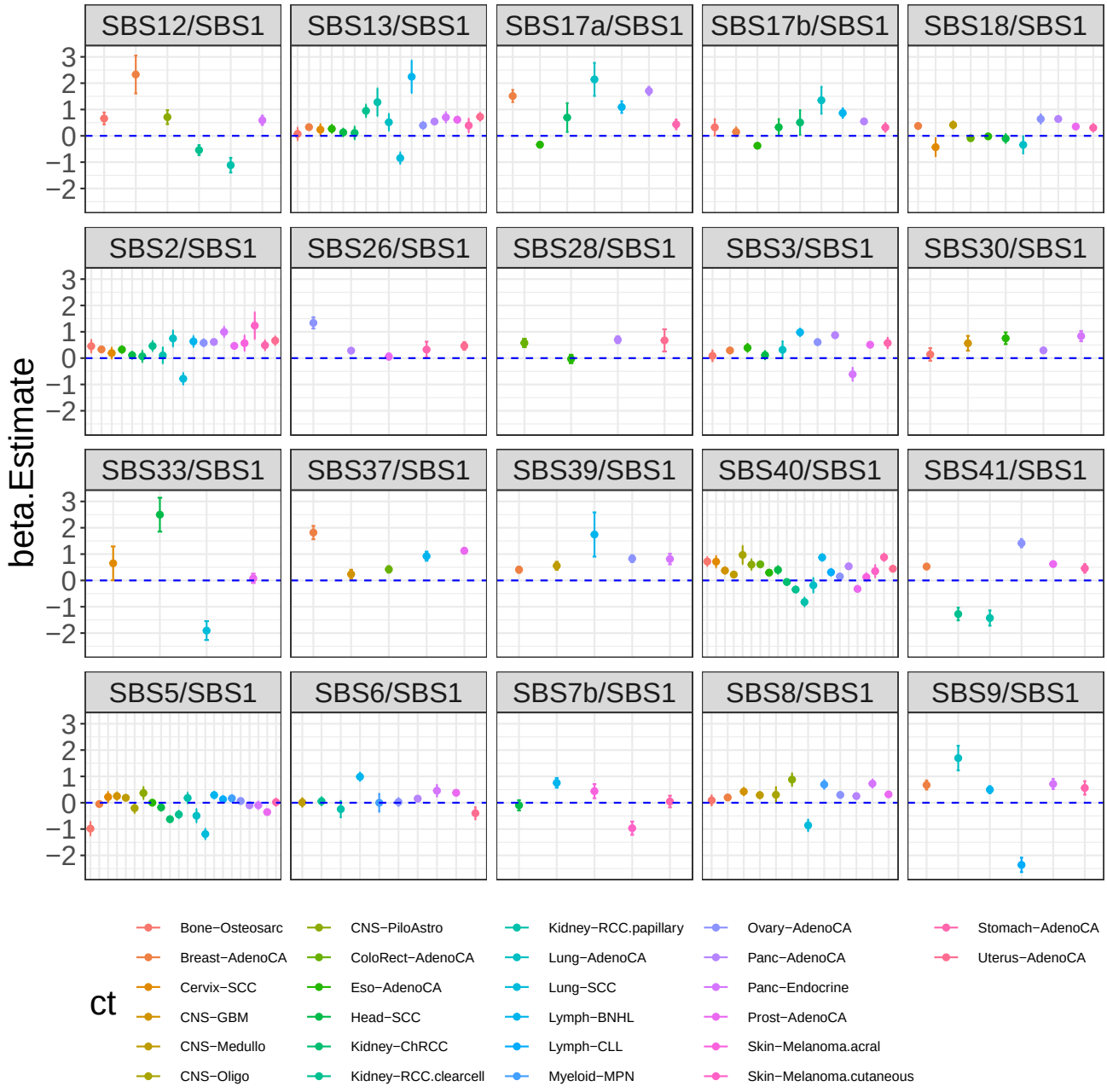
ct

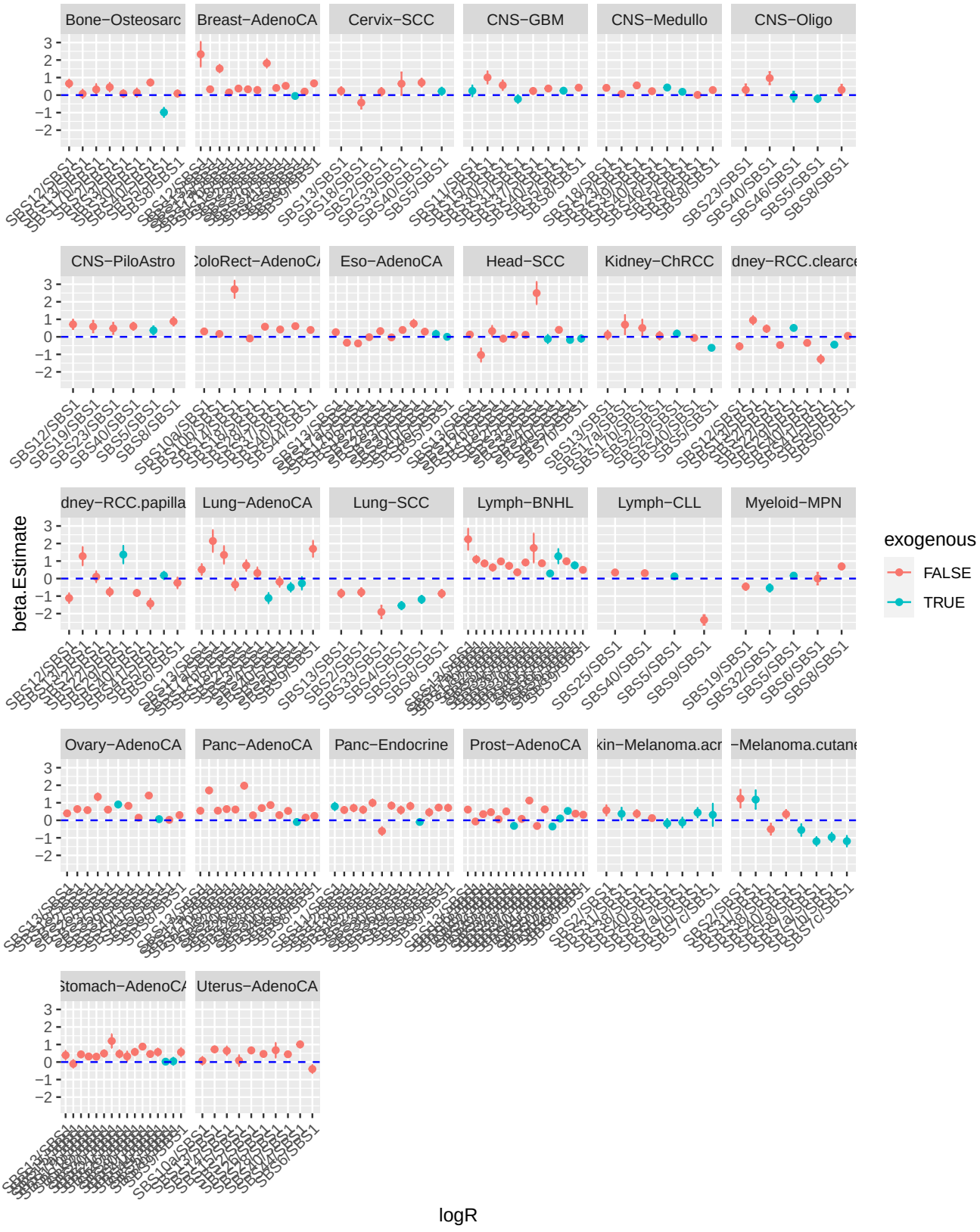
Bone−Osteosarc	ColoRect−AdenoCA	Lung−AdenoCA	Panc−Endocrine
Breast−AdenoCA	Eso−AdenoCA	Lung−SCC	Prost−AdenoCA
Cervix−SCC	Head−SCC	Lymph−BNHL	Skin−Melanoma.acral
CNS−GBM	Kidney−ChRCC	Lymph−CLL	Skin−Melanoma.cutaneous
CNS−Medullo	Kidney−RCC.clearcell	Myeloid−MPN	Stomach−AdenoCA
CNS−Oligo	Kidney−RCC.papillary	Ovary−AdenoCA	Thy−AdenoCA
CNS−PiloAstro	Liver−HCC	Panc−AdenoCA	Uterus−AdenoCA

All betas with SBS1 as baseline




SBS2/SBS1
SBS3/SBS1
SBS5/SBS1
SBS6/SBS1
SBS7b/SBS1
SBS8/SBS1
SBS9/SBS1
SBS12/SBS1
SBS13/SBS1
SBS17b/SBS1
SBS17a/SBS1
SBS18/SBS1
SBS26/SBS1
SBS28/SBS1
SBS30/SBS1
SBS33/SBS1
SBS37/SBS1
SBS39/SBS1
SBS40/SBS1
SBS41/SBS1
beta.Estimate
3
2
1
0
−1
−2
ct
Bone−Osteosarc
Breast−AdenoCA
Cervix−SCC
CNS−GBM
CNS−Medullo
CNS−Oligo
CNS−PiloAstro
ColoRect−AdenoCA
Eso−AdenoCA
Head−SCC
Kidney−ChRCC
Kidney−RCC.clearcell
Kidney−RCC.papillary
Lung−AdenoCA
Lung−SCC
Lymph−BNHL
Lymph−CLL
Myeloid−MPN
Ovary−AdenoCA
Panc−AdenoCA
Panc−Endocrine
Prost−AdenoCA
Skin−Melanoma.acral
Skin−Melanoma.cutaneous
Stomach−AdenoCA
Uterus−AdenoCA

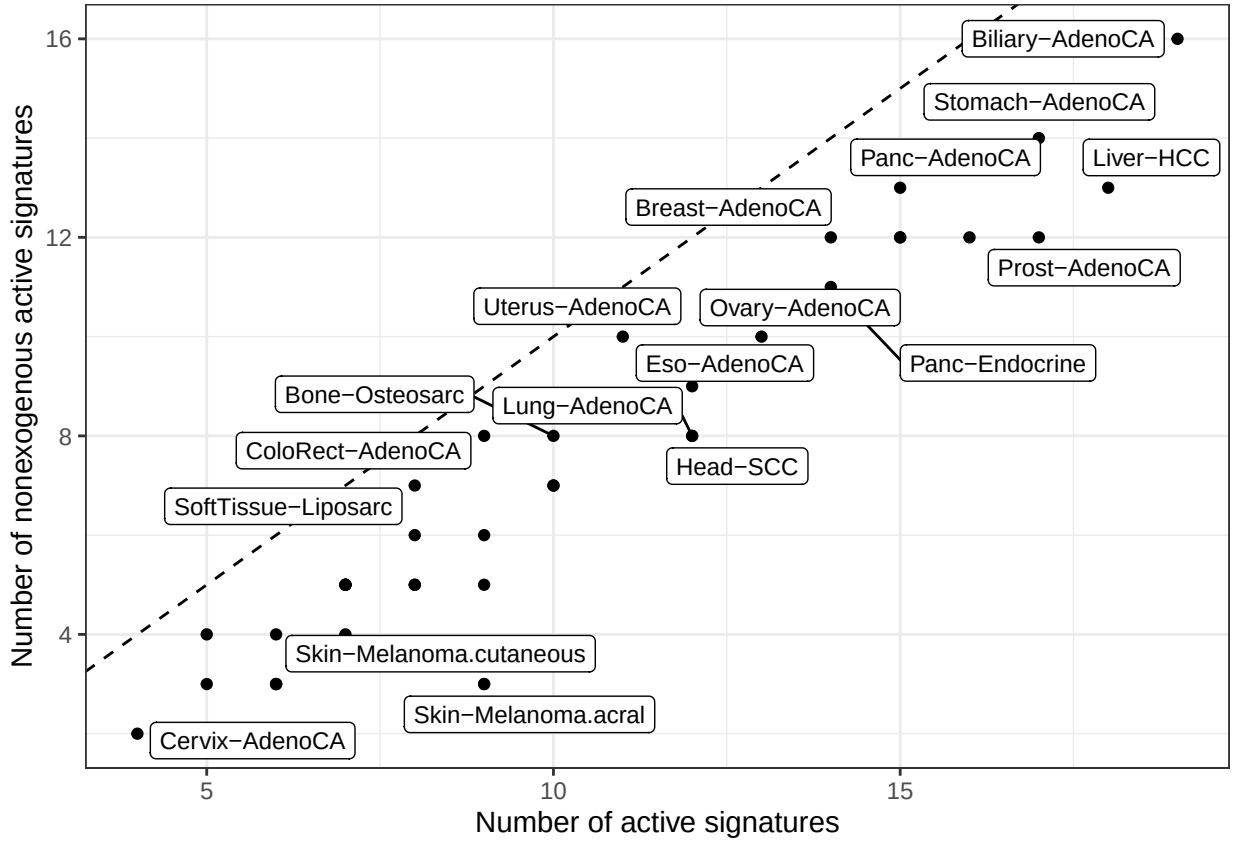

SBS12/SBS1
SBS13/SBS1
SBS17a/SBS1
SBS17b/SBS1
SBS18/SBS1
SBS2/SBS1
SBS26/SBS1
SBS28/SBS1
SBS3/SBS1
SBS30/SBS1
SBS33/SBS1
SBS37/SBS1
SBS39/SBS1
SBS40/SBS1
SBS41/SBS1
SBS5/SBS1
SBS6/SBS1
SBS7b/SBS1
SBS8/SBS1
SBS9/SBS1
beta.Estimate
3
2
1
0
−1
−2
ct
Bone−Osteosarc
Breast−AdenoCA
Cervix−SCC
CNS−GBM
CNS−Medullo
CNS−Oligo
CNS−PiloAstro
ColoRect−AdenoCA
Eso−AdenoCA
Head−SCC
Kidney−ChRCC
Kidney−RCC.clearcell
Kidney−RCC.papillary
Lung−AdenoCA
Lung−SCC
Lymph−BNHL
Lymph−CLL
Myeloid−MPN
Ovary−AdenoCA
Panc−AdenoCA
Panc−Endocrine
Prost−AdenoCA
Skin−Melanoma.acral
Skin−Melanoma.cutaneous
Stomach−AdenoCA
Uterus−AdenoCA


Bone−Osteosarc
Breast−AdenoCA
Cervix−SCC
CNS−GBM
CNS−Medullo
CNS−Oligo
CNS−PiloAstro
ColoRect−AdenoCA
Eso−AdenoCA
Head−SCC
Kidney−ChRCC
Kidney−RCC.clear
Kidney−RCC.papilla
Lung−AdenoCA
Lung−SCC
Lymph−BNHL
Lymph−CLL
Myeloid−MPN
Ovary−AdenoCA
Panc−AdenoCA
Panc−Endocrine
Prost−AdenoCA
Skin−Melanoma.acr
Skin−Melanoma.cutane
Stomach−AdenoCA
Uterus−AdenoCA
beta.Estimate
exogenous
FALSE
TRUE
logR

How many signatures so we have in total and how many nonexogenous ones?

```
## Error in slot(i, "count_matrices_active") :
##   cannot get a slot ("count_matrices_active") from an object of type "logical"
```

```
## Error in signature_roo_active[[j]][[1]][, !(colnames(signature_roo_active[[j]][[1]]) %in%  :
##   incorrect number of dimensions
## Error in signature_roo_active[[j]][[1]][, !(colnames(signature_roo_active[[j]][[1]]) %in%  :
##   incorrect number of dimensions
```



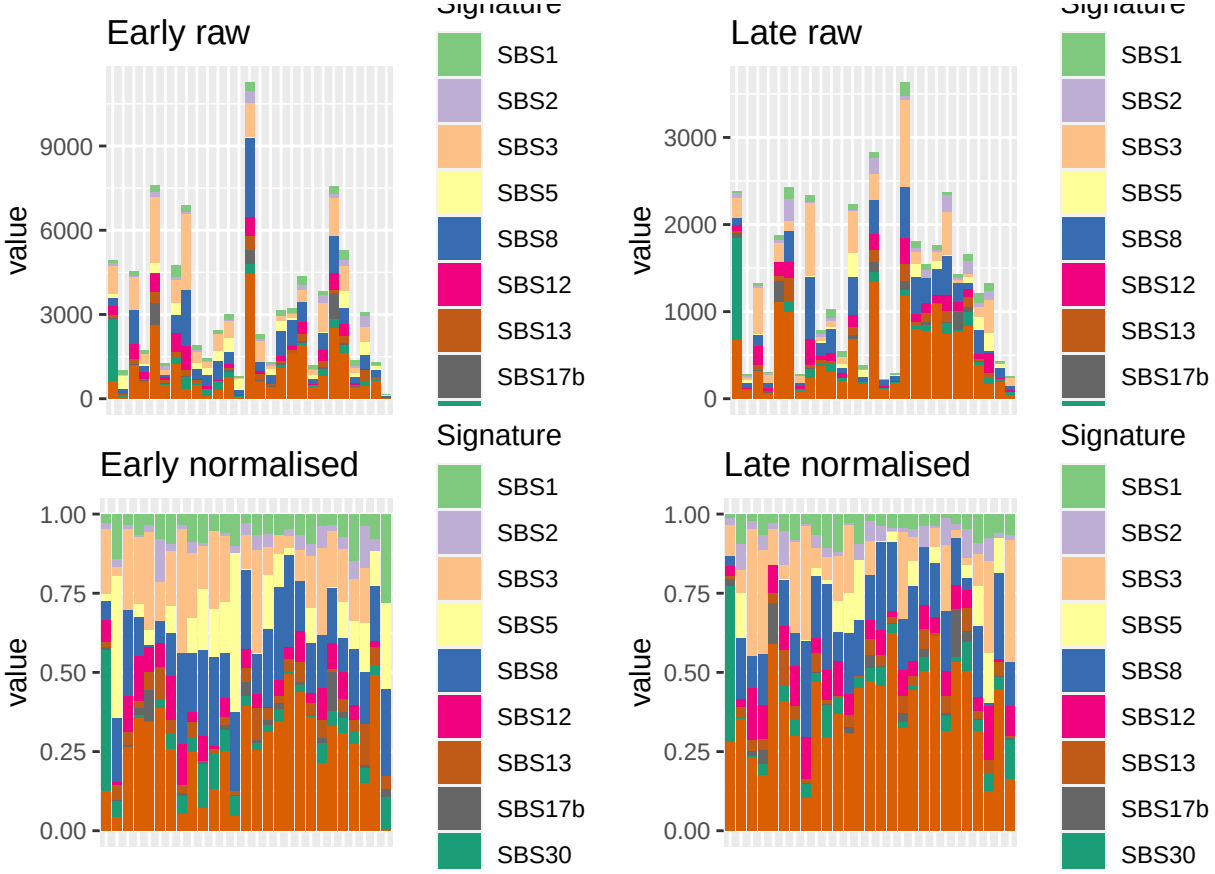
Analysis per cancer type

Bone osteosarcoma

Barplot and general statistics

```
## [1] 27
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 27
## Creating plot... it might take some time if the data are large. Number of samples: 27
## Creating plot... it might take some time if the data are large. Number of samples: 27
## Creating plot... it might take some time if the data are large. Number of samples: 27
```



The number of samples and signatures is:

```
## [1] 54 10
```

The signatures are:

```
##  [1] "SBS1"   "SBS2"   "SBS3"   "SBS5"   "SBS8"   "SBS12"  "SBS13"  "SBS17b"
##  [9] "SBS30"  "SBS40"
```

Convergence table

We only have converged results for the multinomial with full RE, and the DM with a single lambda (diag and full RE). It is the same for nonexogenous signatures.

```
##             value                                L2                  L1
## 1  Bone-Osteosarc    hessian_positivedefinite_bool              diagRE_M
## 2  Bone-Osteosarc    hessian_positivedefinite_bool              fullRE_M
## 3  Bone-Osteosarc hessian_nonpositivedefinite_bool           diagRE_DMDL
## 4  Bone-Osteosarc hessian_nonpositivedefinite_bool         fullRE_halfDM
## 5  Bone-Osteosarc hessian_nonpositivedefinite_bool           fullRE_DMDL
## 6  Bone-Osteosarc    hessian_positivedefinite_bool           diagRE_DMSL
## 7  Bone-Osteosarc    hessian_positivedefinite_bool         sparseRE_DMSL
## 8  Bone-Osteosarc hessian_nonpositivedefinite_bool           fullRE_DMSL
## 9  Bone-Osteosarc hessian_nonpositivedefinite_bool      fullRE_DMSL_SBS1
## 10 Bone-Osteosarc    hessian_positivedefinite_bool       fullRE_M_nonexo
## 11 Bone-Osteosarc    hessian_positivedefinite_bool    diagRE_DMSL_nonexo
```

```
## 12 Bone-Osteosarc                           Timeout     sparseRE_DMSL_nonexo
## 13 Bone-Osteosarc hessian_nonpositivedefinite_bool       fullRE_DMSL_nonexo
## 14 Bone-Osteosarc hessian_nonpositivedefinite_bool       fullRE_DMDL_nonexo
## 15 Bone-Osteosarc hessian_nonpositivedefinite_bool fullRE_DMDL_sortednonexo
```

Re-running of fitting

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

If we use the values of the fullRE M as initial values for the fullRE DM, we also don't get convergence:

```
## [1] FALSE
```

Potentially problematic signatures

We notice that we have several signatures with low exposures, and many zero exposures

```
colSums(obj_Bone_Osteosarc$Y == 0)/nrow(obj_Bone_Osteosarc$Y)
```

```
##       SBS1       SBS2       SBS3       SBS5       SBS8      SBS12      SBS13
## 0.00000000 0.03703704 0.14814815 0.37037037 0.01851852 0.09259259 0.00000000
##     SBS17b      SBS30      SBS40
## 0.37037037 0.12962963 0.01851852
```

```
colSums(obj_Bone_Osteosarc$Y)/sum(obj_Bone_Osteosarc$Y)
```

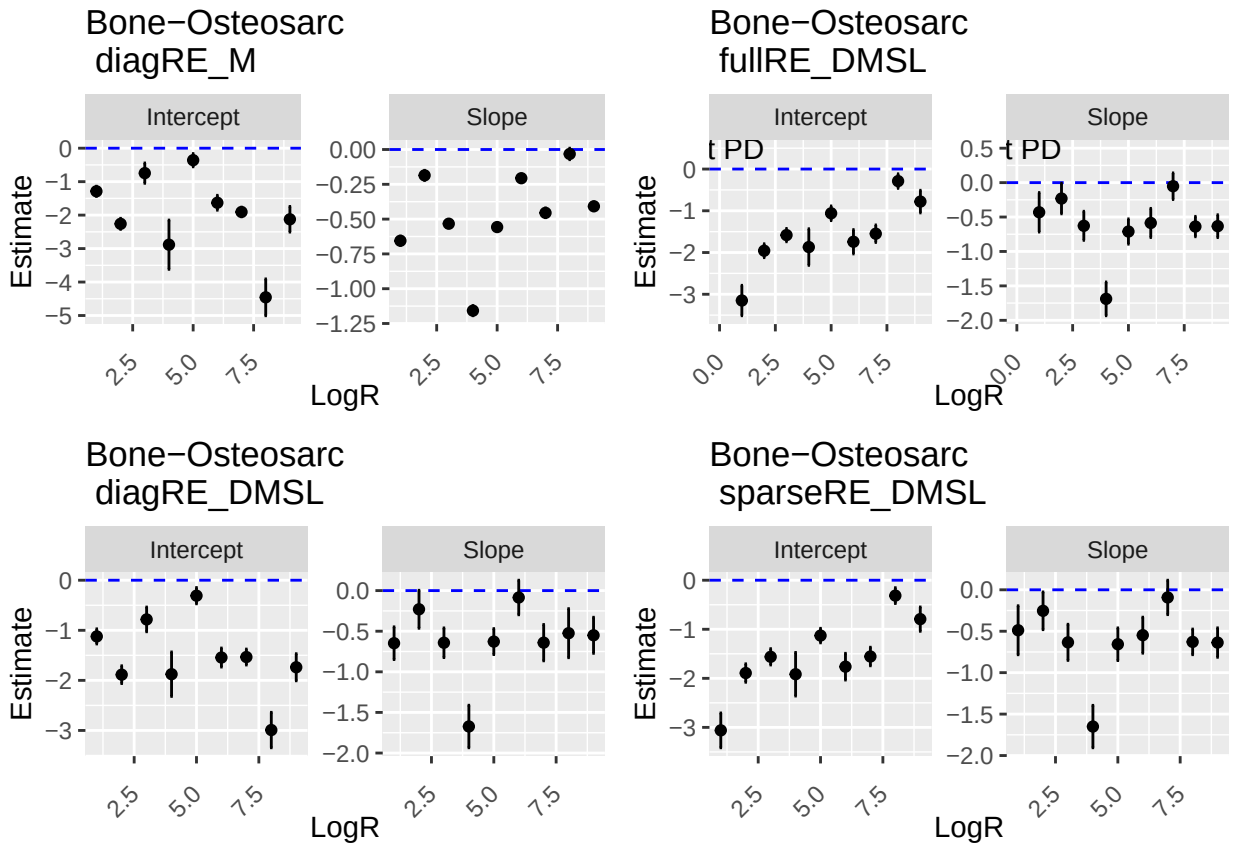
```
##       SBS1       SBS2       SBS3       SBS5       SBS8      SBS12      SBS13
## 0.05099661 0.03376971 0.17876022 0.05053018 0.17164713 0.07538325 0.04159022
##     SBS17b      SBS30      SBS40
## 0.02866227 0.06128922 0.30737119
```

E.g.

- SBS17b is 0 in 37% of cases and has an overall exposure of 2.9%
- SBS30 is 0 in 13% of cases and overal has an exposure of only 6.1%
- SBS5 is 0 in 37% of cases and has an overall exposure of 5.1%

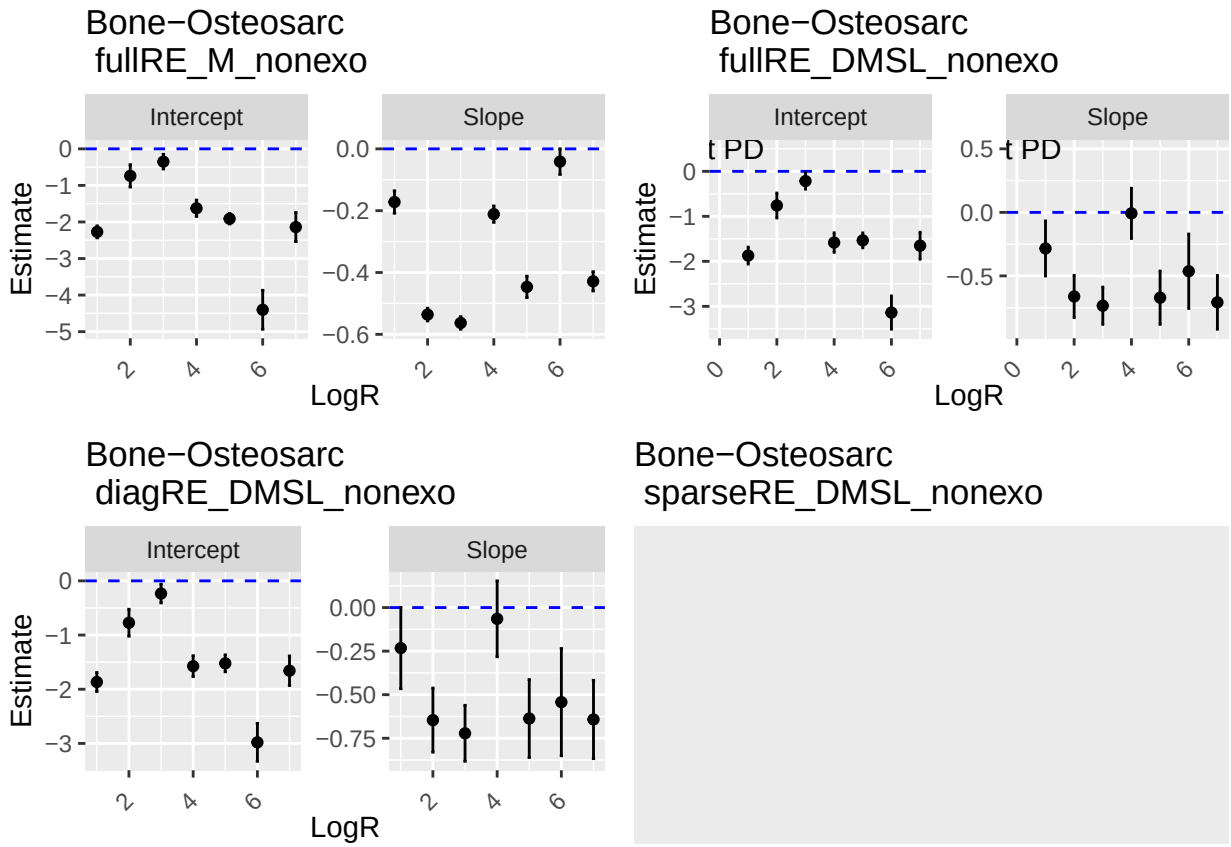
Betas

```
ct <- "Bone-Osteosarc"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```




```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(fullRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct
```

```
## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used
```

```
## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

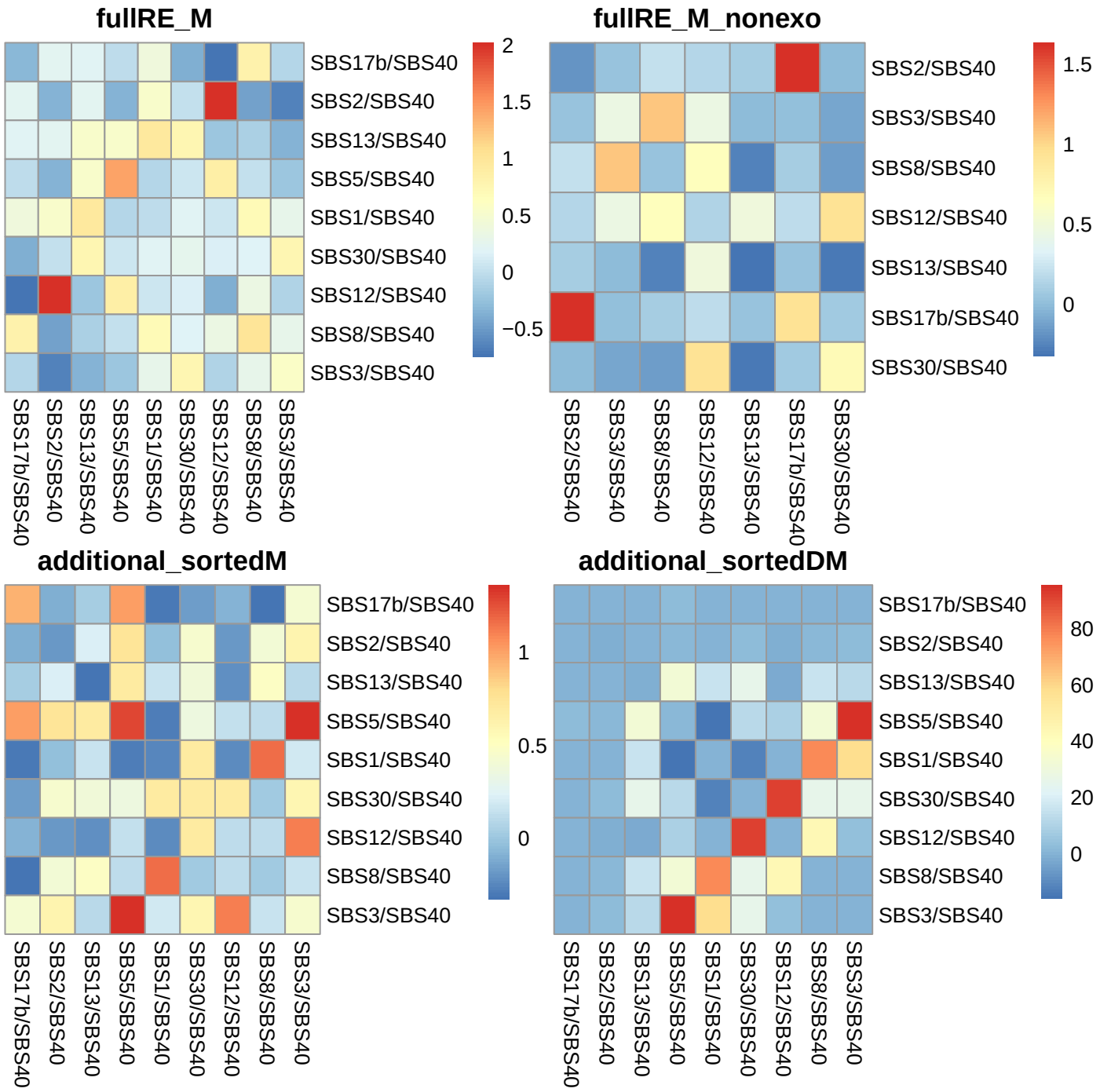
We use the results from the diagonal single lambda DM to test for differential abundance, giving a p-value of 3.8923434×10^{-5}.

Covariance matrices

```
ct <- "Bone-Osteosarc"
additional_sortedM <- list()
additional_sortedDM <- list()
additional_sortedM[[ct]] <- sortedM
additional_sortedDM[[ct]] <- sortedDM
```

Note that sortedDM did not convergence.

Nevertheless, both versions of fullRE M – both of which converged and use the same baseline – give very different covariances matrices.

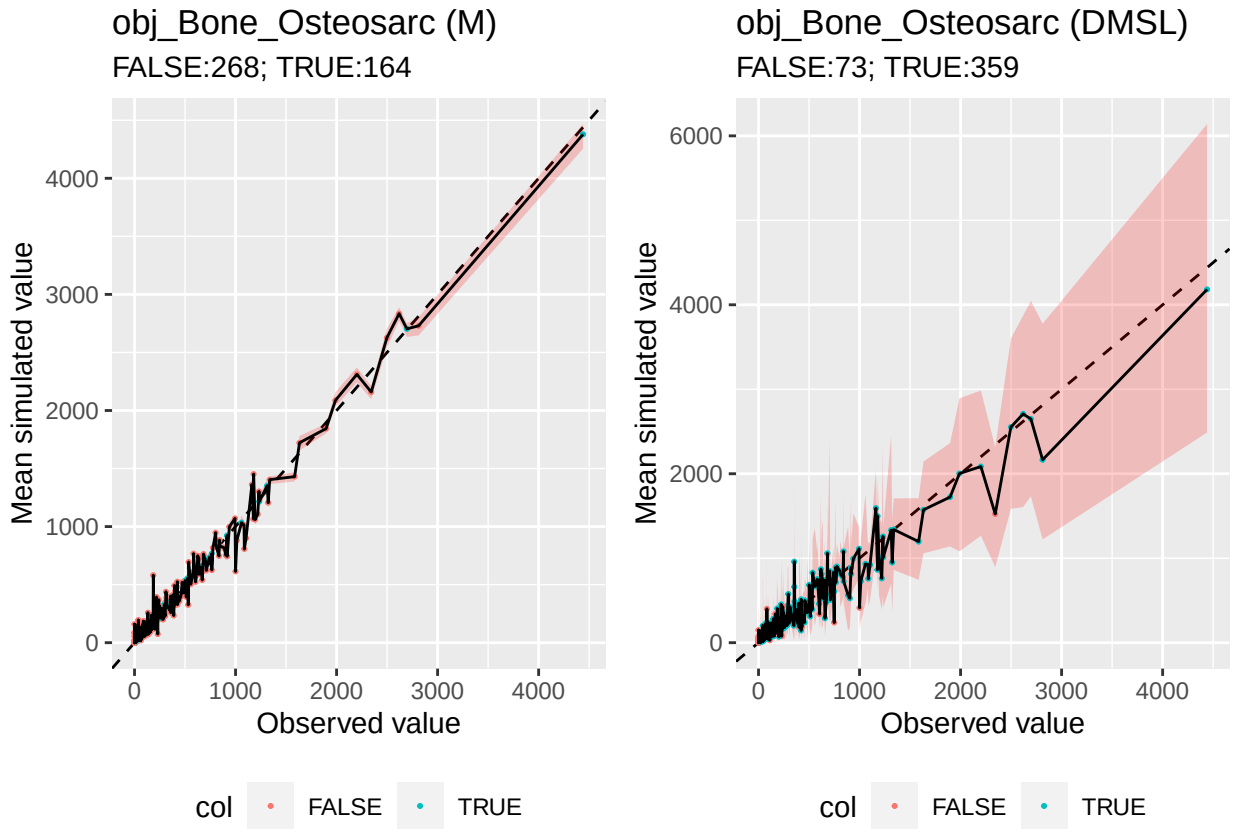


Simulation under inferred data

Have not been able to simulate

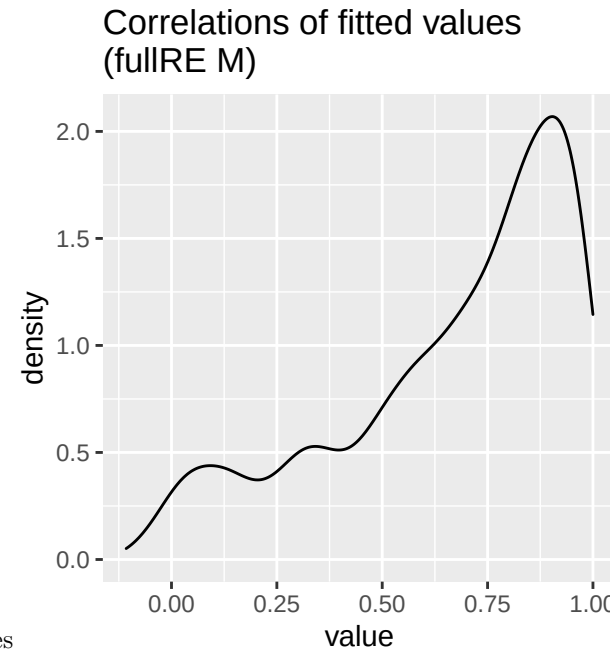
Ranked plot for coverage

```
ct <- "Bone-Osteosarc"
integer_overdispersion_param_DMSL <- 1
obj_Bone_Osteosarc_nonexo <- give_subset_sigs_TMBobj(obj_Bone_Osteosarc, sigs_to_remove = nonexogenous$V1
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                  data_object = obj_Bone_Osteosarc_nonexo,
                  print_plot = F, nreps = 20, model = "M")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Bone_Osteosarc_nonexo,
                  loglog = F, title = 'obj_Bone_Osteosarc (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = fullRE_DMSL_nor
                  data_object = obj_Bone_Osteosarc_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Bone_Osteosarc_nonexo,
                  loglog = F, title = 'obj_Bone_Osteosarc (DMSL)'), ncol=2)
```



73/359=20% of values are not included in the confidence interval of the DMSL.

Correlations of signatures



To add: the observed values, and the correlations of the normalised signatures

Signatures from mutSigExtractor

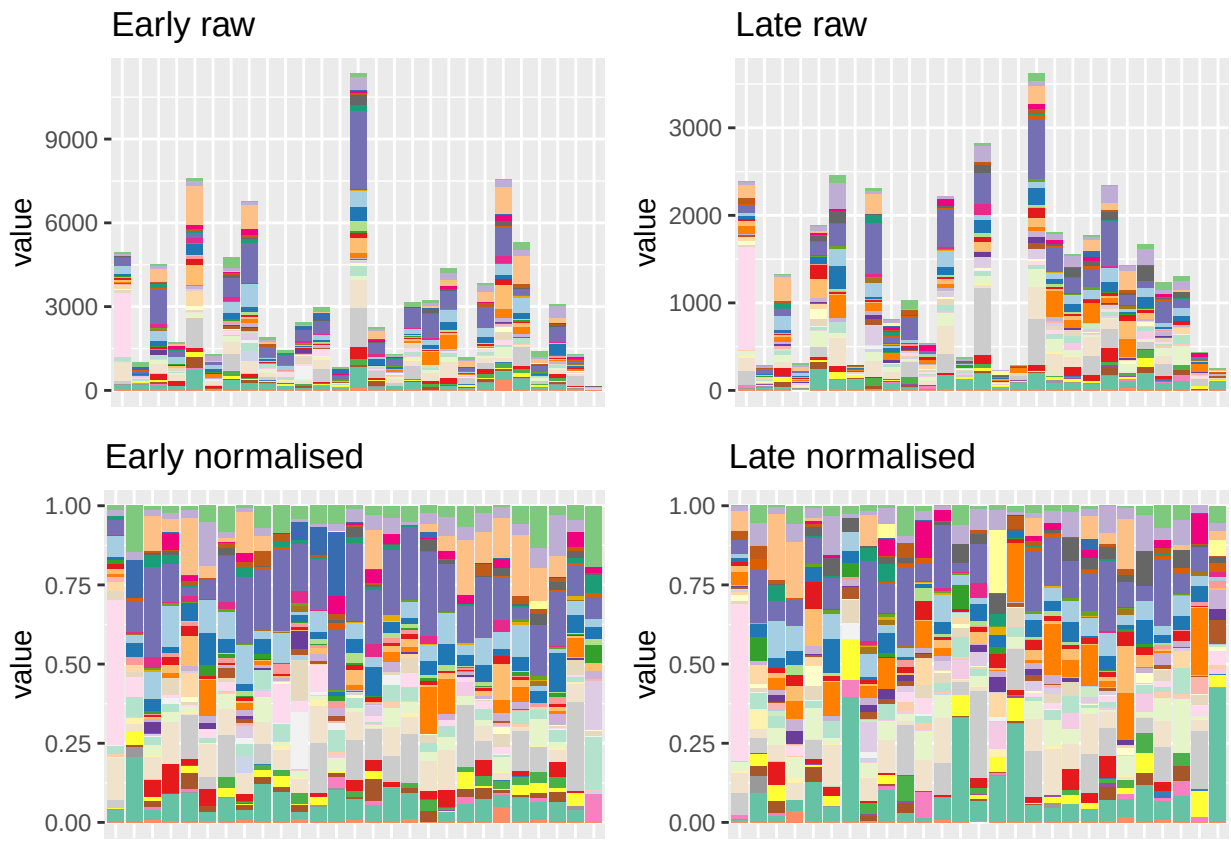
The signatures from mutSigExtractor are a bit more chaotic:

```
obj_Bone_Osteosarc_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

```
## [1] 27
```

```
give_barplot_from_obj(obj = obj_Bone_Osteosarc_mutSigExtractor, legend_on = FALSE)
```

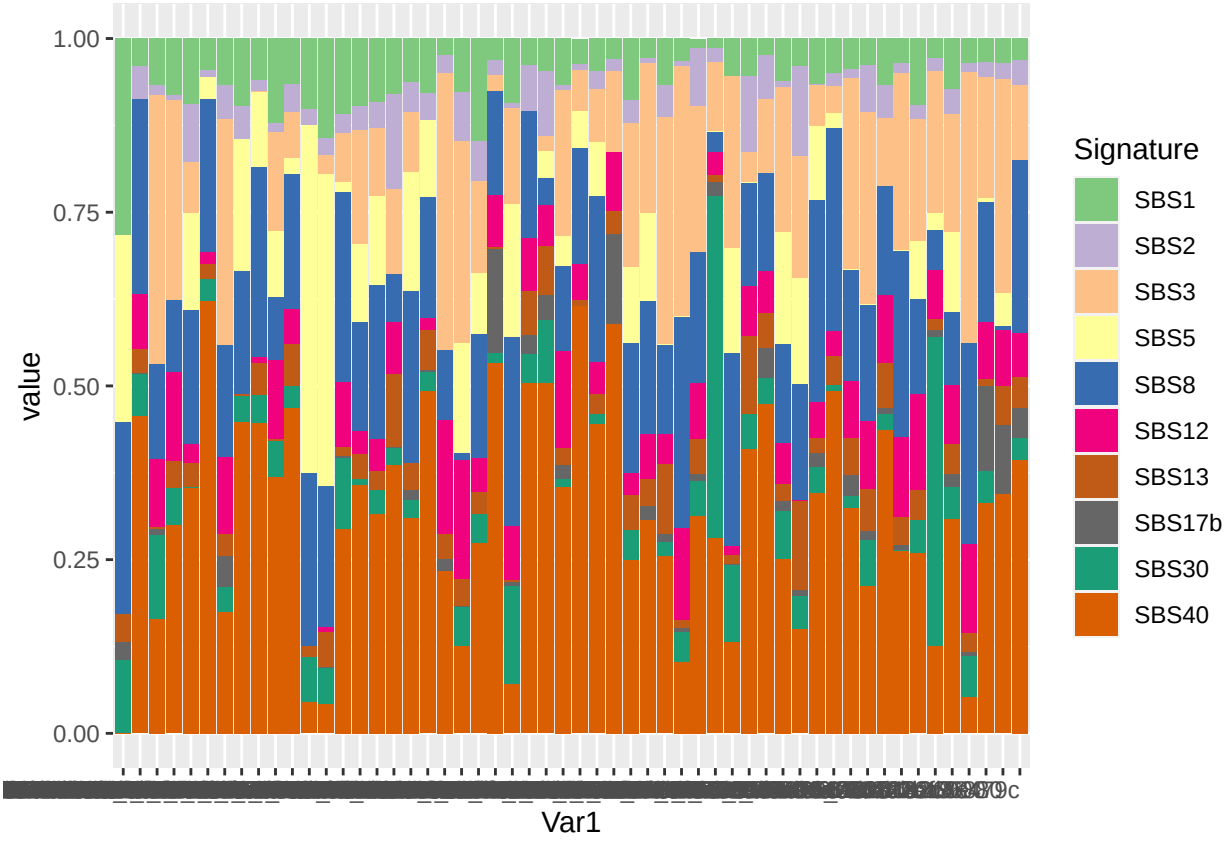
```
## Creating plot... it might take some time if the data are large. Number of samples: 27
## Creating plot... it might take some time if the data are large. Number of samples: 27
## Creating plot... it might take some time if the data are large. Number of samples: 27
## Creating plot... it might take some time if the data are large. Number of samples: 27
```



Exposures sorted by increasing number of mutations

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Bone_Osteosarc$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Bone_Osteosarc$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 54
```

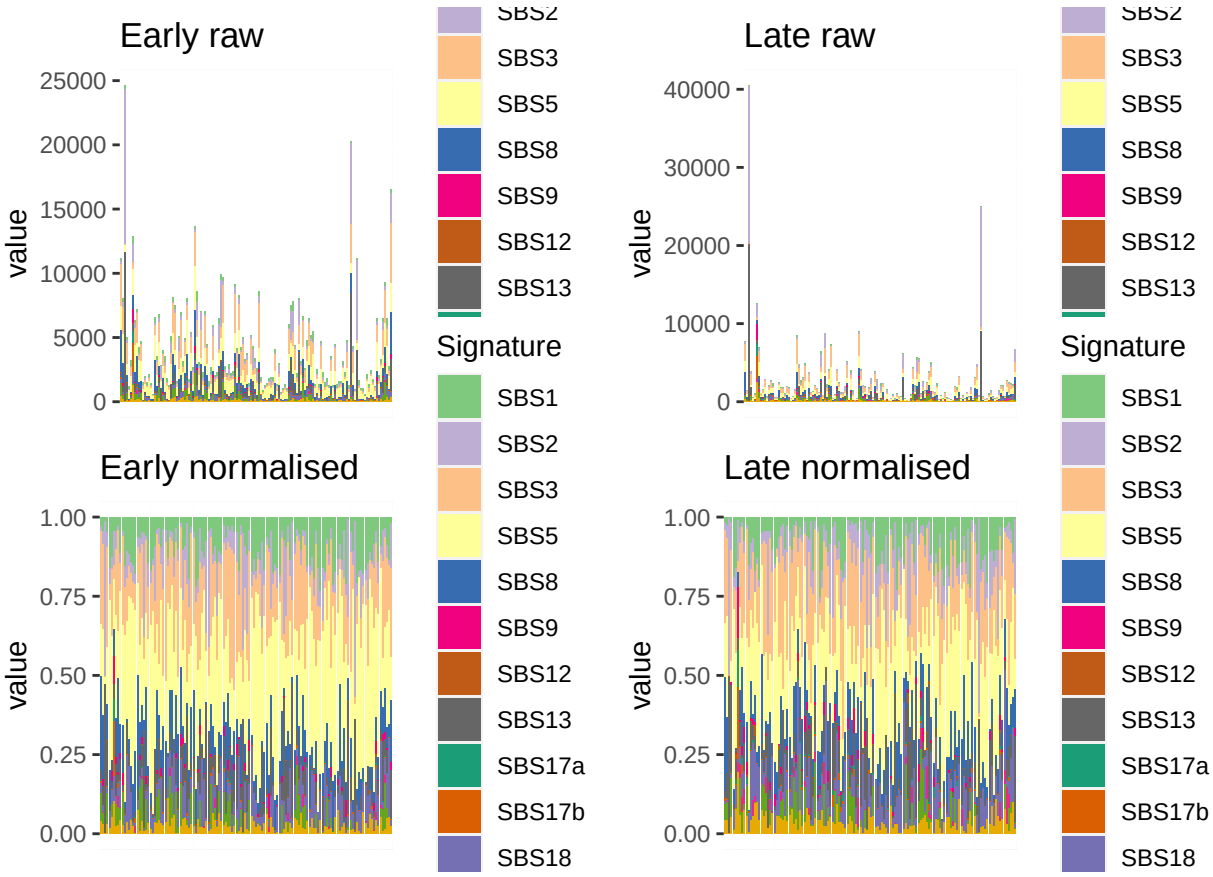


Breast-AdenoCA

Barplot and general statistics

```
## [1] 136
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 136
## Creating plot... it might take some time if the data are large. Number of samples: 136
## Creating plot... it might take some time if the data are large. Number of samples: 136
## Creating plot... it might take some time if the data are large. Number of samples: 136
```



There are many signatures, and also many samples.

The number of samples and signatures is:

```
## [1] 272  14
```

The signatures are:

```
##  [1] "SBS1"   "SBS2"   "SBS3"   "SBS5"   "SBS8"   "SBS9"   "SBS12"  "SBS13"
##  [9] "SBS17a" "SBS17b" "SBS18"  "SBS37"  "SBS39"  "SBS41"
```

Convergence table

We only have converged results for the diagRE_DMSL, with diagonal or sparse covariance structure, and diagonal M. This is probably due to the very high number of signatures, which make it impossible to infer the whole covariance structure.

```
##              value                                L2                 L1
## 1  Breast-AdenoCA    hessian_positivedefinite_bool           diagRE_M
## 2  Breast-AdenoCA hessian_nonpositivedefinite_bool           fullRE_M
## 3  Breast-AdenoCA hessian_nonpositivedefinite_bool         diagRE_DMDL
## 4  Breast-AdenoCA hessian_nonpositivedefinite_bool        fullRE_halfDM
## 5  Breast-AdenoCA hessian_nonpositivedefinite_bool         fullRE_DMDL
## 6  Breast-AdenoCA    hessian_positivedefinite_bool         diagRE_DMSL
## 7  Breast-AdenoCA    hessian_positivedefinite_bool        sparseRE_DMSL
## 8  Breast-AdenoCA hessian_nonpositivedefinite_bool         fullRE_DMSL
## 9  Breast-AdenoCA hessian_nonpositivedefinite_bool   fullRE_DMSL_SBS1
```

```
## 10 Breast-AdenoCA hessian_nonpositivedefinite_bool          fullRE_M_nonexo
## 11 Breast-AdenoCA    hessian_positivedefinite_bool       diagRE_DMSL_nonexo
## 12 Breast-AdenoCA    hessian_positivedefinite_bool     sparseRE_DMSL_nonexo
## 13 Breast-AdenoCA hessian_nonpositivedefinite_bool       fullRE_DMSL_nonexo
## 14 Breast-AdenoCA hessian_nonpositivedefinite_bool       fullRE_DMDL_nonexo
## 15 Breast-AdenoCA                          Timeout fullRE_DMDL_sortednonexo
```

Re-running of fitting

If we use the values of the diagRE M as initial values for the diagRE DM, we that it has converged. This is probably due to a combination of things: we are using the optimiser nlminb (better in general than the alternative, optim) and we are starting with these - better - values, and we are sorting the columns so that the category with highest total value is the baseline.

```
## [1] TRUE
```

```
ct <- "Breast-AdenoCA"
additional_sorteddiagM <- list()
additional_sorteddiagDM <- list()
additional_sorteddiagM[[ct]] <- sortedM_Breast_Adeno
additional_sorteddiagDM[[ct]] <- sortedDM_Breast_Adeno
```

Potentially problematic signatures

We notice that we have several signatures with low exposures, and many zero exposures

```
colSums(obj_Breast_AdenoCA$Y == 0)/nrow(obj_Breast_AdenoCA$Y)
```

```
##         SBS1         SBS2         SBS3         SBS5         SBS8         SBS9
## 0.000000000 0.000000000 0.025735294 0.007352941 0.088235294 0.562500000
##        SBS12        SBS13       SBS17a       SBS17b        SBS18        SBS37
## 0.955882353 0.073529412 0.709558824 0.500000000 0.036764706 0.772058824
##        SBS39        SBS41
## 0.599264706 0.084558824
```

```
colSums(obj_Breast_AdenoCA$Y)/sum(obj_Breast_AdenoCA$Y)
```

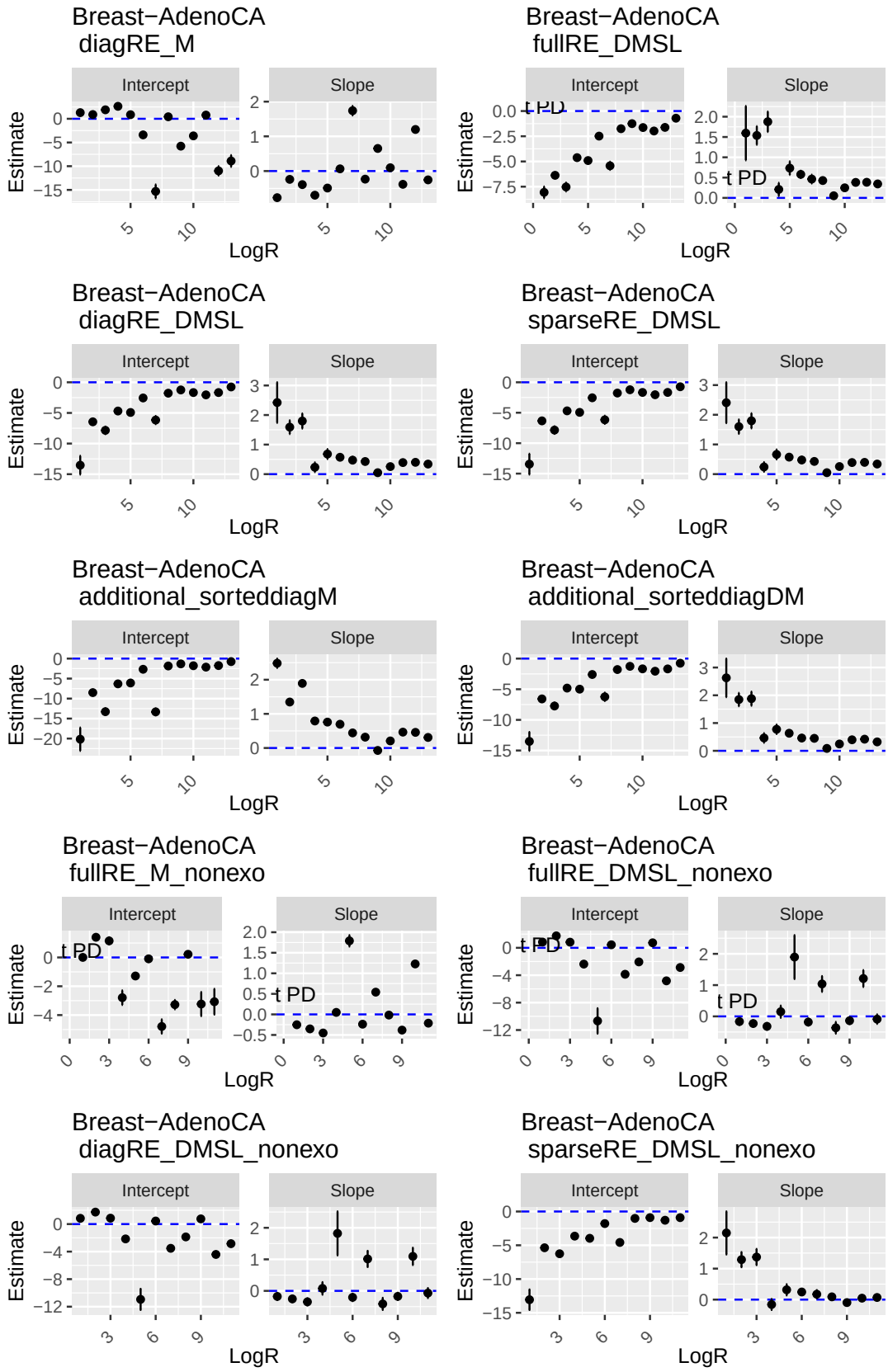
```
##          SBS1          SBS2          SBS3          SBS5          SBS8          SBS9
## 0.0553410311 0.1376261991 0.1993274971 0.2185906789 0.0969490005 0.0132833987
##         SBS12         SBS13        SBS17a        SBS17b         SBS18         SBS37
## 0.0003532317 0.1360853961 0.0036266519 0.0081714966 0.0531199688 0.0057240307
##         SBS39         SBS41
## 0.0402034279 0.0315979909
```

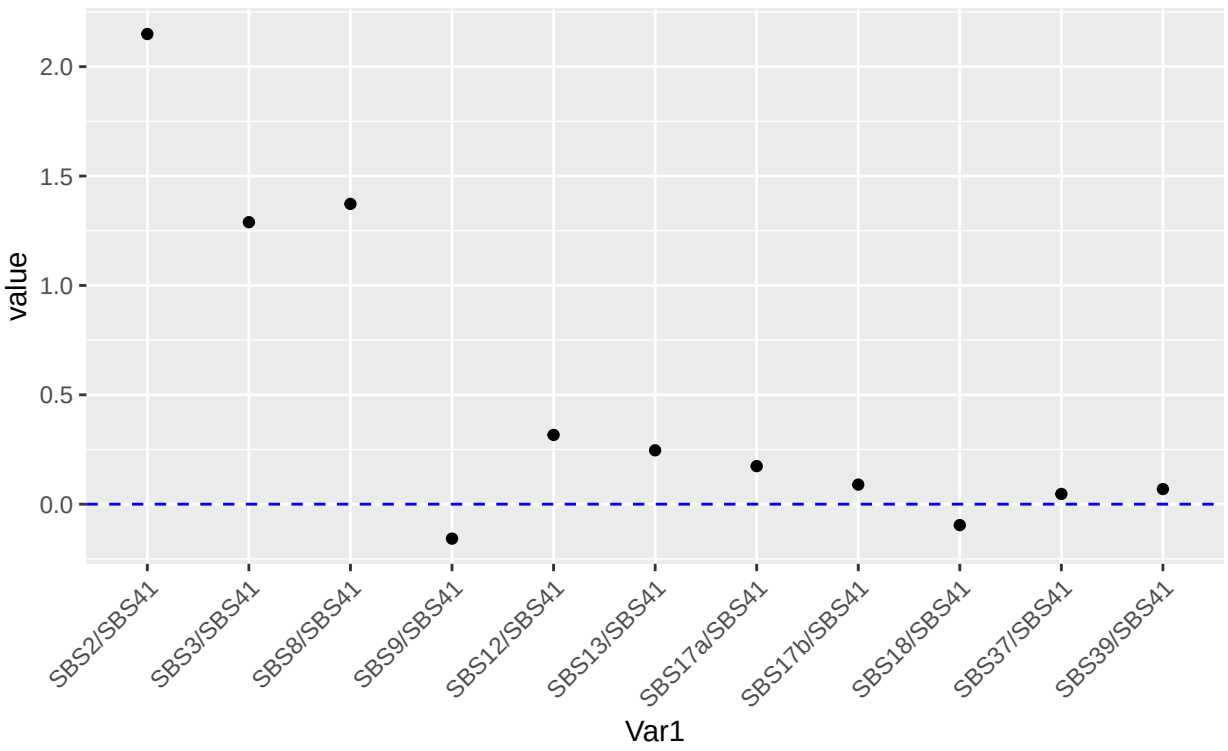
E.g.

- SBS9 is 0 in 56.2% of cases and has an overall exposure of 1.3%
- SBS12 is 0 in 95.6% of cases and has an overall exposure of 0%
- SBS17a is 0 in 71% of cases and has an overall exposure of 0.4%
- SBS17b is 0 in 50% of cases and has an overall exposure of 0.8%
- SBS37 is 0 in 77.2% of cases and has an overall exposure of 0.6%
- SBS39 is 0 in 59.9% of cases and has an overall exposure of 4%

Betas

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
## Warning in sqrt(as.numeric(object$diag.cov.random)): NaNs produced
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
## Warning in sqrt(as.numeric(object$diag.cov.random)): NaNs produced
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```


Breast−AdenoCA
diagRE_M
Intercept
Slope
Estimate
LogR
Breast−AdenoCA
fullRE_DMSL
t PD
Breast−AdenoCA
diagRE_DMSL
Breast−AdenoCA
sparseRE_DMSL
Breast−AdenoCA
additional_sorteddiagM
Breast−AdenoCA
additional_sorteddiagDM
Breast−AdenoCA
fullRE_M_nonexo
Breast−AdenoCA
fullRE_DMSL_nonexo
Breast−AdenoCA
diagRE_DMSL_nonexo
Breast−AdenoCA
sparseRE_DMSL_nonexo



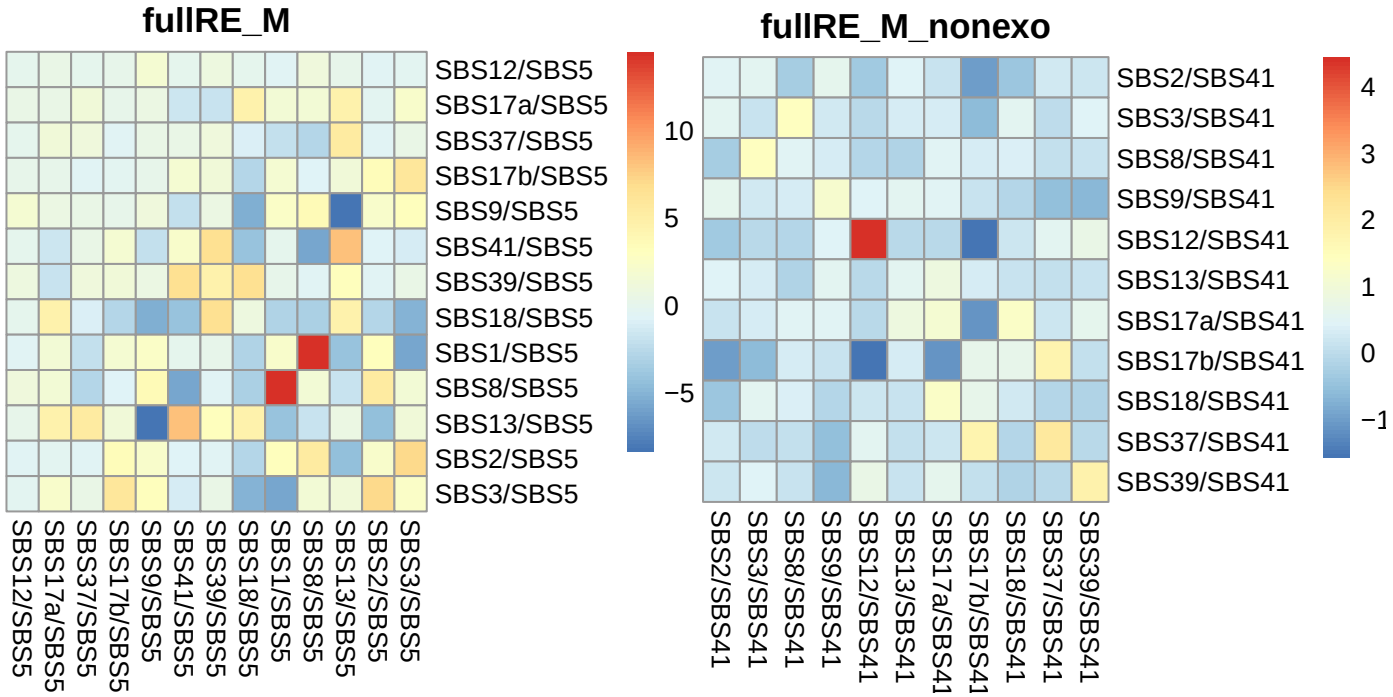

```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct
```

```
## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used
```

```
## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the diagonal single lambda DM to test for differential abundance, giving a p-value of 7.748574×10^{-12}.

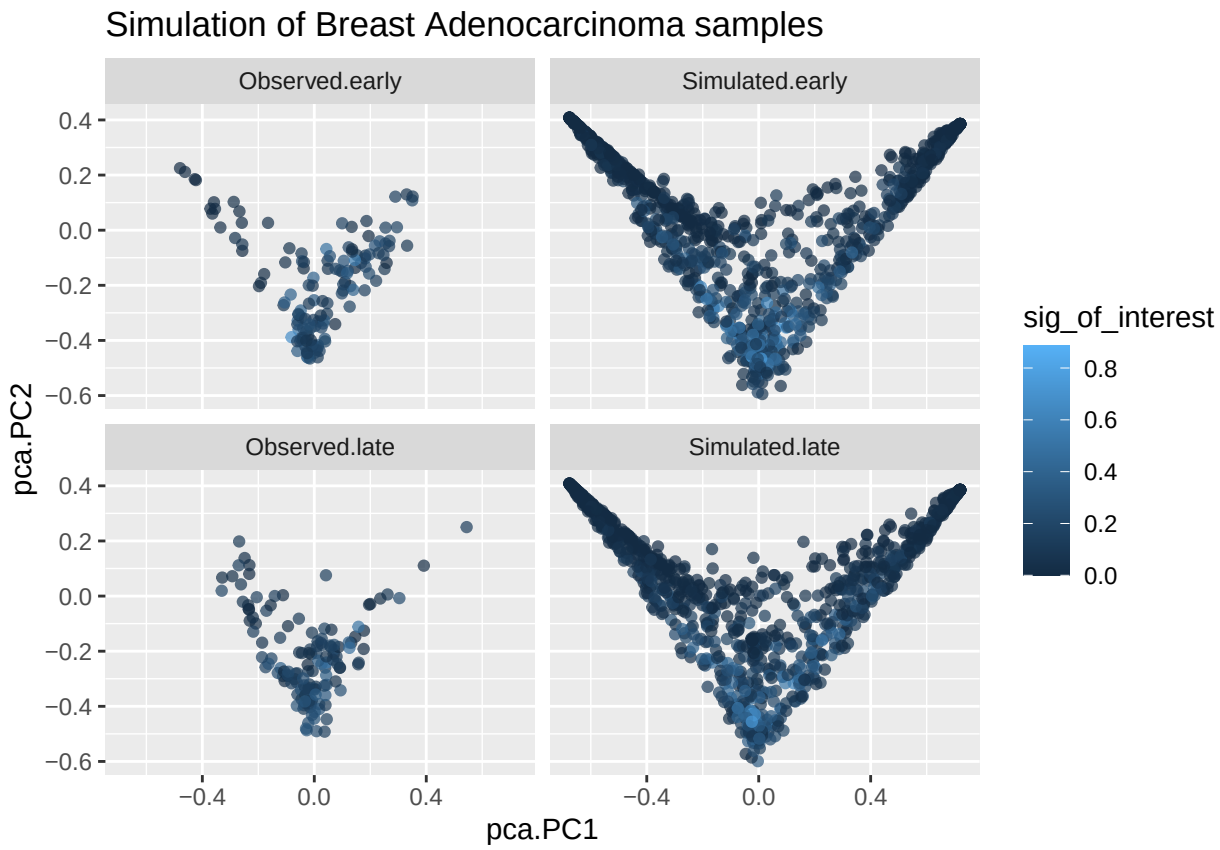
Covariance matrices



Simulation under inferred data

```
## [1] 136
```

```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```

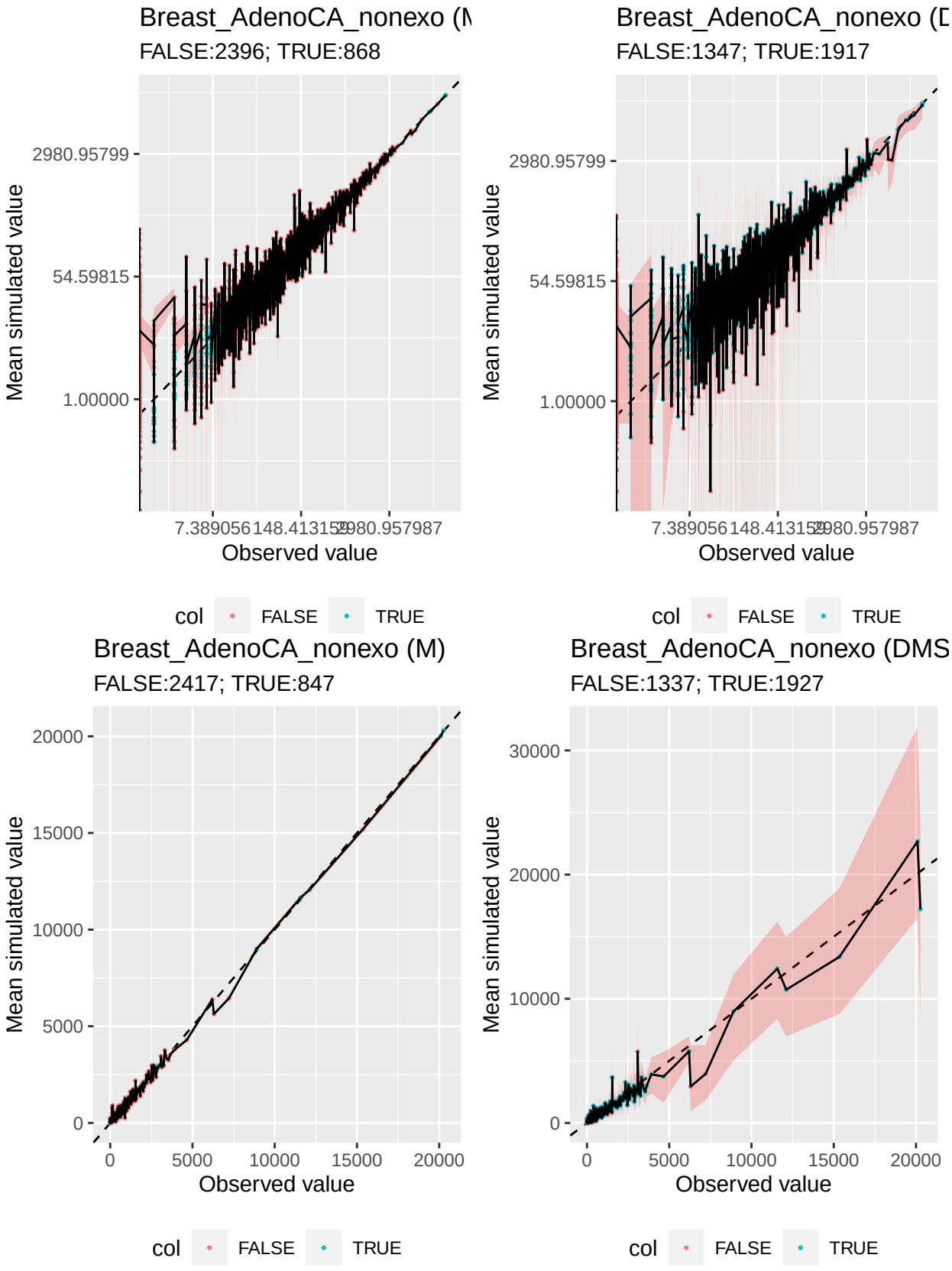


Ranked plot for coverage

```
ct <- "Breast-AdenoCA"
integer_overdispersion_param_DMSL <- 1
obj_Breast_AdenoCA_nonexo <- give_subset_sigs_TMBobj(obj_Breast_AdenoCA, sigs_to_remove = nonexogenous$V1

for(loglog_it in c(T,F)){
  grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = f
                 data_object = obj_Breast_AdenoCA_nonexo,
                 print_plot = F, nreps = 20, model = "M")), function(i){
                   lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                          rank_number=1:length(j)) )})[[1]],
                 data_object = obj_Breast_AdenoCA_nonexo,
                 loglog = loglog_it, title = 'Breast_AdenoCA_nonexo (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = fullRE_DMSL_nor
                 data_object = obj_Breast_AdenoCA_nonexo,
                 print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                   lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                          rank_number=1:length(j)) )})[[1]],
                 data_object = obj_Breast_AdenoCA_nonexo,
                 loglog = loglog_it, title = 'Breast_AdenoCA_nonexo (DMSL)'), ncol=2)
}
```

```
## Warning: Transformation introduced infinite values in continuous y-axis
```

```
## Warning: Transformation introduced infinite values in continuous y-axis
## Warning: Transformation introduced infinite values in continuous x-axis
## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis
## Warning: Transformation introduced infinite values in continuous x-axis
## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis
## Warning: Transformation introduced infinite values in continuous x-axis
## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis
## Warning: Transformation introduced infinite values in continuous x-axis
## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis
## Warning: Transformation introduced infinite values in continuous x-axis
## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis
## Warning: Transformation introduced infinite values in continuous x-axis
```


Breast_AdenoCA_nonexo (M
FALSE:2396; TRUE:868
Breast_AdenoCA_nonexo (D
FALSE:1347; TRUE:1917
Breast_AdenoCA_nonexo (M)
FALSE:2417; TRUE:847
Breast_AdenoCA_nonexo (DMS
FALSE:1337; TRUE:1927
Mean simulated value
Observed value
col
FALSE
TRUE

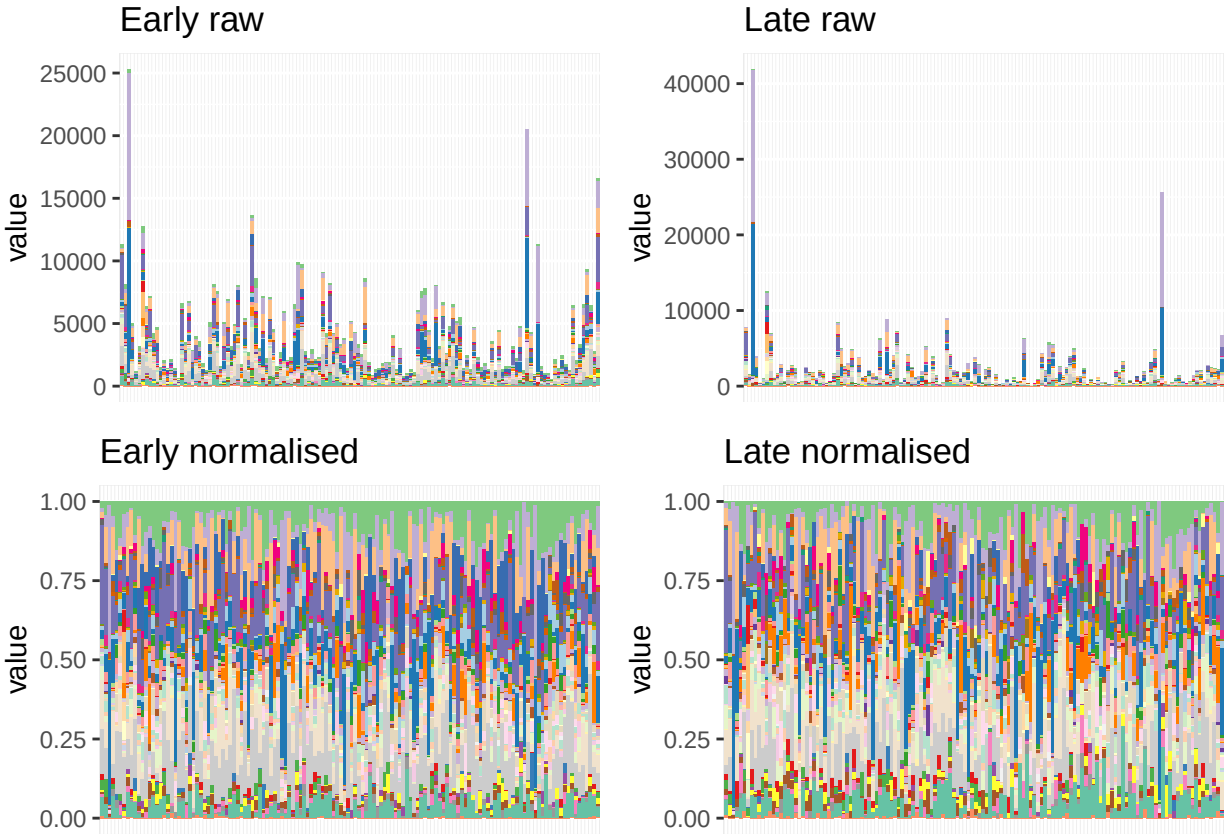
Signatures from mutSigExtractor

```
obj_Breast_AdenoCA_mutSigExtractor <- load_PCAWG(ct = "Breast-AdenoCA",
                                                 typedata = "signaturesmutSigExtractor",
                                                 path_to_data = "../../data/")
```

```
## [1] 136
```

```
give_barplot_from_obj(obj = obj_Breast_AdenoCA_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 136
## Creating plot... it might take some time if the data are large. Number of samples: 136
## Creating plot... it might take some time if the data are large. Number of samples: 136
## Creating plot... it might take some time if the data are large. Number of samples: 136
```

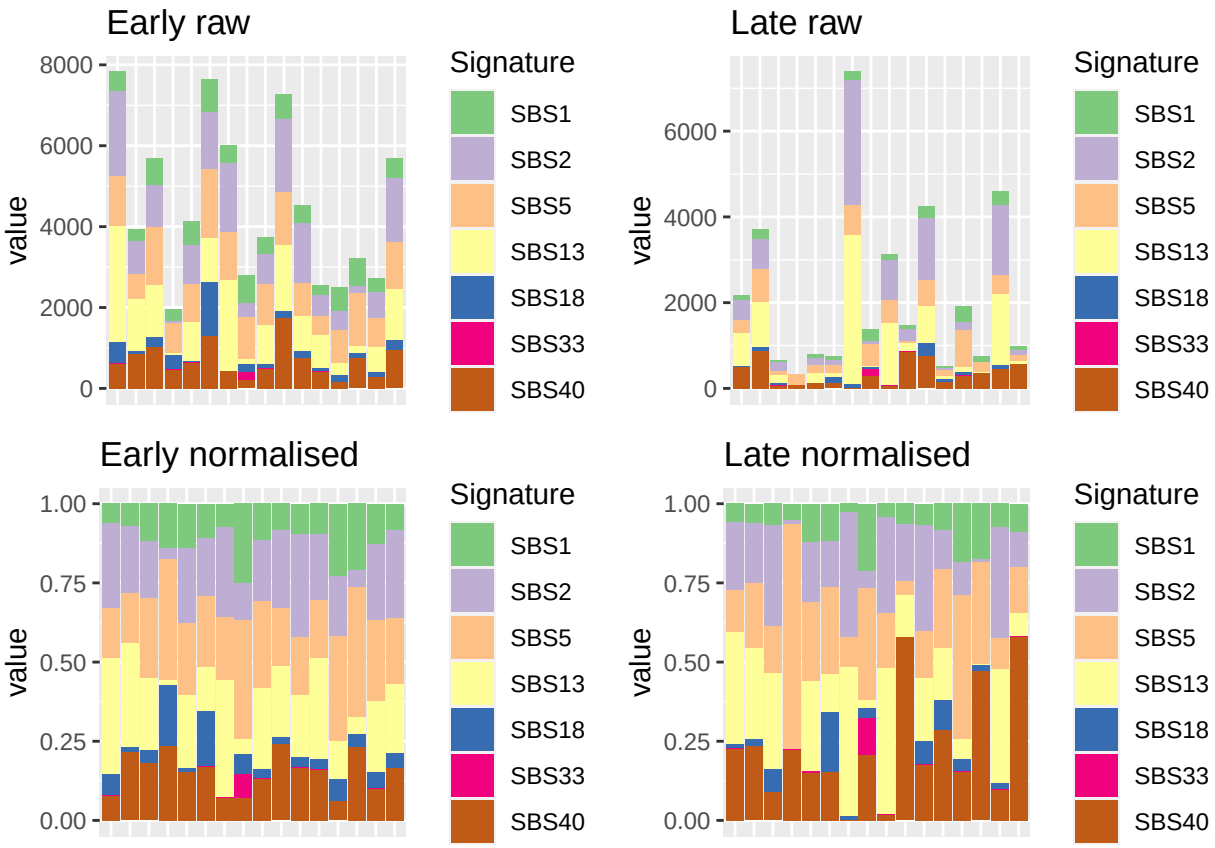


Cervix-SCC

Barplot and general statistics

```
## [1] 16
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 16
## Creating plot... it might take some time if the data are large. Number of samples: 16
## Creating plot... it might take some time if the data are large. Number of samples: 16
## Creating plot... it might take some time if the data are large. Number of samples: 16
```



The number of samples and signatures is:

```
## [1] 32  7
```

The signatures are:

```
## [1] "SBS1"  "SBS2"  "SBS5"  "SBS13" "SBS18" "SBS33" "SBS40"
```

Convergence table

```
##         value                                L2                    L1
## 1  Cervix-SCC    hessian_positivedefinite_bool                diagRE_M
## 2  Cervix-SCC hessian_nonpositivedefinite_bool                fullRE_M
## 3  Cervix-SCC    hessian_positivedefinite_bool             diagRE_DMDL
## 4  Cervix-SCC hessian_nonpositivedefinite_bool           fullRE_halfDM
## 5  Cervix-SCC hessian_nonpositivedefinite_bool             fullRE_DMDL
## 6  Cervix-SCC    hessian_positivedefinite_bool             diagRE_DMSL
## 7  Cervix-SCC    hessian_positivedefinite_bool           sparseRE_DMSL
## 8  Cervix-SCC hessian_nonpositivedefinite_bool             fullRE_DMSL
## 9  Cervix-SCC hessian_nonpositivedefinite_bool        fullRE_DMSL_SBS1
## 10 Cervix-SCC    hessian_positivedefinite_bool         fullRE_M_nonexo
## 11 Cervix-SCC    hessian_positivedefinite_bool      diagRE_DMSL_nonexo
## 12 Cervix-SCC    hessian_positivedefinite_bool    sparseRE_DMSL_nonexo
## 13 Cervix-SCC    hessian_positivedefinite_bool      fullRE_DMSL_nonexo
## 14 Cervix-SCC    hessian_positivedefinite_bool      fullRE_DMDL_nonexo
## 15 Cervix-SCC    hessian_positivedefinite_bool fullRE_DMDL_sortednonexo
```

Potentially problematic signatures

SBS33 is a potentially problematic signature, being 0 in 81.2% of cases and with an overall exposure of 0.4%.

```
colSums(obj_Cervix_SCC$Y == 0)/nrow(obj_Cervix_SCC$Y)
```

```
##    SBS1    SBS2    SBS5   SBS13   SBS18   SBS33   SBS40
## 0.00000 0.00000 0.00000 0.03125 0.15625 0.81250 0.03125
```

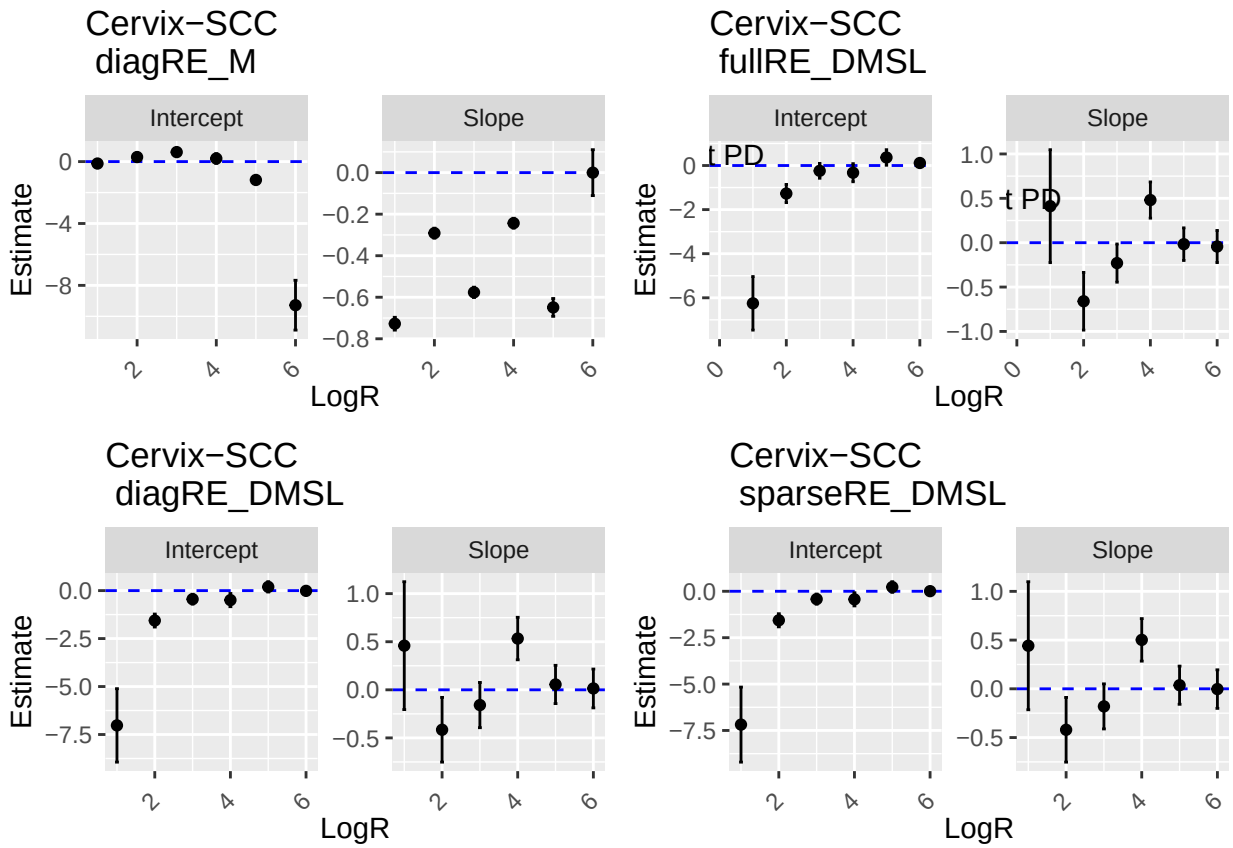
```
colSums(obj_Cervix_SCC$Y)/sum(obj_Cervix_SCC$Y)
```

```
##         SBS1         SBS2         SBS5         SBS13        SBS18        SBS33
## 0.099164517 0.235000561 0.211562185 0.250439236 0.046577698 0.003560615
##        SBS40
## 0.153695189
```

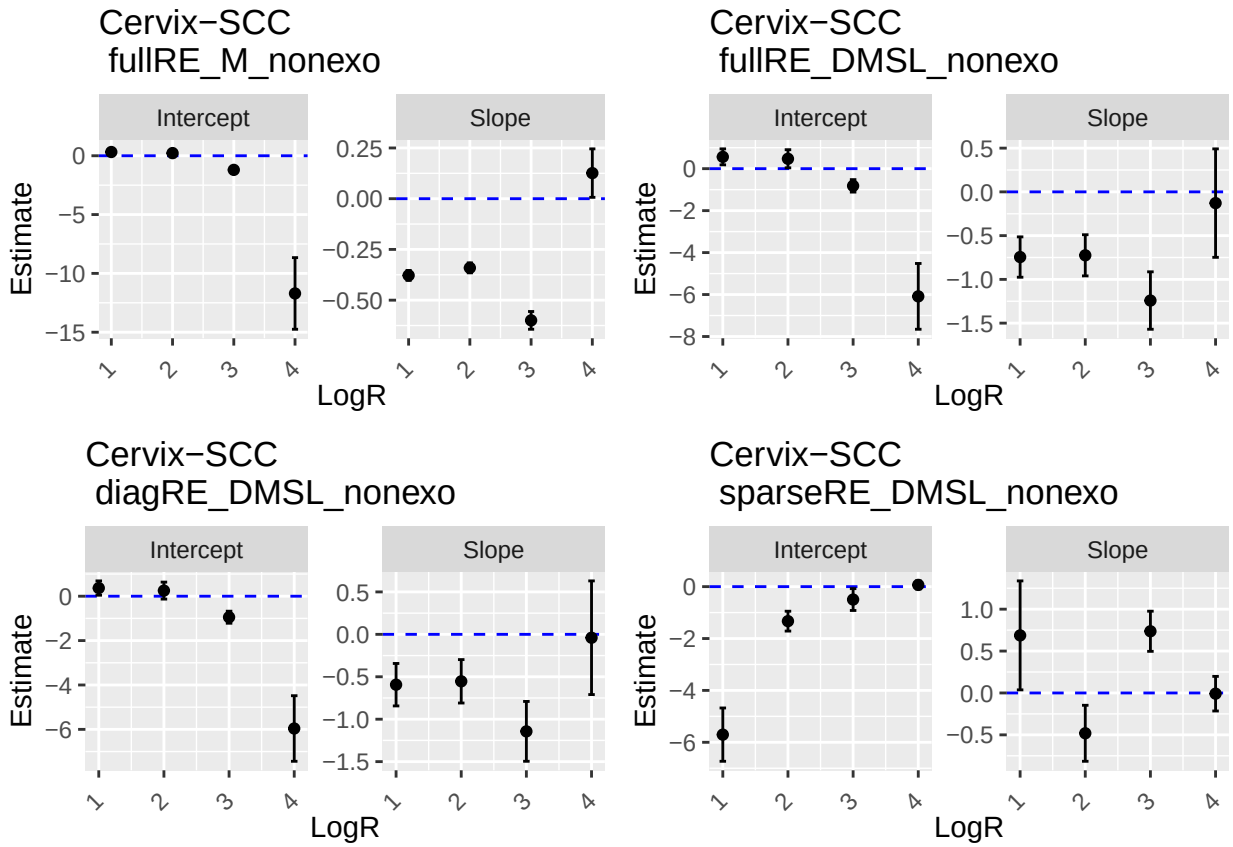
Betas

```
ct <- "Cervix-SCC"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
             plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
             plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
             plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```



```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(fullRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
  plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
  plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct
```

```
## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used
```

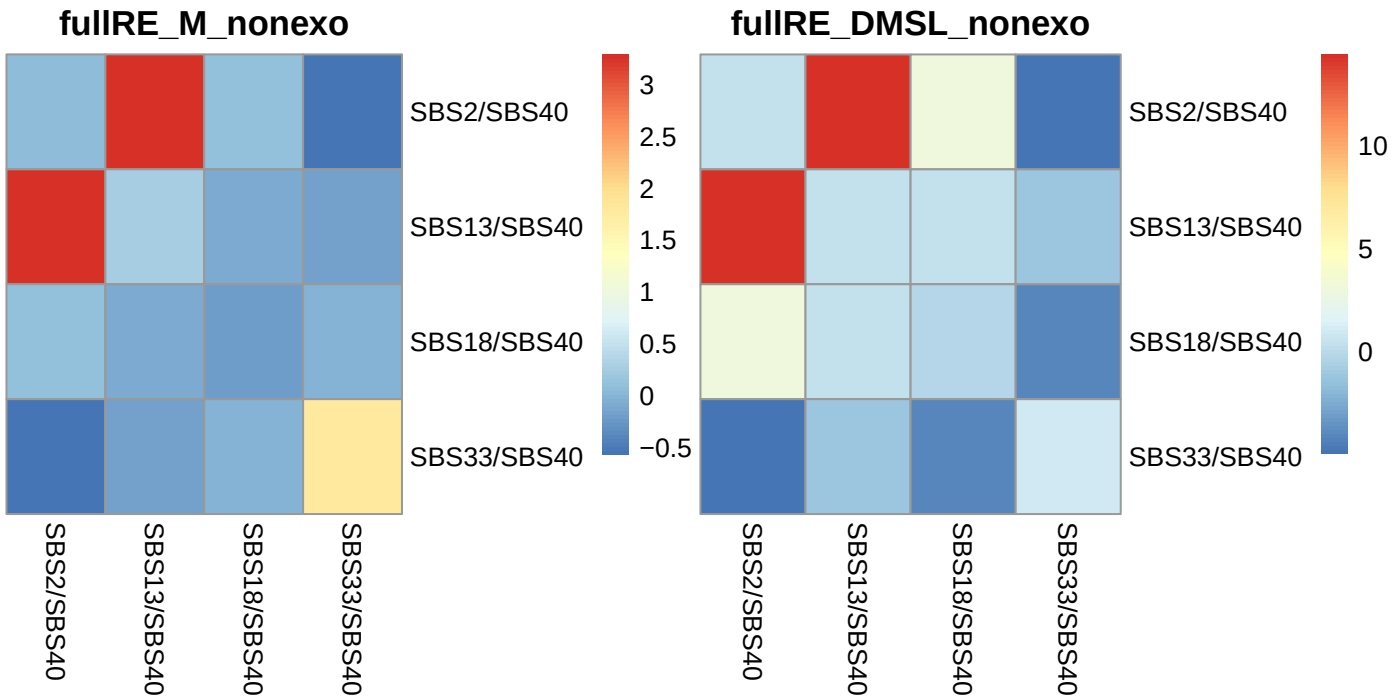
```
## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the fullRE single lambda DM to test for differential abundance, giving a p-value of 3.8923434×10^{-5}.

Covariance matrices

```
# ct <- "Bone-Osteosarc"
# additional_sortedM <- list()
# additional_sortedDM <- list()
```

```
# additional_sortedM[[ct]] <- sortedM
# additional_sortedDM[[ct]] <- sortedDM
```



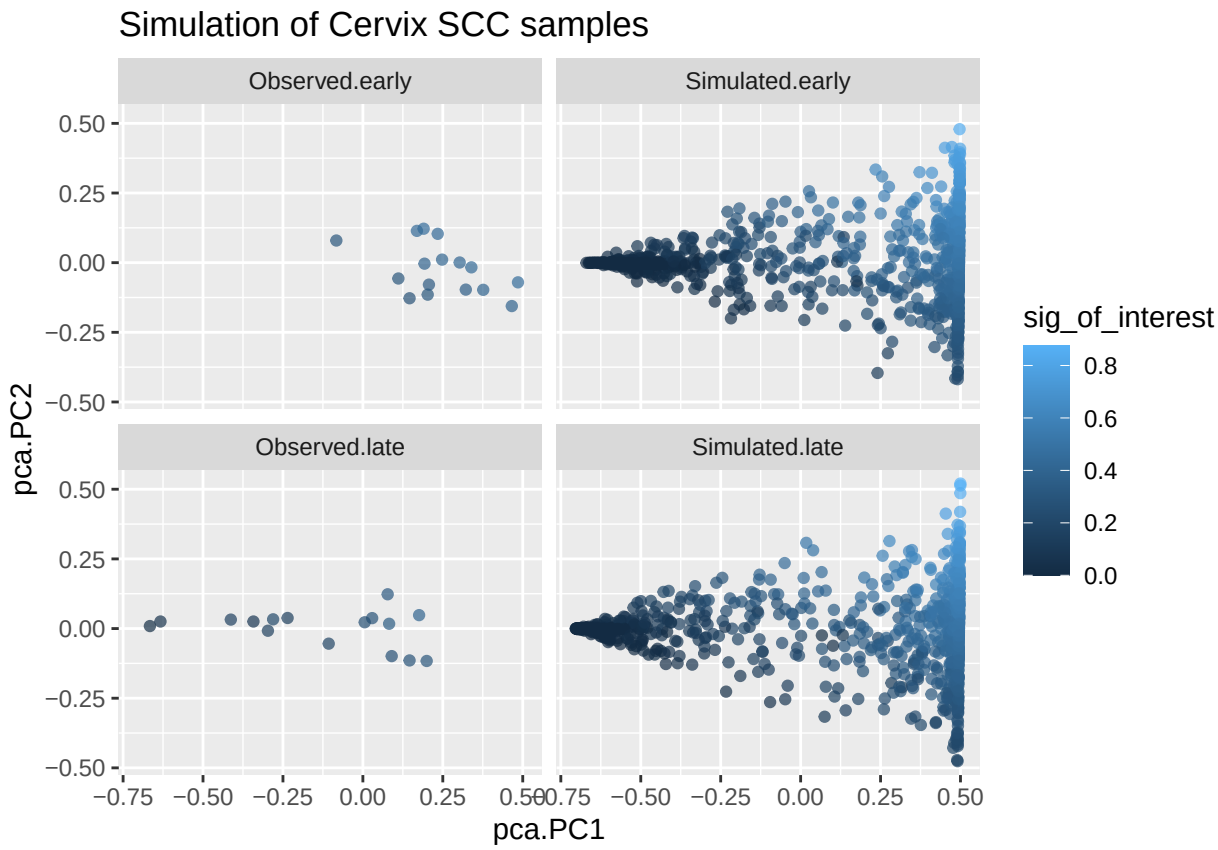
Simulation under inferred data

```
unique(nonexogenous$V1)
```

```
##  [1] "SBS1"  "SBS4"  "SBS5"  "SBS7a" "SBS7b" "SBS7c" "SBS7d" "SBS11" "SBS29"
## [10] "SBS31" "SBS32" "SBS35" "SBS87" "SBS92" "SBS27" "SBS43" "SBS45" "SBS46"
## [19] "SBS47" "SBS48" "SBS49" "SBS50" "SBS51" "SBS52" "SBS53" "SBS54" "SBS55"
## [28] "SBS56" "SBS57" "SBS58" "SBS59" "SBS60"
```

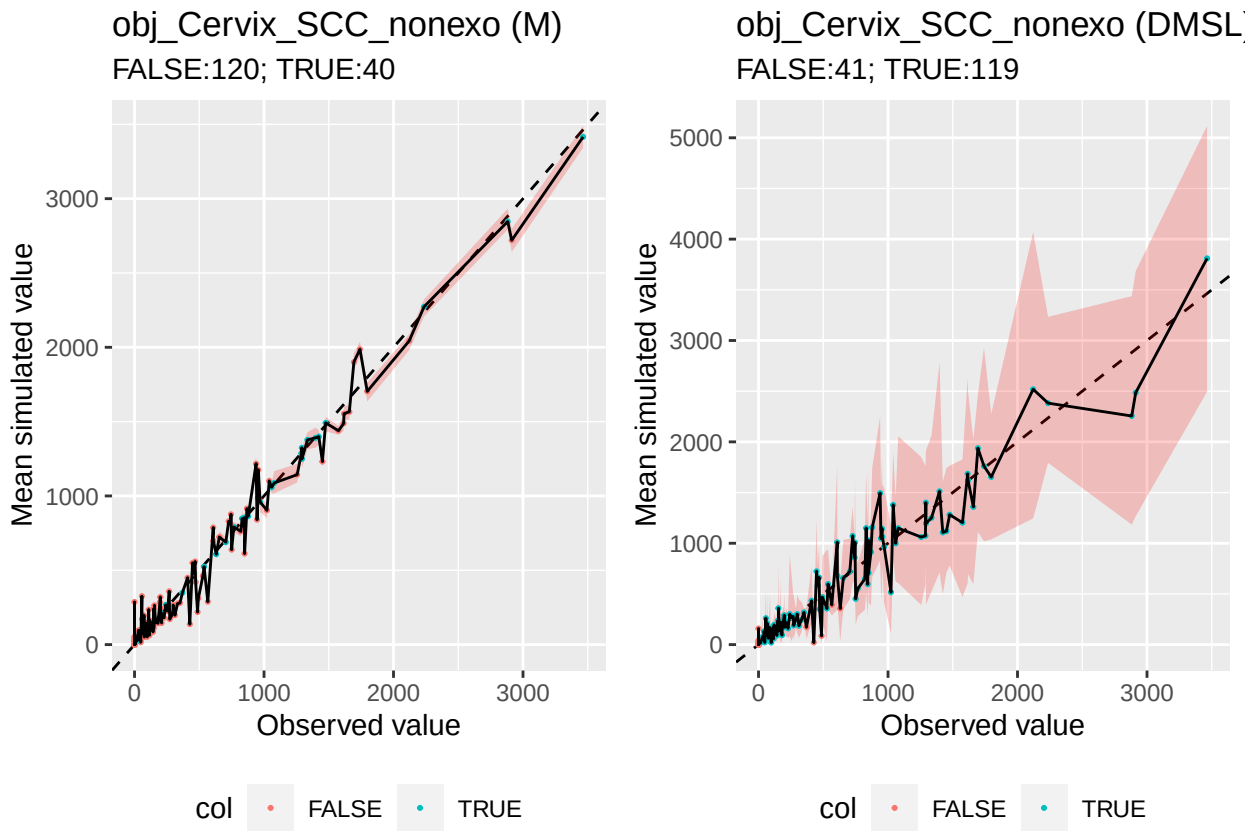
```
## [1] 16
```

```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```



Ranked plot for coverage

```
ct <- "Cervix-SCC"
integer_overdispersion_param_DMSL <- 1
obj_Cervix_SCC_nonexo <- give_subset_sigs_TMBobj(obj_Cervix_SCC, sigs_to_remove = nonexogenous$V1)
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                  data_object = obj_Cervix_SCC_nonexo,
                  print_plot = F, nreps = 20, model = "M")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Cervix_SCC_nonexo,
                  loglog = F, title = 'obj_Cervix_SCC_nonexo (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = fullRE_DMSL_nor
                  data_object = obj_Cervix_SCC_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Cervix_SCC_nonexo,
                  loglog = F, title = 'obj_Cervix_SCC_nonexo (DMSL)'), ncol=2)
```



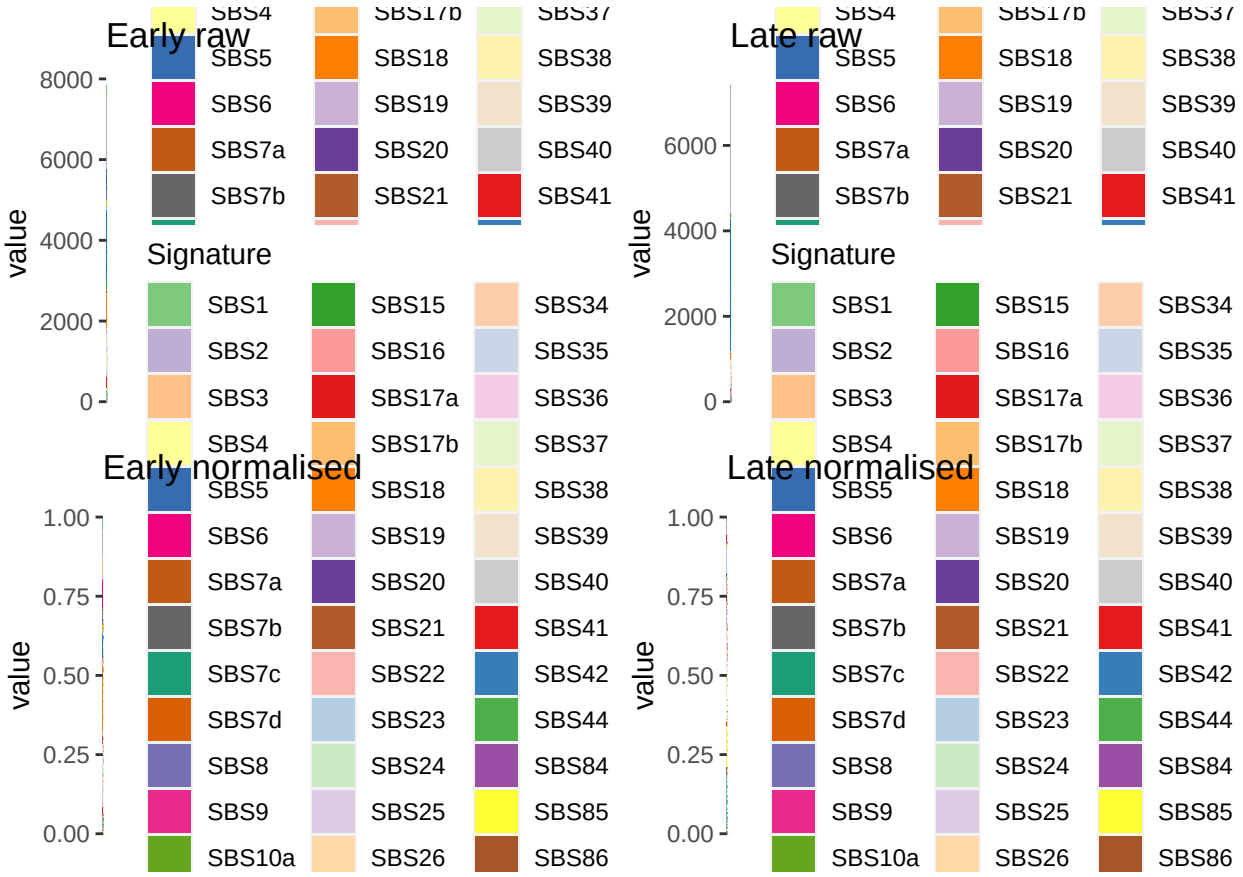
Signatures from mutSigExtractor

```
obj_Cervix_SCC_mutSigExtractor <- load_PCAWG(ct = "Cervix-SCC", typedata = "signaturesmutSigExtractor",
                                     path_to_data = "../../data/")
```

```
## [1] 16
```

```
give_barplot_from_obj(obj = obj_Cervix_SCC_mutSigExtractor, legend_on = TRUE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 16
## Creating plot... it might take some time if the data are large. Number of samples: 16
## Creating plot... it might take some time if the data are large. Number of samples: 16
## Creating plot... it might take some time if the data are large. Number of samples: 16
```

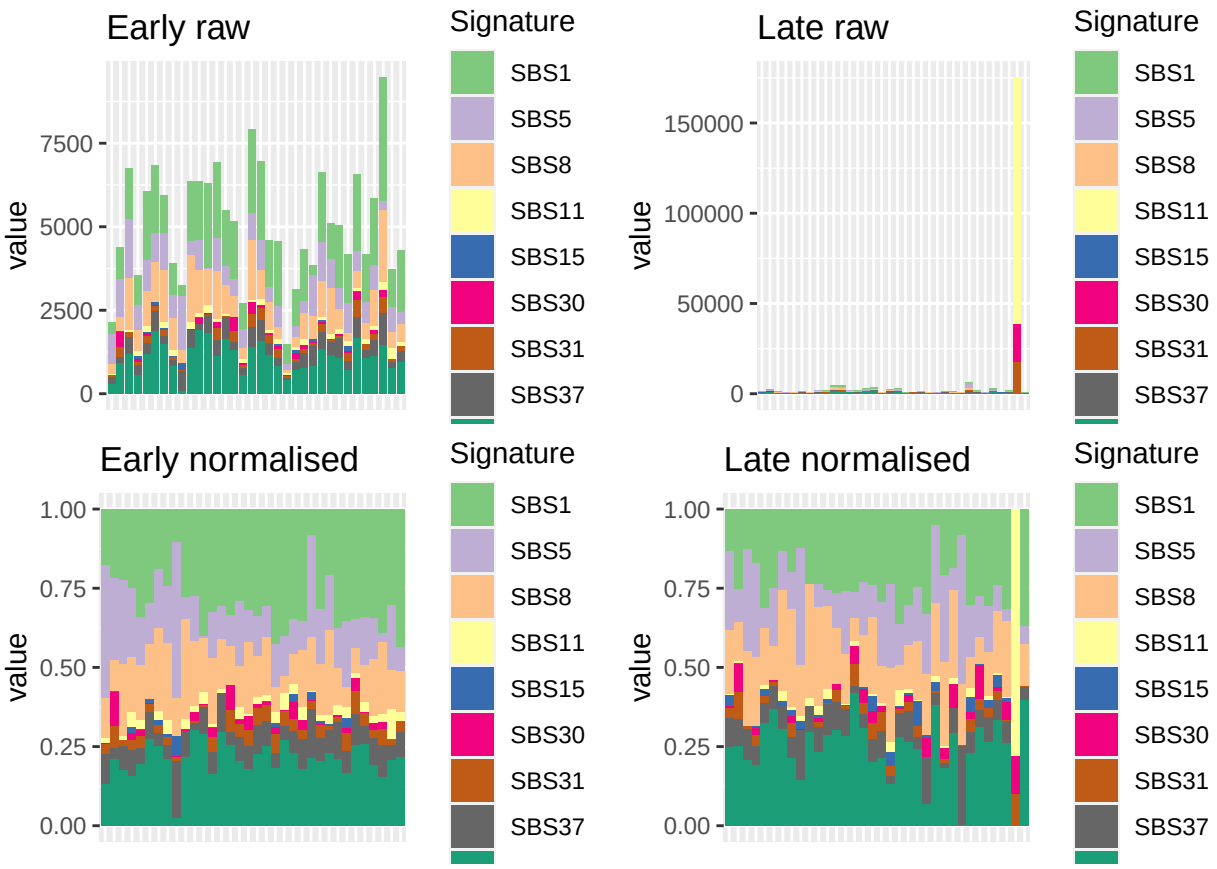


CNS-GBM

Barplot and general statistics

```
## [1] 34
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 34
## Creating plot... it might take some time if the data are large. Number of samples: 34
## Creating plot... it might take some time if the data are large. Number of samples: 34
## Creating plot... it might take some time if the data are large. Number of samples: 34
```



The number of samples and signatures is:

```
## [1] 68  9
```

The signatures are:

```
## [1] "SBS1"  "SBS5"  "SBS8"  "SBS11" "SBS15" "SBS30" "SBS31" "SBS37" "SBS40"
```

Convergence table

We only have converged results for the multinomial with full RE, and the DM with a single lambda (diag and sparse RE). It is the same for nonexogenous signatures.

```
##       value                                L2                  L1
## 1   CNS-GBM    hessian_positivedefinite_bool             diagRE_M
## 2   CNS-GBM    hessian_positivedefinite_bool              fullRE_M
## 3   CNS-GBM hessian_nonpositivedefinite_bool           diagRE_DMDL
## 4   CNS-GBM hessian_nonpositivedefinite_bool          fullRE_halfDM
## 5   CNS-GBM hessian_nonpositivedefinite_bool            fullRE_DMDL
## 6   CNS-GBM    hessian_positivedefinite_bool           diagRE_DMSL
## 7   CNS-GBM    hessian_positivedefinite_bool          sparseRE_DMSL
## 8   CNS-GBM hessian_nonpositivedefinite_bool            fullRE_DMSL
## 9   CNS-GBM hessian_nonpositivedefinite_bool       fullRE_DMSL_SBS1
## 10  CNS-GBM    hessian_positivedefinite_bool        fullRE_M_nonexo
## 11  CNS-GBM    hessian_positivedefinite_bool      diagRE_DMSL_nonexo
## 12  CNS-GBM    hessian_positivedefinite_bool    sparseRE_DMSL_nonexo
```

```
## 13 CNS-GBM hessian_nonpositivedefinite_bool       fullRE_DMSL_nonexo
## 14 CNS-GBM hessian_nonpositivedefinite_bool       fullRE_DMDL_nonexo
## 15 CNS-GBM                          Timeout fullRE_DMDL_sortednonexo
```

Re-running of fitting

Using fullRE_M_nonexo to fit fullRE_DMSL_nonexo

If we use the values of the fullRE M exo as initial values for the fullRE DMSL exo do converge:

```
## [1] TRUE
```

Potentially problematic signatures

We notice that there are no truly problematic signatures (SBS15 has the most zeros; 50%).

```
colSums(obj_CNS_GBM$Y == 0)/nrow(obj_CNS_GBM$Y)
```

```
##       SBS1       SBS5       SBS8      SBS11      SBS15      SBS30      SBS31
## 0.01470588 0.02941176 0.01470588 0.20588235 0.50000000 0.33823529 0.13235294
##      SBS37      SBS40
## 0.01470588 0.02941176
```

```
colSums(obj_CNS_GBM$Y)/sum(obj_CNS_GBM$Y)
```

```
##        SBS1        SBS5        SBS8       SBS11       SBS15       SBS30
## 0.164856854 0.087757118 0.103223676 0.345294365 0.004258098 0.060917020
##       SBS31       SBS37       SBS40
## 0.060793210 0.046931329 0.125968329
```

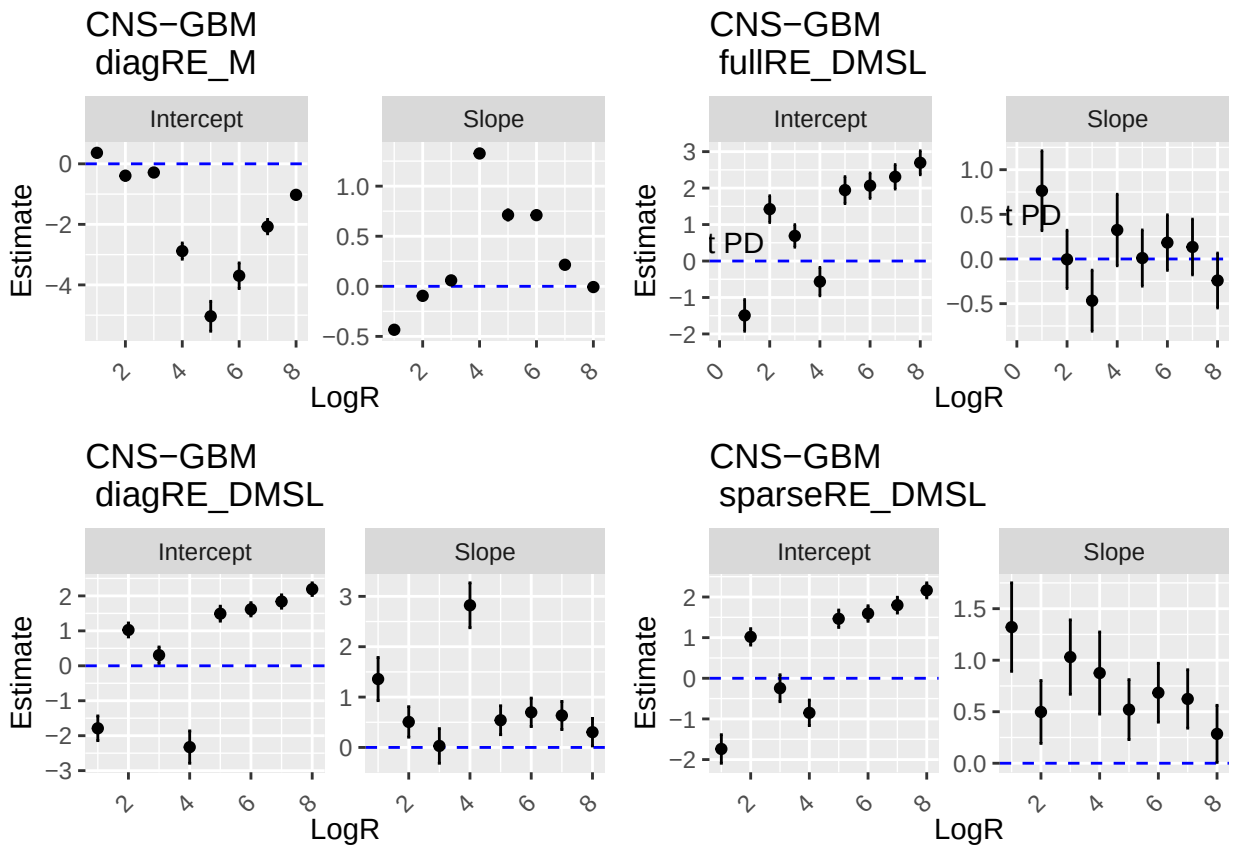
```
additional_sortedMnonexo <- list()
additional_sortedDMSLnonexo <- list()
```

```
additional_sortedMnonexo[["CNS-GBM"]] <- sortedM_CNSGBM
additional_sortedDMSLnonexo[["CNS-GBM"]] <- sortedDM_CNSGBM
```

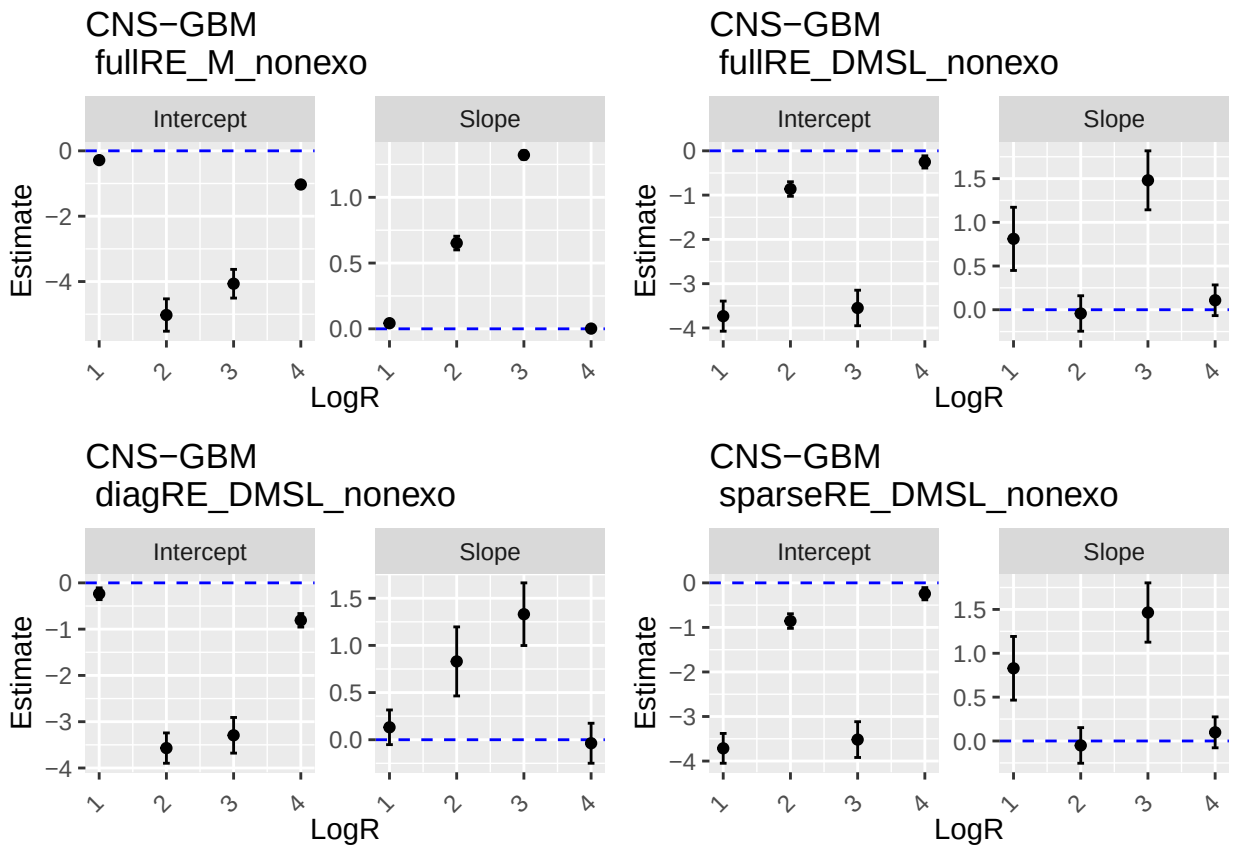
Betas

```
ct <- "CNS-GBM"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```



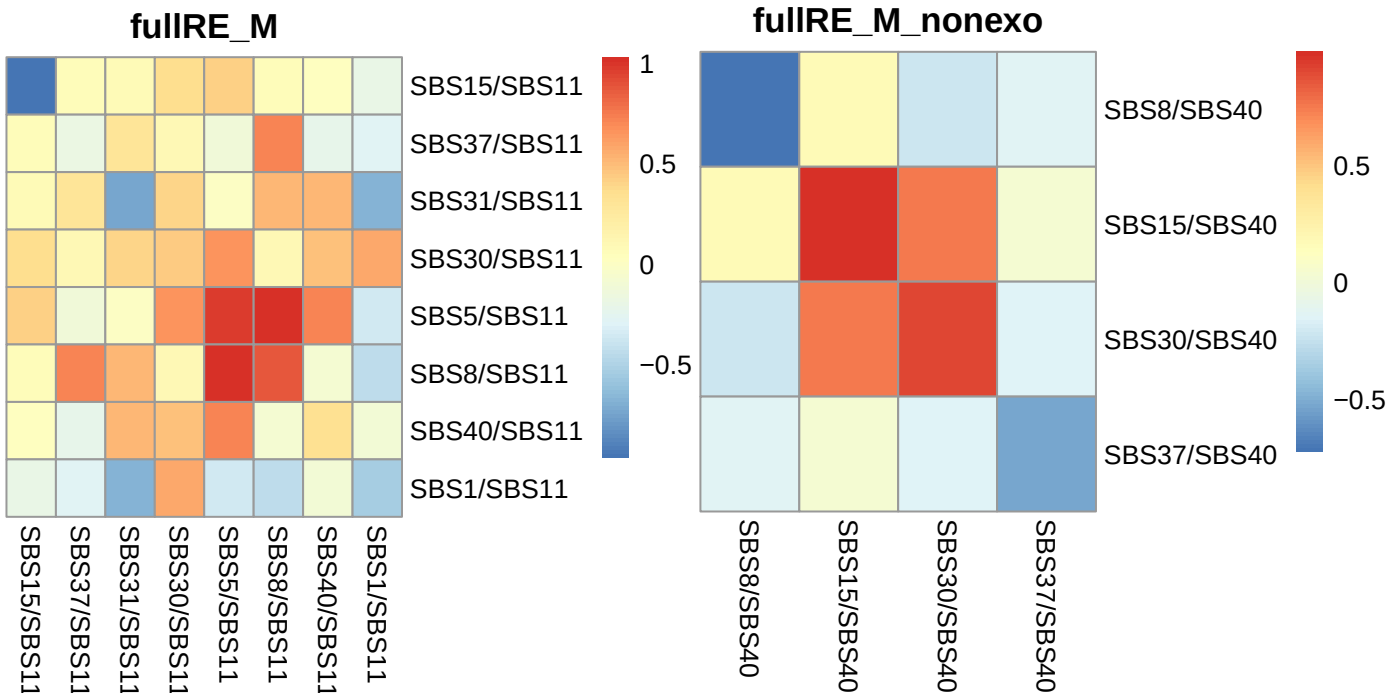

```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(sortedDM_CNSGBM)+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```

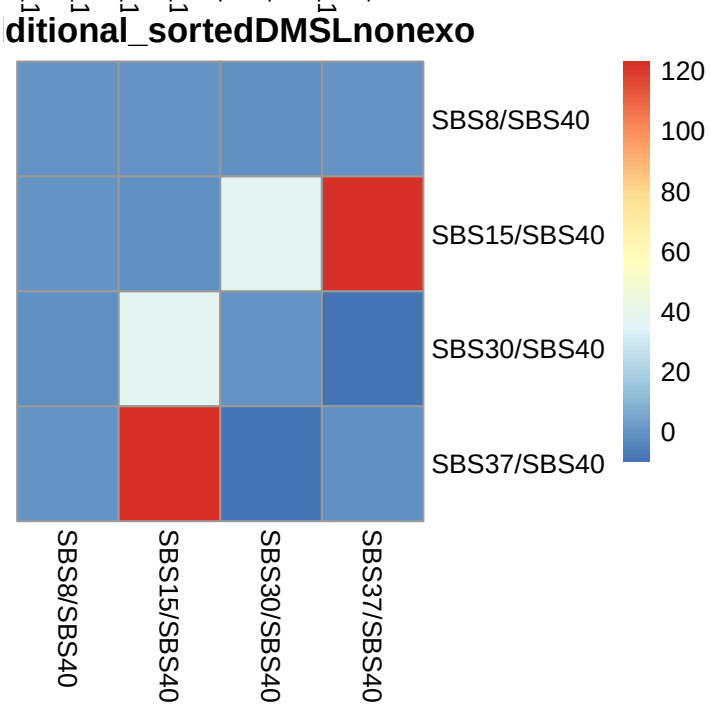



```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct

## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used

## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 6.6827492×10^{-5}.

Covariance matrices

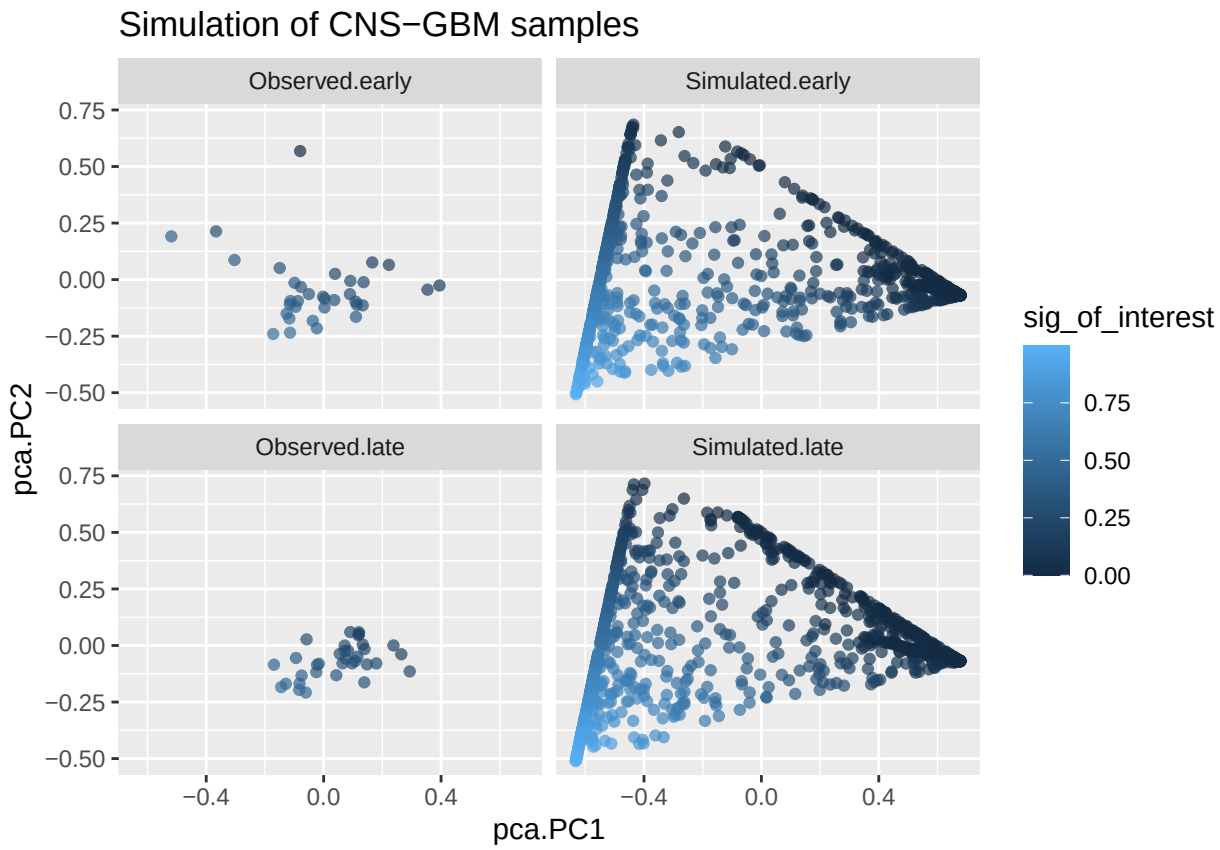




Simulation under inferred data

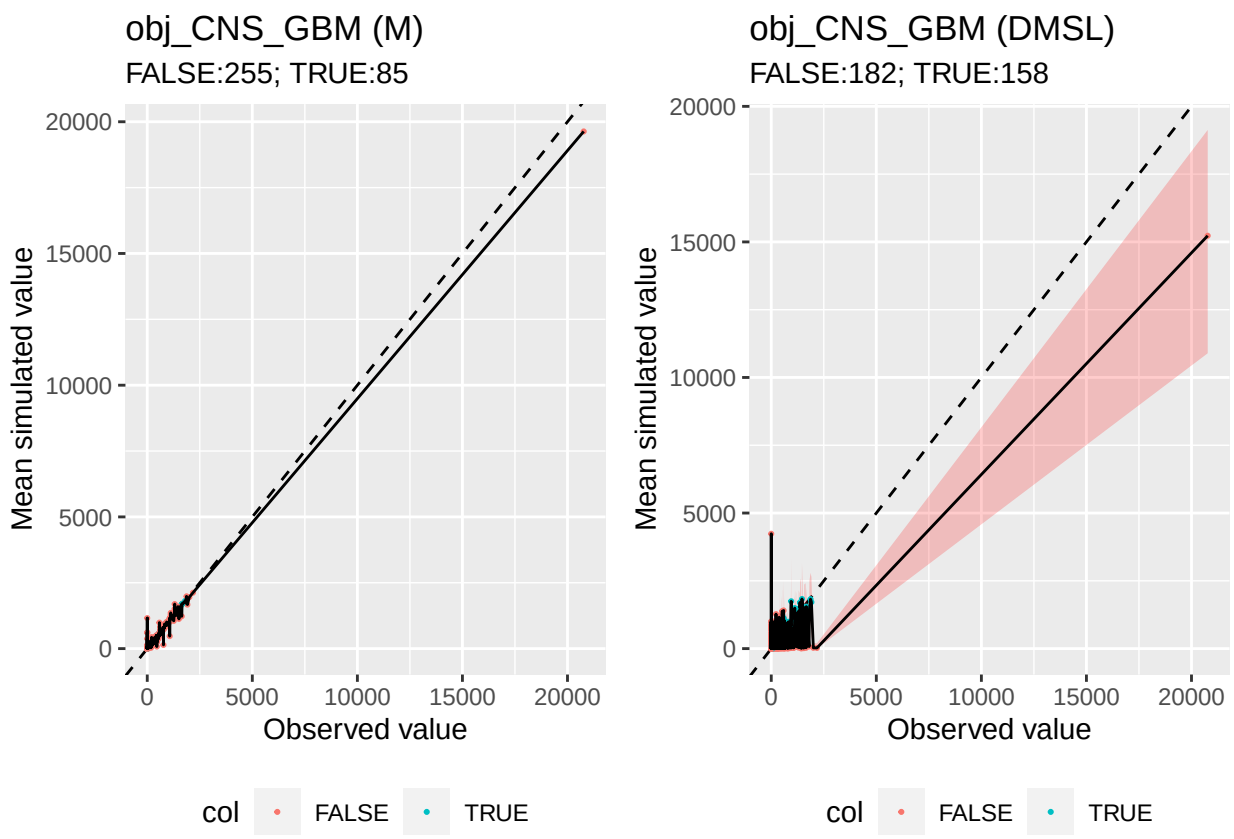
```
## [1] 34
```

```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```



Ranked plot for coverage

```
ct <- "CNS-GBM"
integer_overdispersion_param_DMSL <- 1
obj_CNS_GBM_nonexo <- give_subset_sigs_TMBobj(obj_CNS_GBM, sigs_to_remove = nonexogenous$V1)
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                  data_object = obj_CNS_GBM_nonexo,
                  print_plot = F, nreps = 20, model = "M")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_CNS_GBM_nonexo,
                  loglog = F, title = 'obj_CNS_GBM (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = sortedDM_CNSGBM
                  data_object = obj_CNS_GBM_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_CNS_GBM_nonexo,
            loglog = F, title = 'obj_CNS_GBM (DMSL)'), ncol=2)
```



Surprisingly, the values for DMSL look even worse than the multinomial, for high values

Signatures from mutSigExtractor

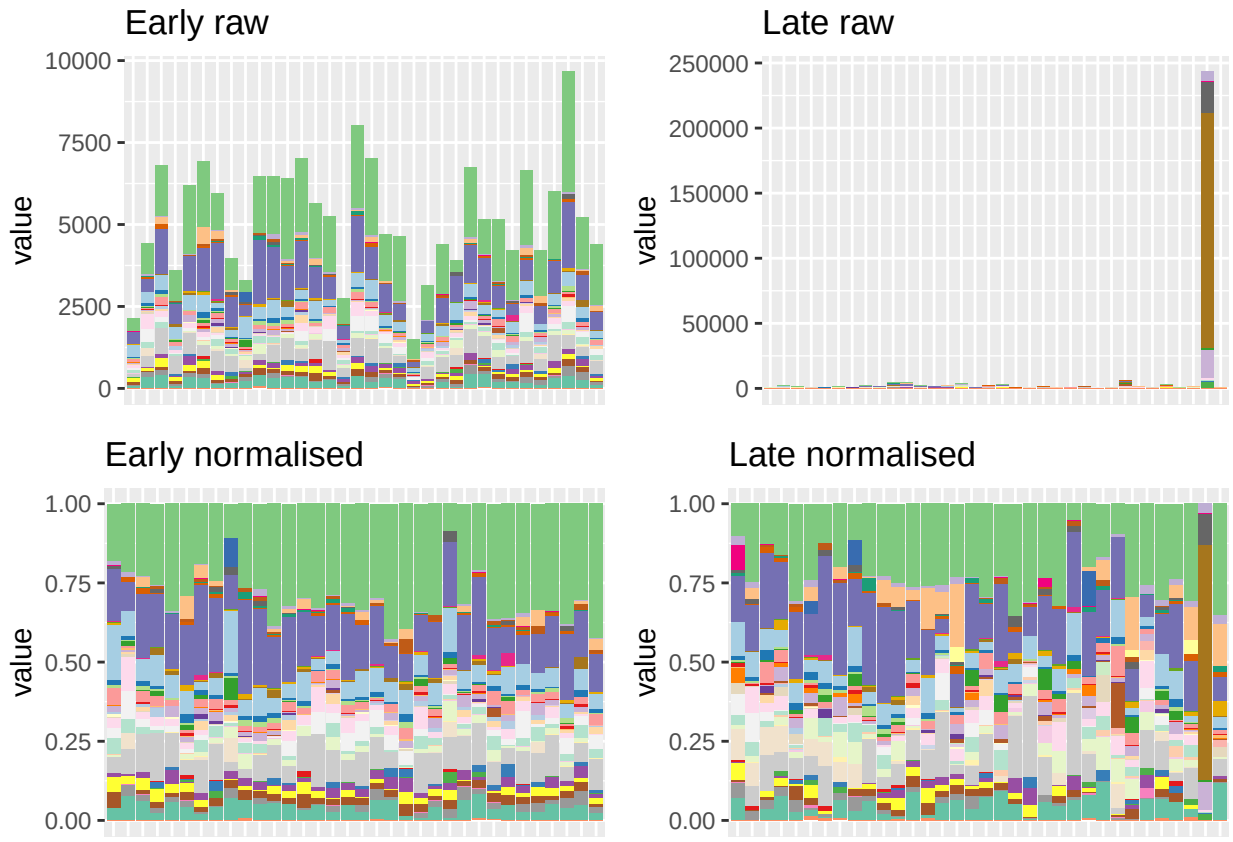
The signatures from mutSigExtractor are a bit more chaotic:

```
obj_CNS_GBM_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                          path_to_data = "../../data/")
```

```
## [1] 34
```

```
give_barplot_from_obj(obj = obj_CNS_GBM_mutSigExtractor, legend_on = FALSE)
```

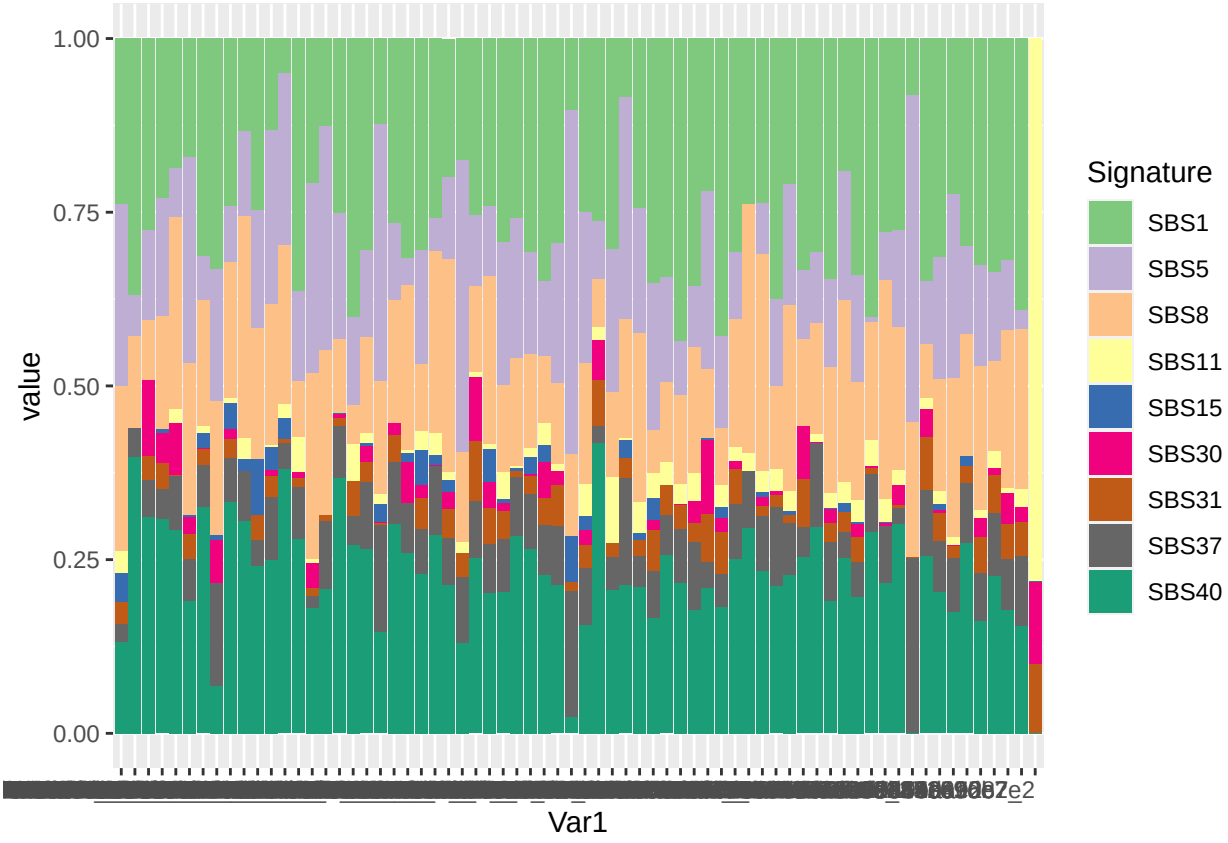
```
## Creating plot... it might take some time if the data are large. Number of samples: 34
## Creating plot... it might take some time if the data are large. Number of samples: 34
## Creating plot... it might take some time if the data are large. Number of samples: 34
## Creating plot... it might take some time if the data are large. Number of samples: 34
```



Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_CNS_GBM$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_CNS_GBM$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 68
```

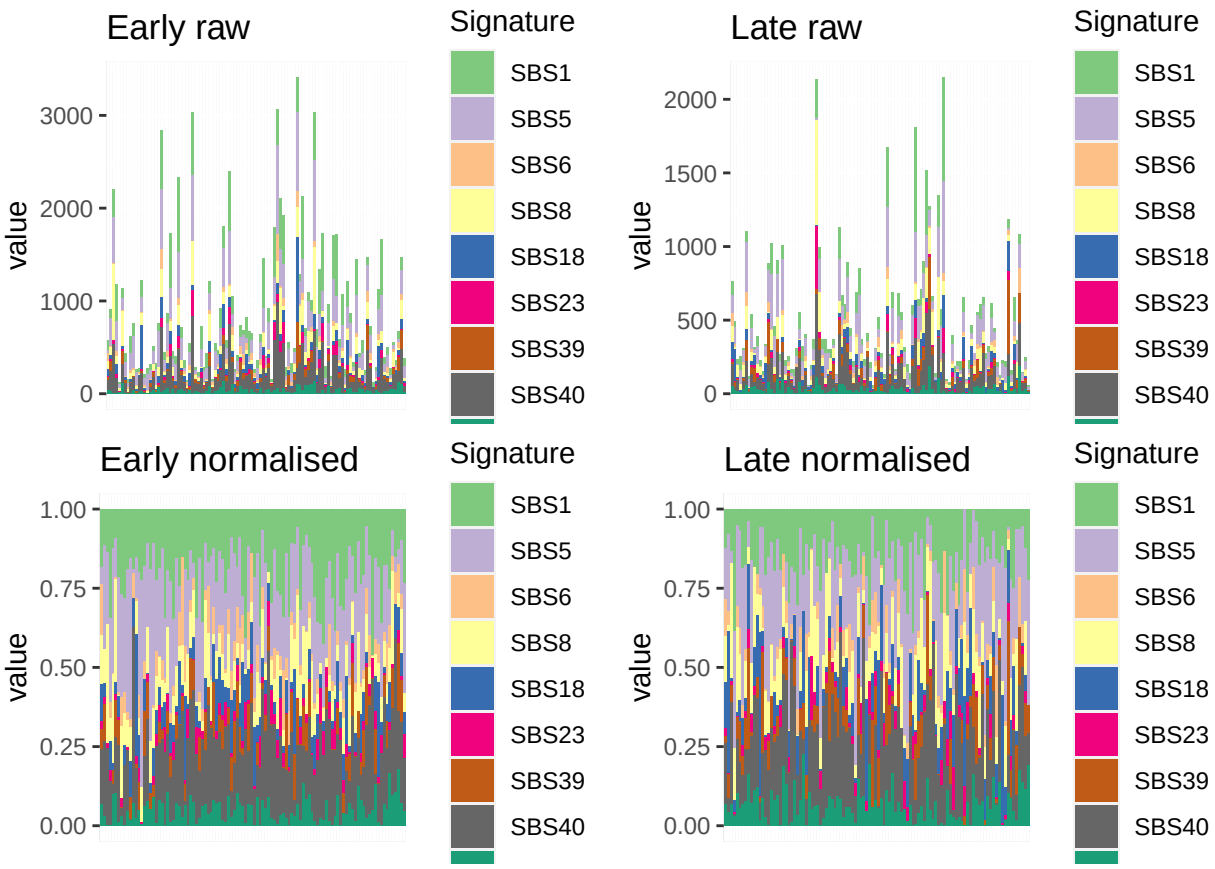


CNS-Medullo

Barplot and general statistics

```
## [1] 106
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 106
## Creating plot... it might take some time if the data are large. Number of samples: 106
## Creating plot... it might take some time if the data are large. Number of samples: 106
## Creating plot... it might take some time if the data are large. Number of samples: 106
```



The number of samples and signatures is:

```
## [1] 212   9
```

The signatures are:

```
## [1] "SBS1"  "SBS5"  "SBS6"  "SBS8"  "SBS18" "SBS23" "SBS39" "SBS40" "SBS46"
```

Convergence table

Pretty much everything has converged in this case

```
##          value                                L2                    L1
## 1  CNS-Medullo    hessian_positivedefinite_bool             diagRE_M
## 2  CNS-Medullo    hessian_positivedefinite_bool             fullRE_M
## 3  CNS-Medullo    hessian_positivedefinite_bool           diagRE_DMDL
## 4  CNS-Medullo hessian_nonpositivedefinite_bool         fullRE_halfDM
## 5  CNS-Medullo hessian_nonpositivedefinite_bool           fullRE_DMDL
## 6  CNS-Medullo    hessian_positivedefinite_bool           diagRE_DMSL
## 7  CNS-Medullo    hessian_positivedefinite_bool         sparseRE_DMSL
## 8  CNS-Medullo hessian_nonpositivedefinite_bool           fullRE_DMSL
## 9  CNS-Medullo hessian_nonpositivedefinite_bool      fullRE_DMSL_SBS1
## 10 CNS-Medullo    hessian_positivedefinite_bool       fullRE_M_nonexo
## 11 CNS-Medullo    hessian_positivedefinite_bool     diagRE_DMSL_nonexo
## 12 CNS-Medullo    hessian_positivedefinite_bool   sparseRE_DMSL_nonexo
## 13 CNS-Medullo    hessian_positivedefinite_bool     fullRE_DMSL_nonexo
```

```
## 14 CNS-Medullo    hessian_positivedefinite_bool       fullRE_DMDL_nonexo
## 15 CNS-Medullo hessian_nonpositivedefinite_bool fullRE_DMDL_sortednonexo
```

As nonexo DMSL has already converged, we don't re-run anything.

Potentially problematic signatures

We notice that there are no truly problematic signatures

```
colSums(obj_CNS_Medullo$Y == 0)/nrow(obj_CNS_Medullo$Y)
```

```
##        SBS1        SBS5        SBS6        SBS8       SBS18       SBS23
## 0.004716981 0.056603774 0.264150943 0.089622642 0.155660377 0.235849057
##       SBS39       SBS40       SBS46
## 0.353773585 0.066037736 0.099056604
```

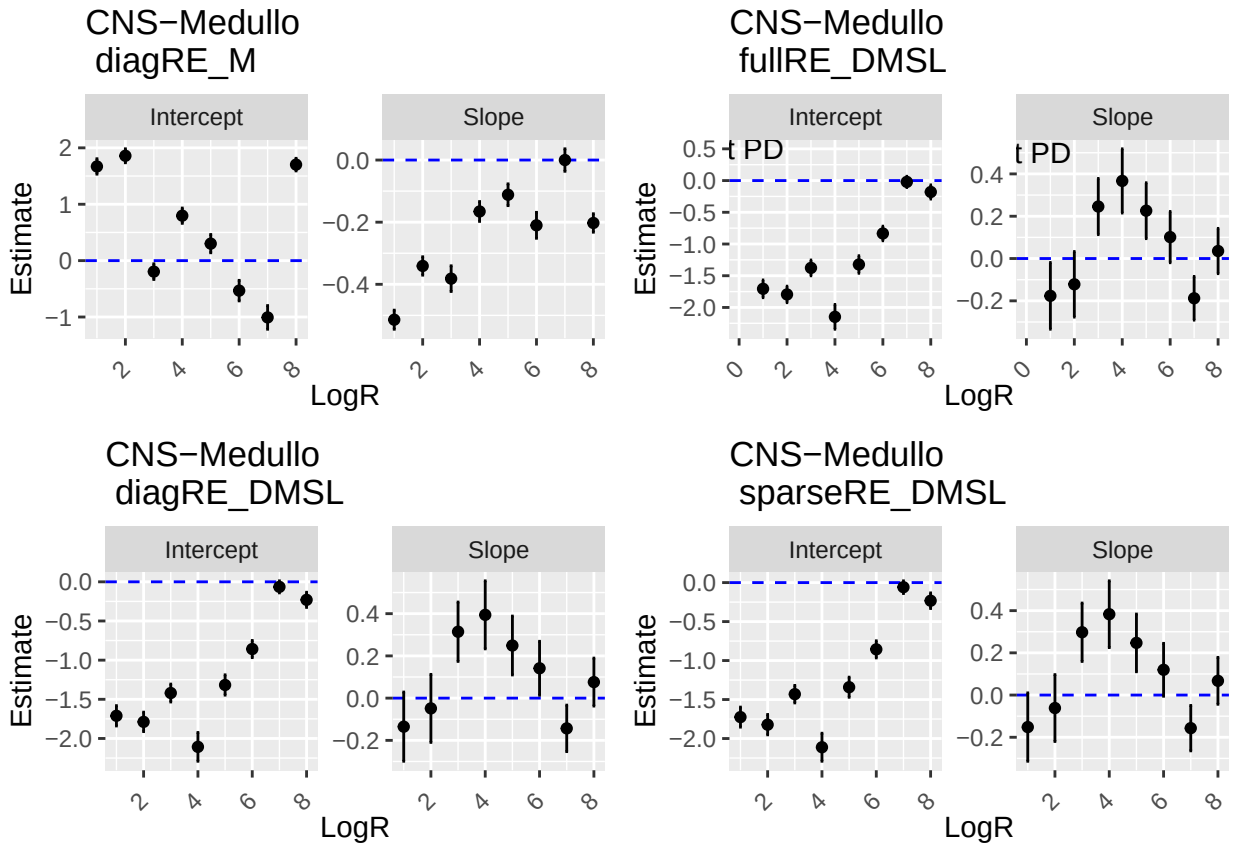
```
colSums(obj_CNS_Medullo$Y)/sum(obj_CNS_Medullo$Y)
```

```
##       SBS1       SBS5       SBS6       SBS8      SBS18      SBS23      SBS39
## 0.19177483 0.22946904 0.03737123 0.11614418 0.07466844 0.03836035 0.05498025
##      SBS40      SBS46
## 0.21065558 0.04657610
```

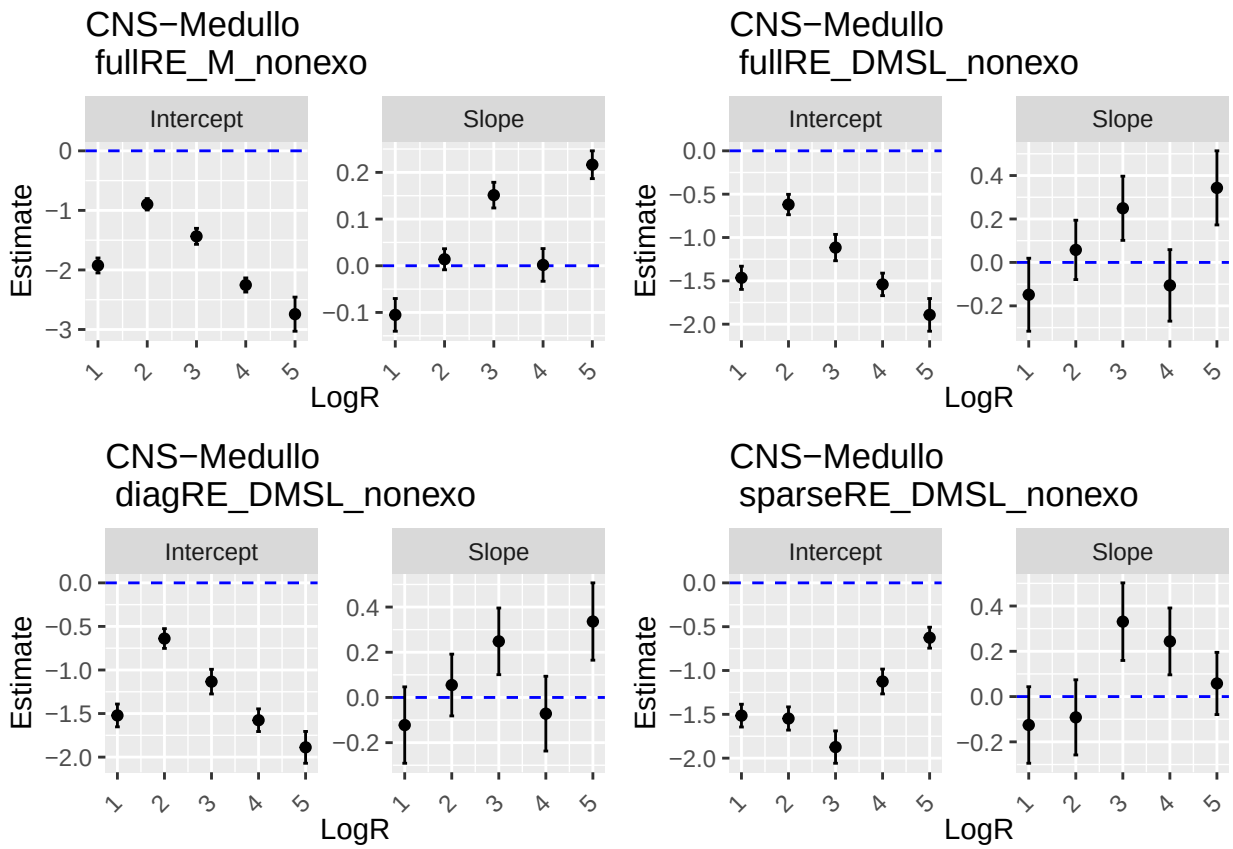
Betas

```
ct <- "CNS-Medullo"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```



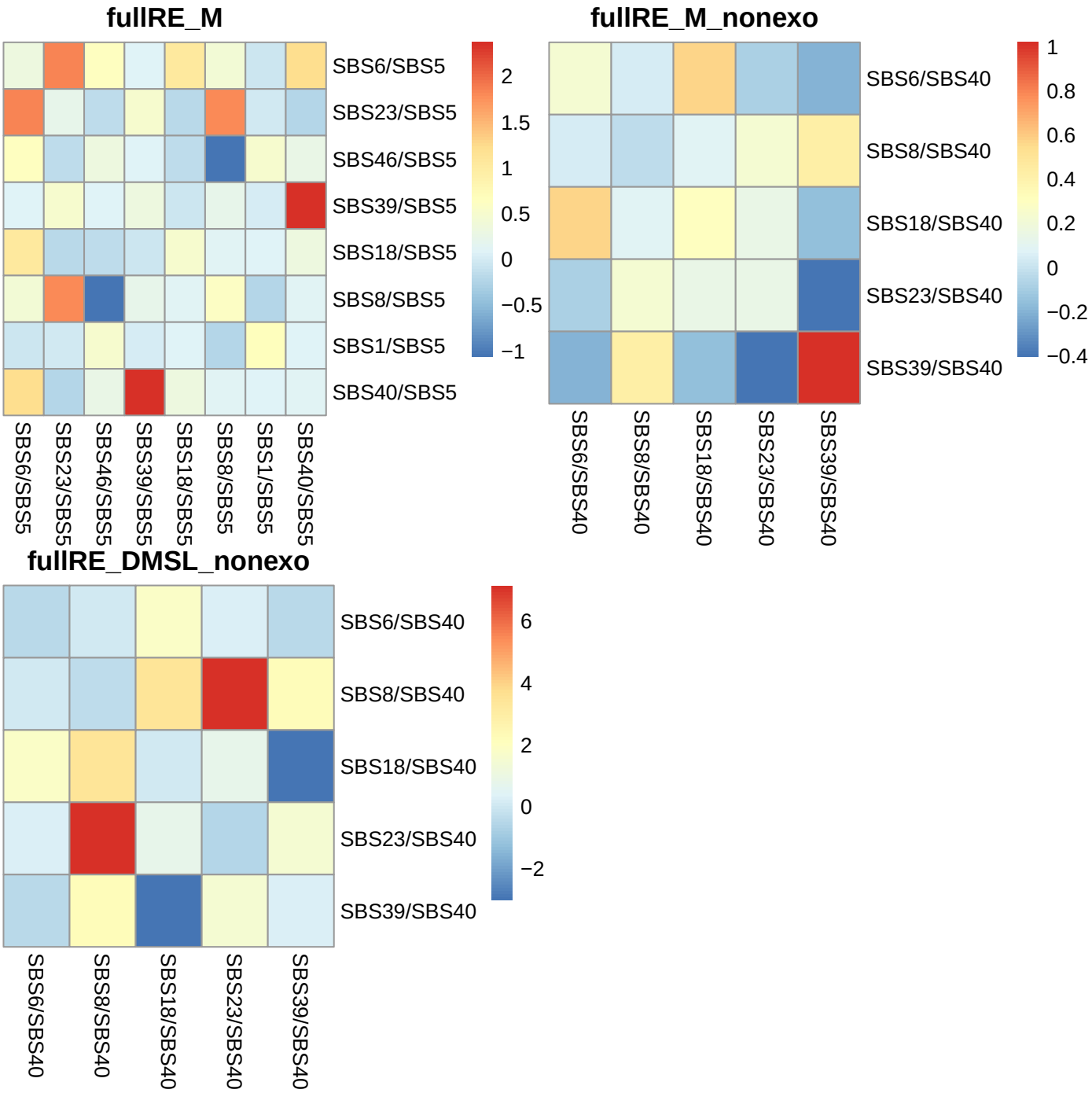

```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(fullRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct

## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used

## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 0.0677062.

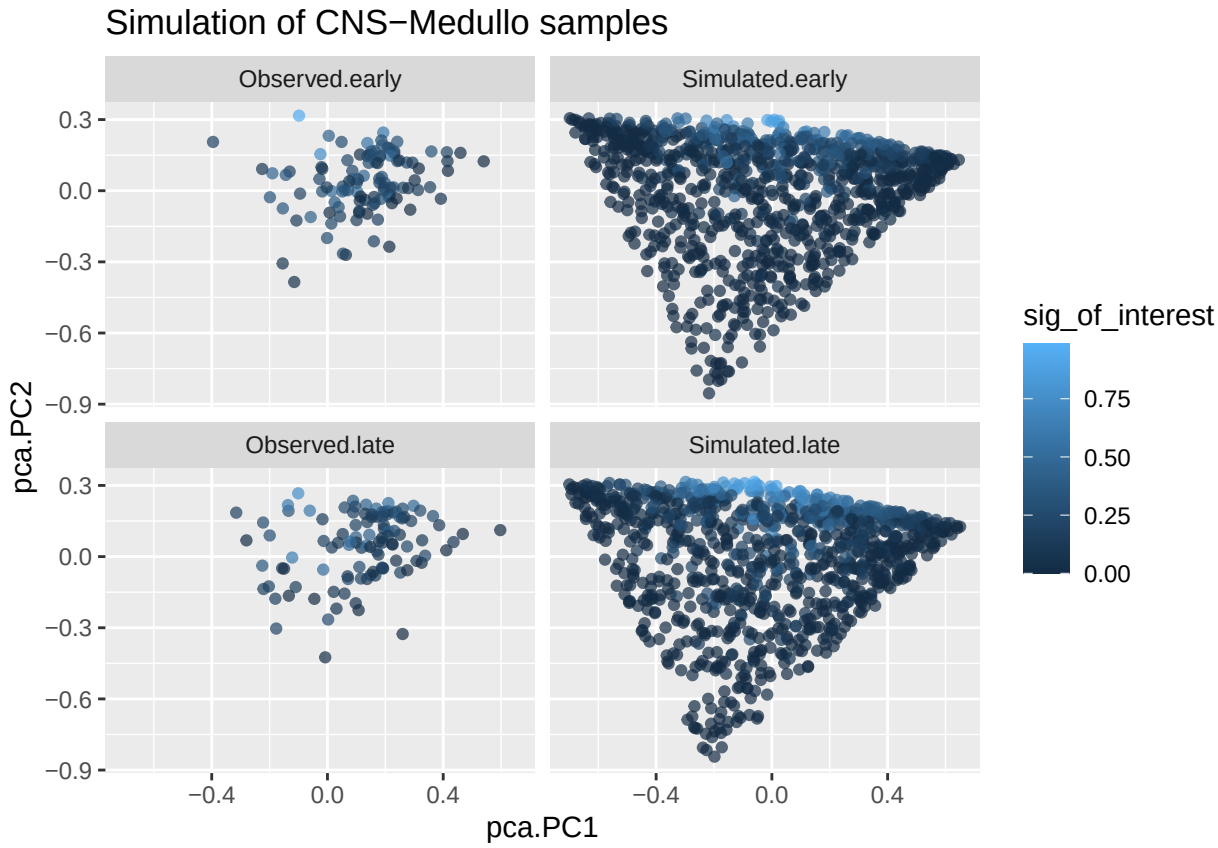
Covariance matrices



Simulation under inferred data

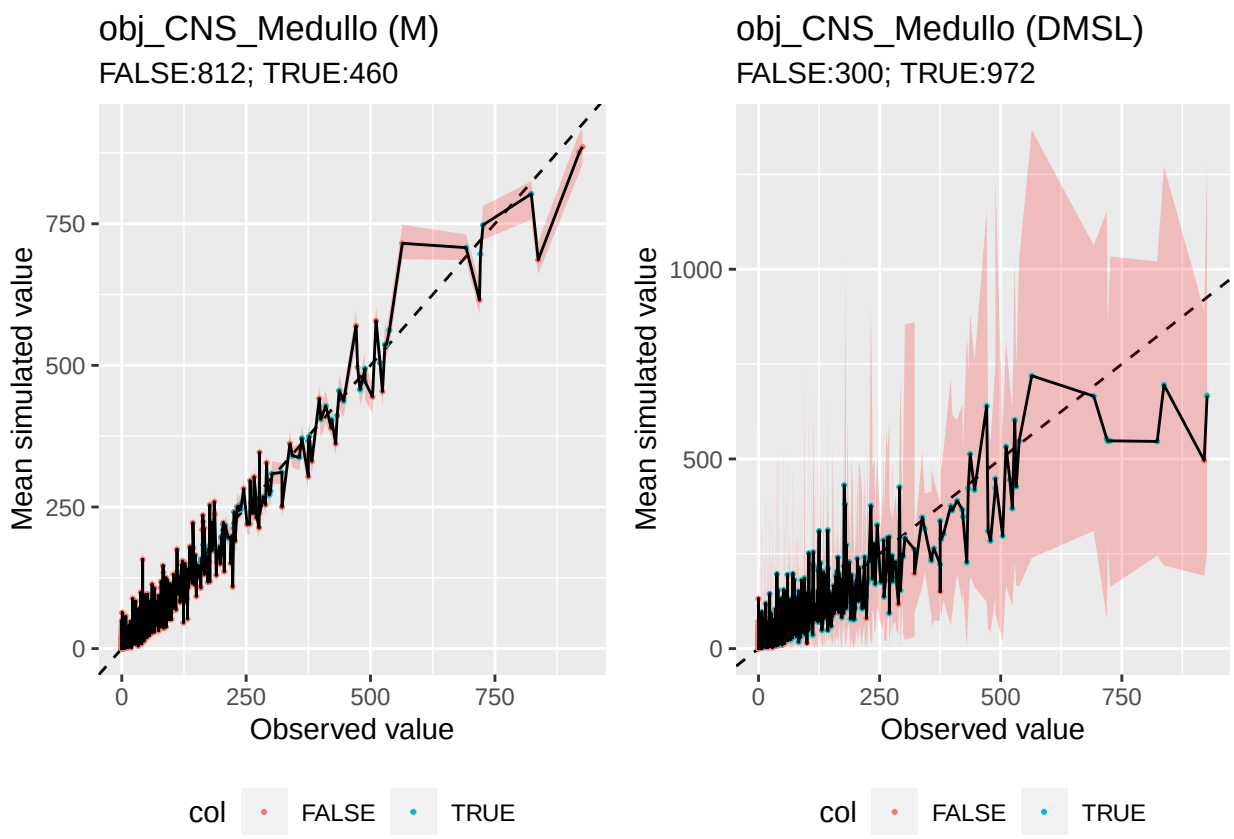
```
## [1] 106
```

```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```



Ranked plot for coverage

```
ct <- "CNS-Medullo"
integer_overdispersion_param_DMSL <- 1
obj_CNS_Medullo_nonexo <- give_subset_sigs_TMBobj(obj_CNS_Medullo, sigs_to_remove = nonexogenous$V1)
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                  data_object = obj_CNS_Medullo_nonexo,
                  print_plot = F, nreps = 20, model = "M")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_CNS_Medullo_nonexo,
                  loglog = F, title = 'obj_CNS_Medullo (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = fullRE_DMSL_nor
                  data_object = obj_CNS_Medullo_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_CNS_Medullo_nonexo,
           loglog = F, title = 'obj_CNS_Medullo (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

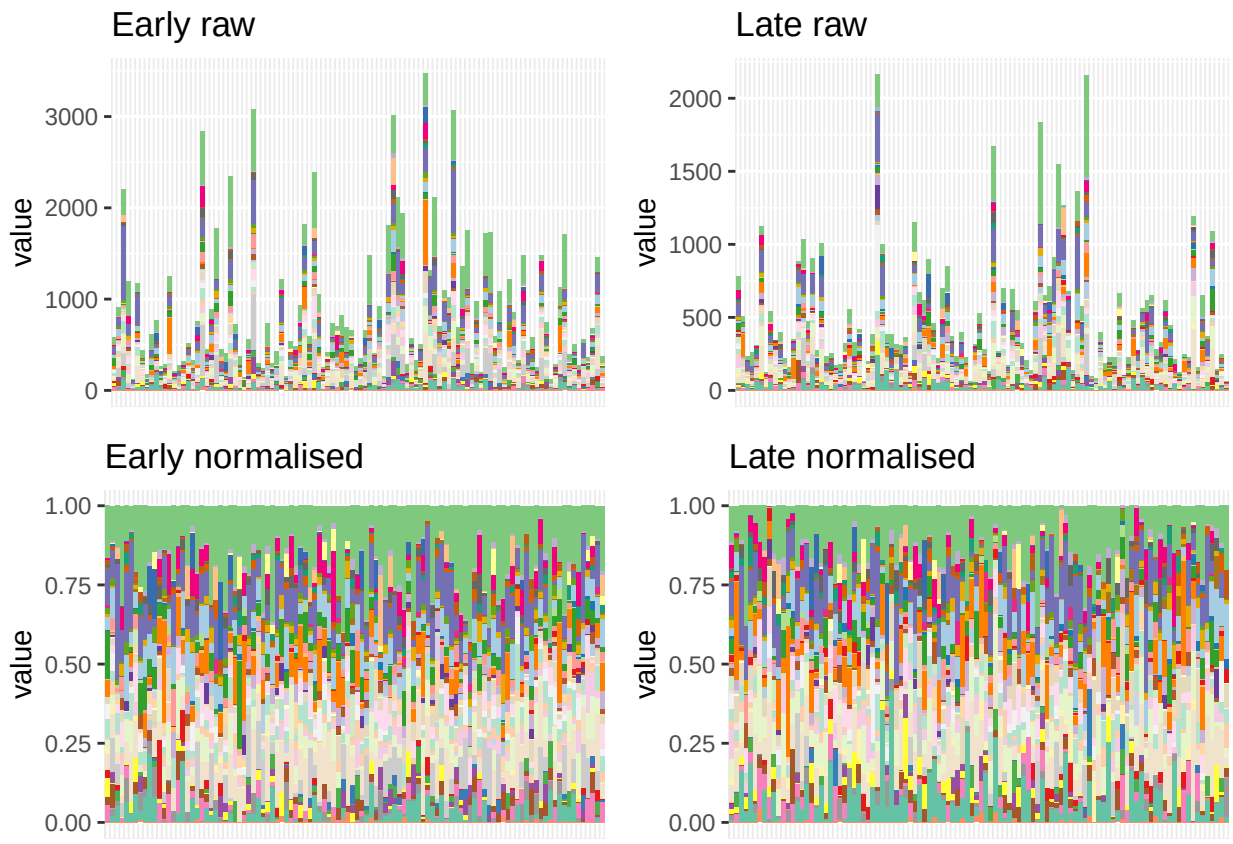
The signatures from mutSigExtractor are a bit more chaotic:

```
obj_CNS_Medullo_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                   path_to_data = "../../data/")
```

```
## [1] 106
```

```
give_barplot_from_obj(obj = obj_CNS_Medullo_mutSigExtractor, legend_on = FALSE)
```

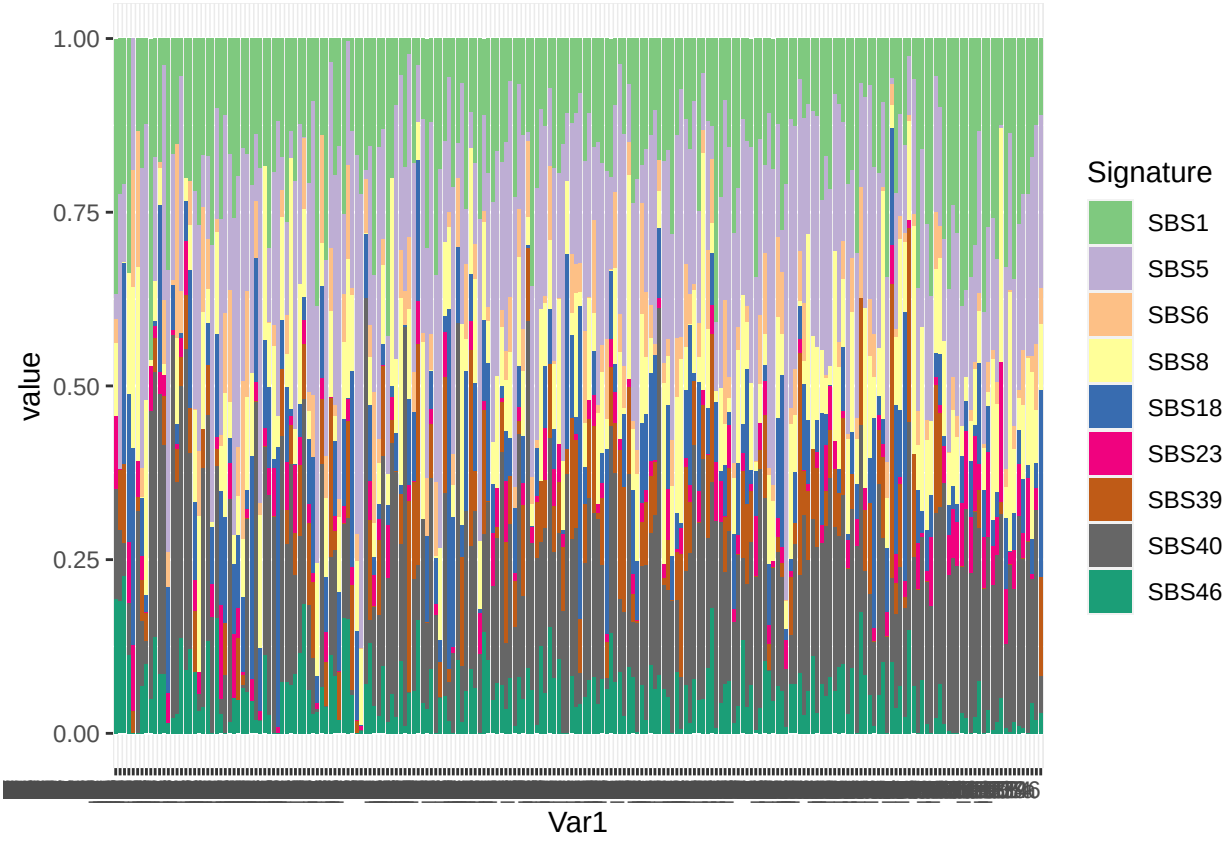
```
## Creating plot... it might take some time if the data are large. Number of samples: 106
## Creating plot... it might take some time if the data are large. Number of samples: 106
## Creating plot... it might take some time if the data are large. Number of samples: 106
## Creating plot... it might take some time if the data are large. Number of samples: 106
```



Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_CNS_Medullo$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_CNS_Medullo$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 212
```

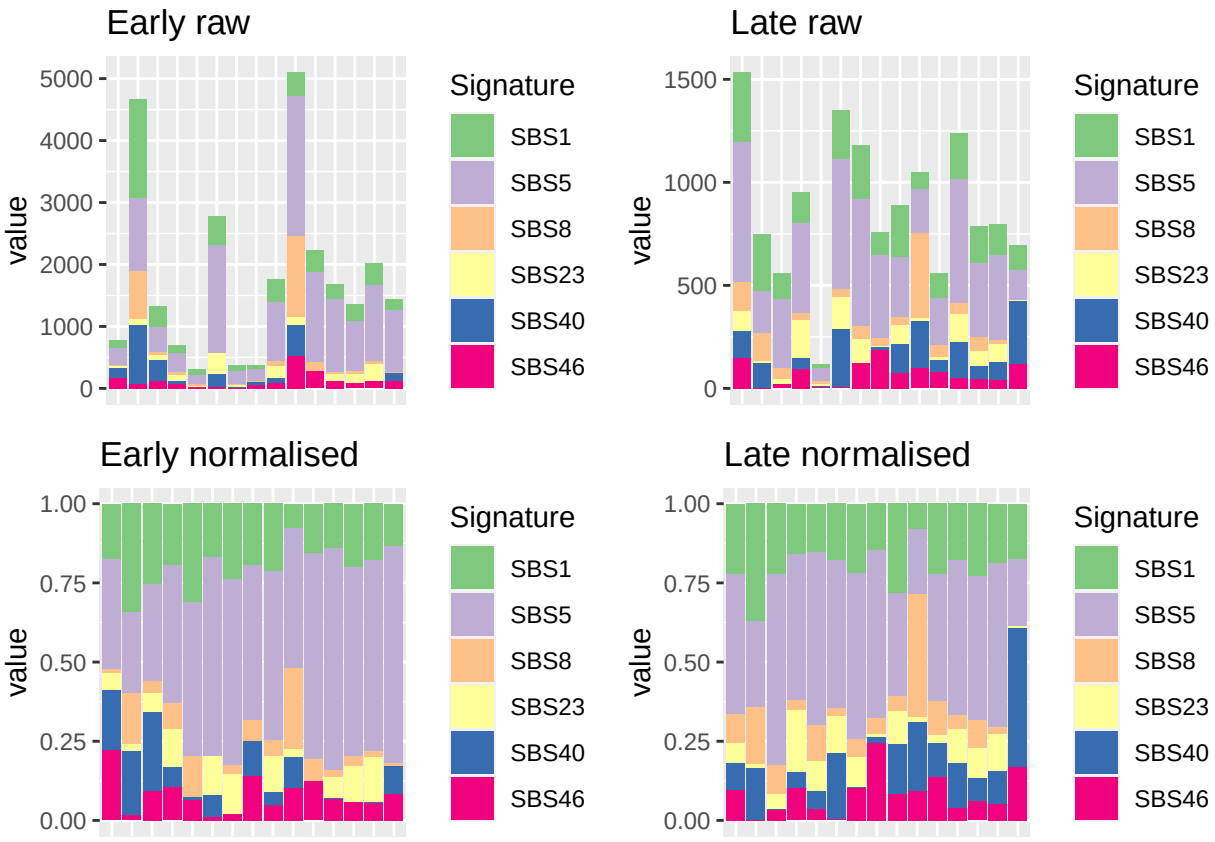


CNS-Oligo

Barplot and general statistics

```
## [1] 15
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 15
## Creating plot... it might take some time if the data are large. Number of samples: 15
## Creating plot... it might take some time if the data are large. Number of samples: 15
## Creating plot... it might take some time if the data are large. Number of samples: 15
```



The number of samples and signatures is:

```
## [1] 30  6
```

The signatures are:

```
## [1] "SBS1"  "SBS5"  "SBS8"  "SBS23" "SBS40" "SBS46"
```

Convergence table

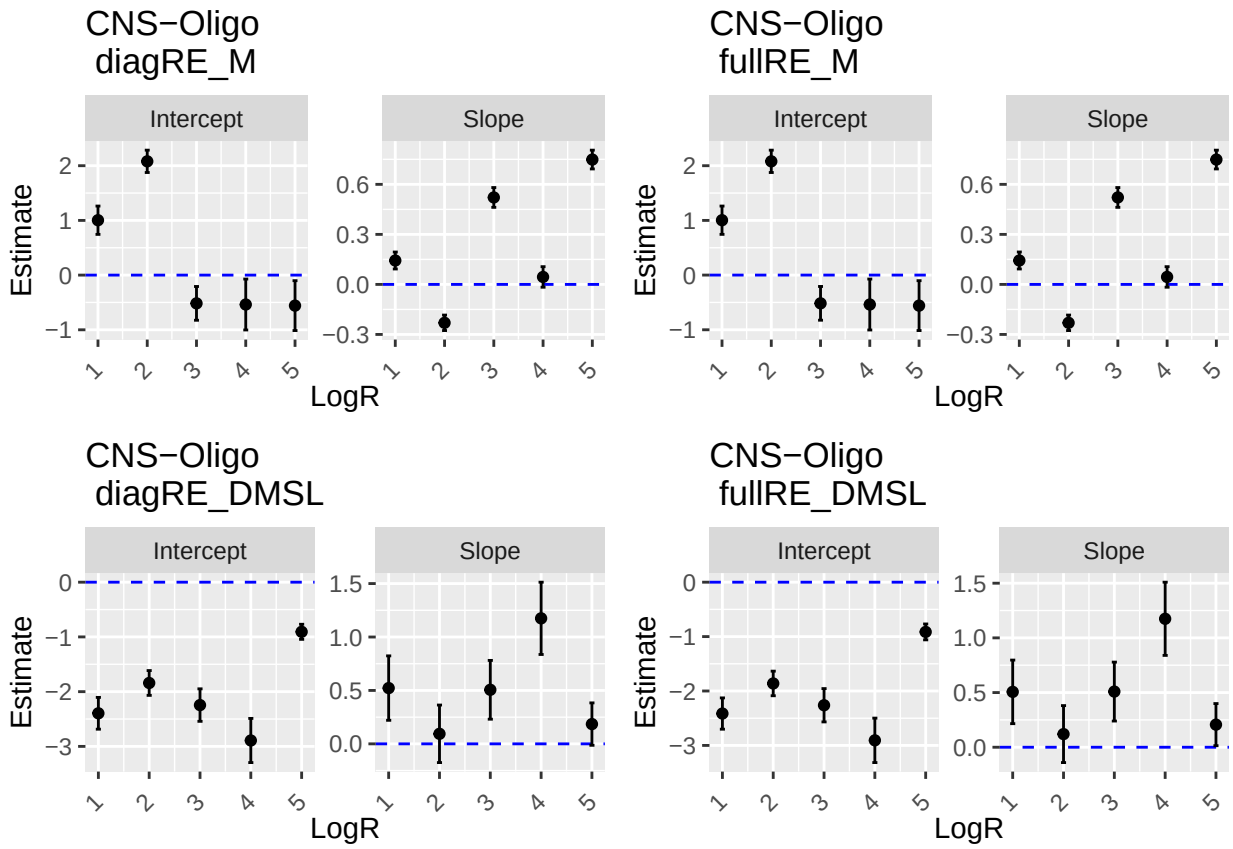
Pretty much everything has converged

```
##        value                                L2                   L1
## 1  CNS-Oligo    hessian_positivedefinite_bool               diagRE_M
## 2  CNS-Oligo    hessian_positivedefinite_bool               fullRE_M
## 3  CNS-Oligo    hessian_positivedefinite_bool            diagRE_DMDL
## 4  CNS-Oligo hessian_nonpositivedefinite_bool          fullRE_halfDM
## 5  CNS-Oligo hessian_nonpositivedefinite_bool            fullRE_DMDL
## 6  CNS-Oligo    hessian_positivedefinite_bool            diagRE_DMSL
## 7  CNS-Oligo    hessian_positivedefinite_bool          sparseRE_DMSL
## 8  CNS-Oligo    hessian_positivedefinite_bool            fullRE_DMSL
## 9  CNS-Oligo hessian_nonpositivedefinite_bool       fullRE_DMSL_SBS1
## 10 CNS-Oligo    hessian_positivedefinite_bool        fullRE_M_nonexo
## 11 CNS-Oligo    hessian_positivedefinite_bool     diagRE_DMSL_nonexo
## 12 CNS-Oligo                          Timeout   sparseRE_DMSL_nonexo
## 13 CNS-Oligo    hessian_positivedefinite_bool     fullRE_DMSL_nonexo
## 14 CNS-Oligo    hessian_positivedefinite_bool     fullRE_DMDL_nonexo
```

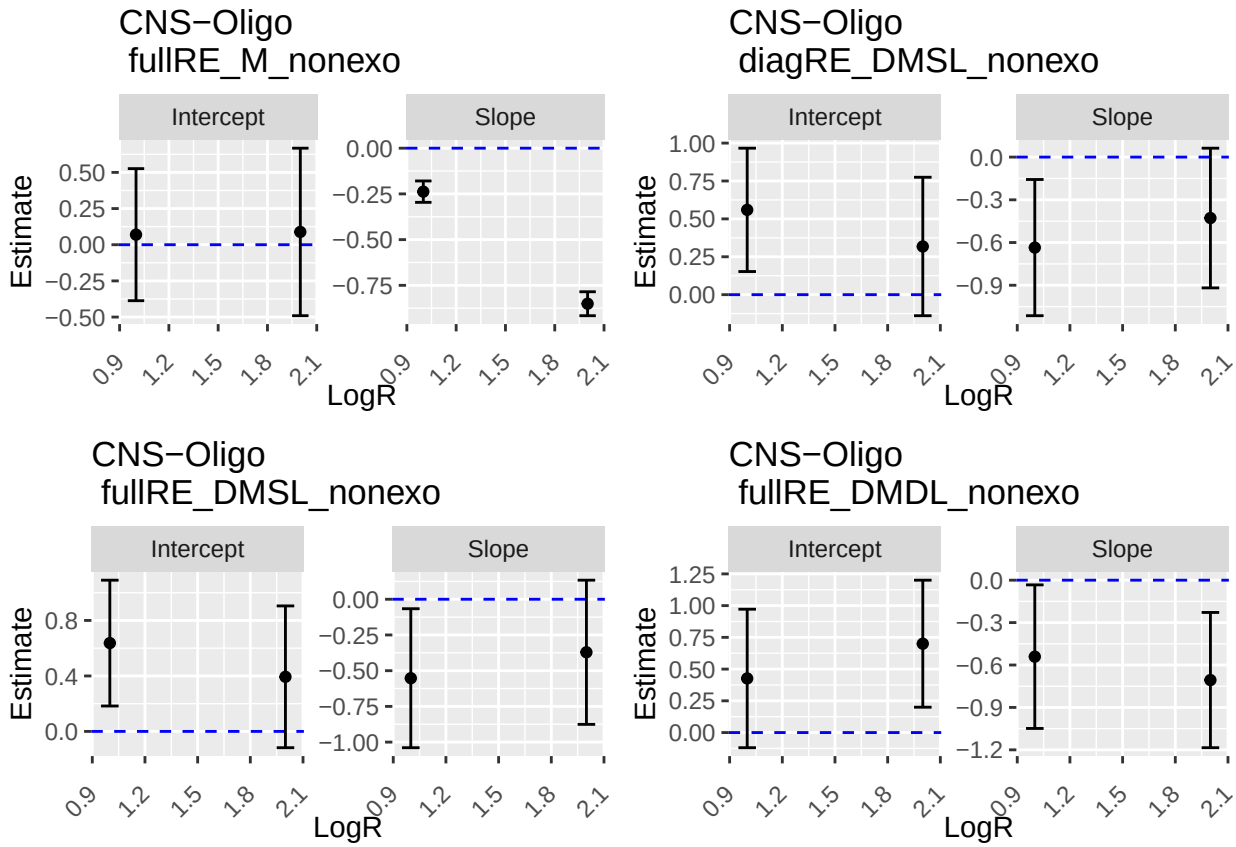
15 CNS-Oligo Timeout fullRE_DMDL_sortednonexo

Betas

```
ct <- "CNS-Oligo"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_M[[ct]])+ggtitle(paste0(ct, '\n fullRE_M')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')), nrow=2)
```



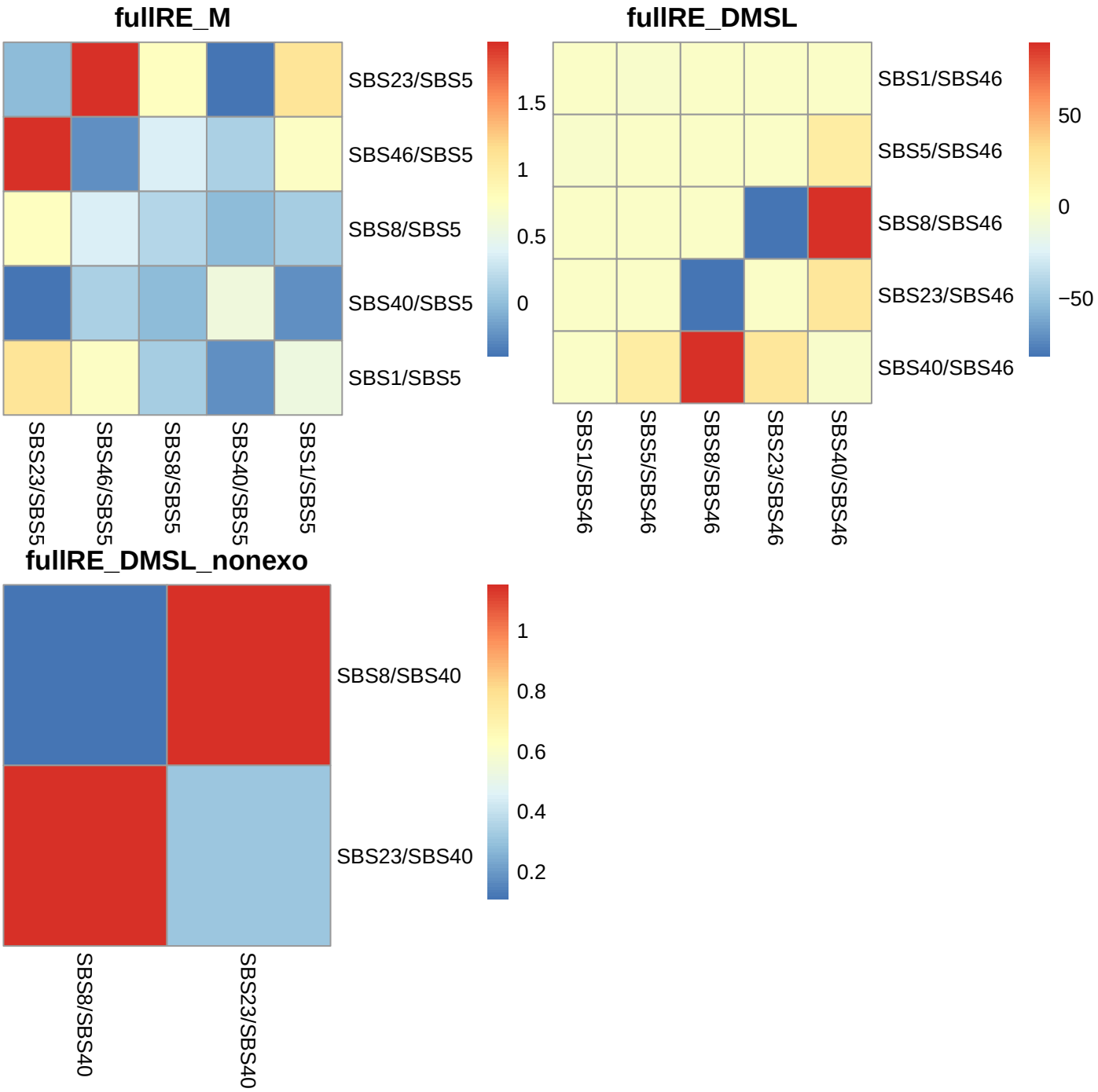

```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
  plot_betas(fullRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
  plot_betas(fullRE_DMDL_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMDL_nonexo')), nrow=2)
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct

## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used

## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

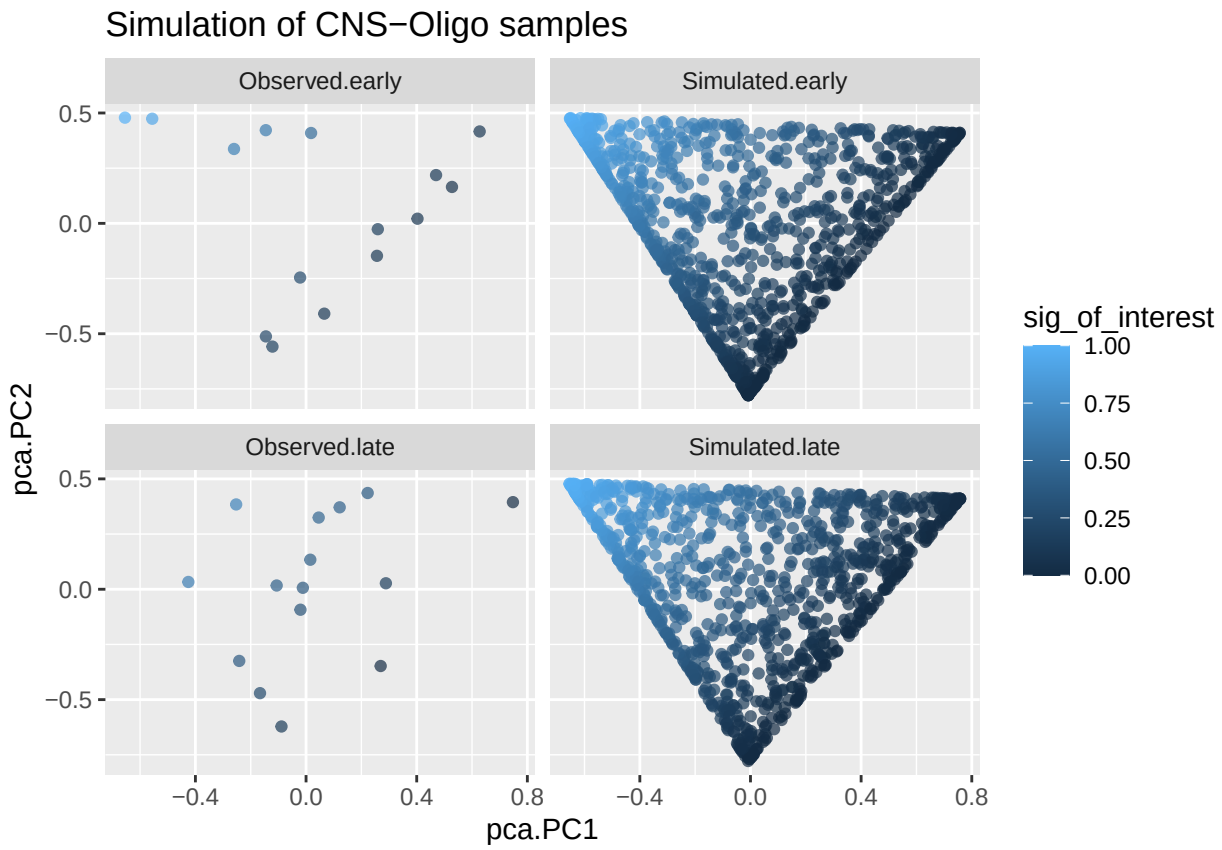
We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 0.5220955.

Covariance matrices



Simulation under inferred data

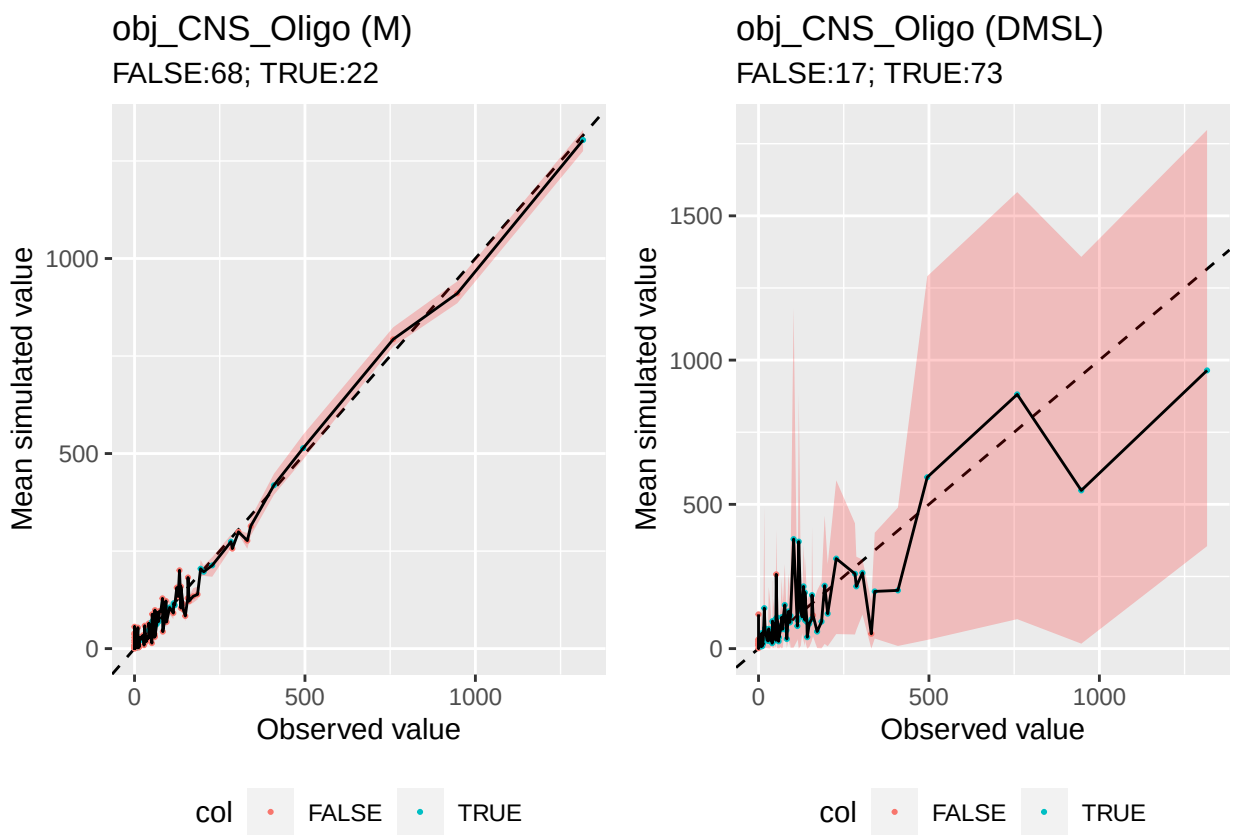
```
## [1] 15
```



Ranked plot for coverage

The values for DMSL nonexo look considerably better than for M nonexo.

```
ct <- "CNS-Oligo"
integer_overdispersion_param_DMSL <- 1
obj_CNS_Oligo_nonexo <- give_subset_sigs_TMBobj(obj_CNS_Oligo, sigs_to_remove = nonexogenous$V1)
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                  data_object = obj_CNS_Oligo_nonexo,
                  print_plot = F, nreps = 20, model = "M")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_CNS_Oligo_nonexo,
                  loglog = F, title = 'obj_CNS_Oligo (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = fullRE_DMSL_nor
                  data_object = obj_CNS_Oligo_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_CNS_Oligo_nonexo,
            loglog = F, title = 'obj_CNS_Oligo (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

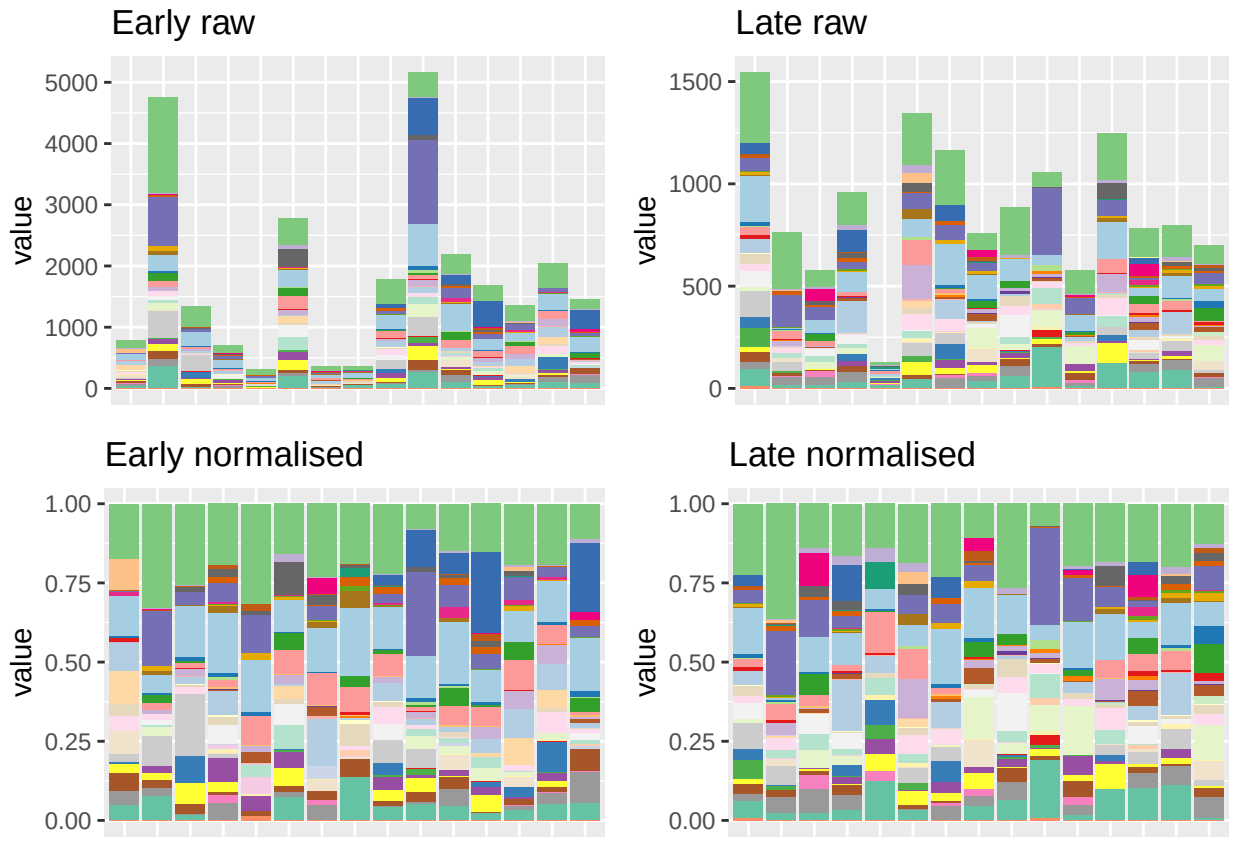
These are the signatures from mutSigExtractor:

```
obj_CNS_Oligo_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

```
## [1] 15
```

```
give_barplot_from_obj(obj = obj_CNS_Oligo_mutSigExtractor, legend_on = FALSE)
```

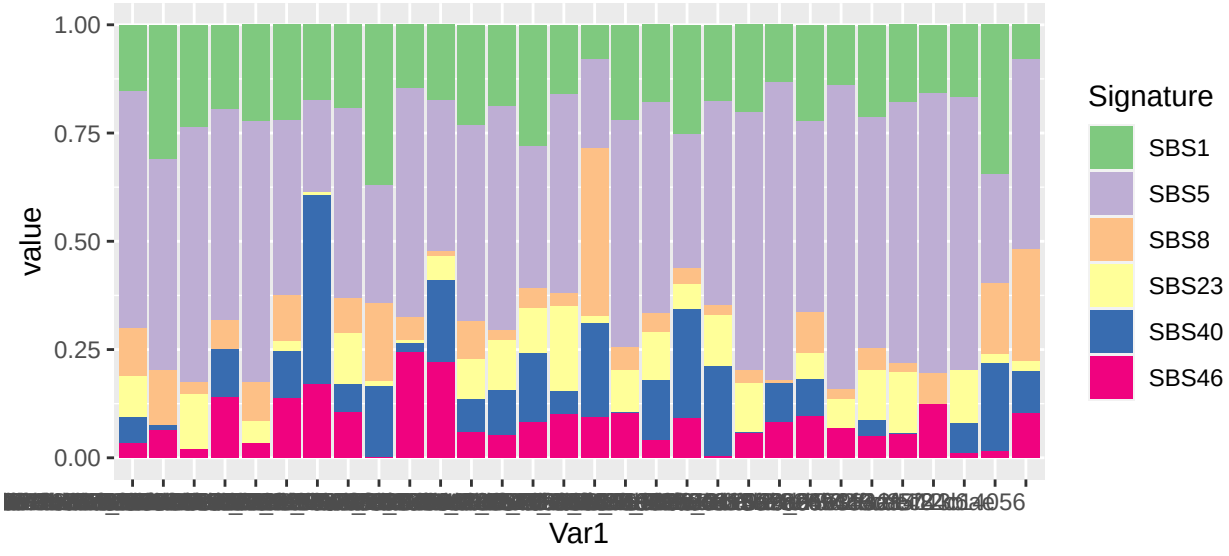
```
## Creating plot... it might take some time if the data are large. Number of samples: 15
## Creating plot... it might take some time if the data are large. Number of samples: 15
## Creating plot... it might take some time if the data are large. Number of samples: 15
## Creating plot... it might take some time if the data are large. Number of samples: 15
```



Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_CNS_Oligo$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_CNS_Oligo$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 30
```



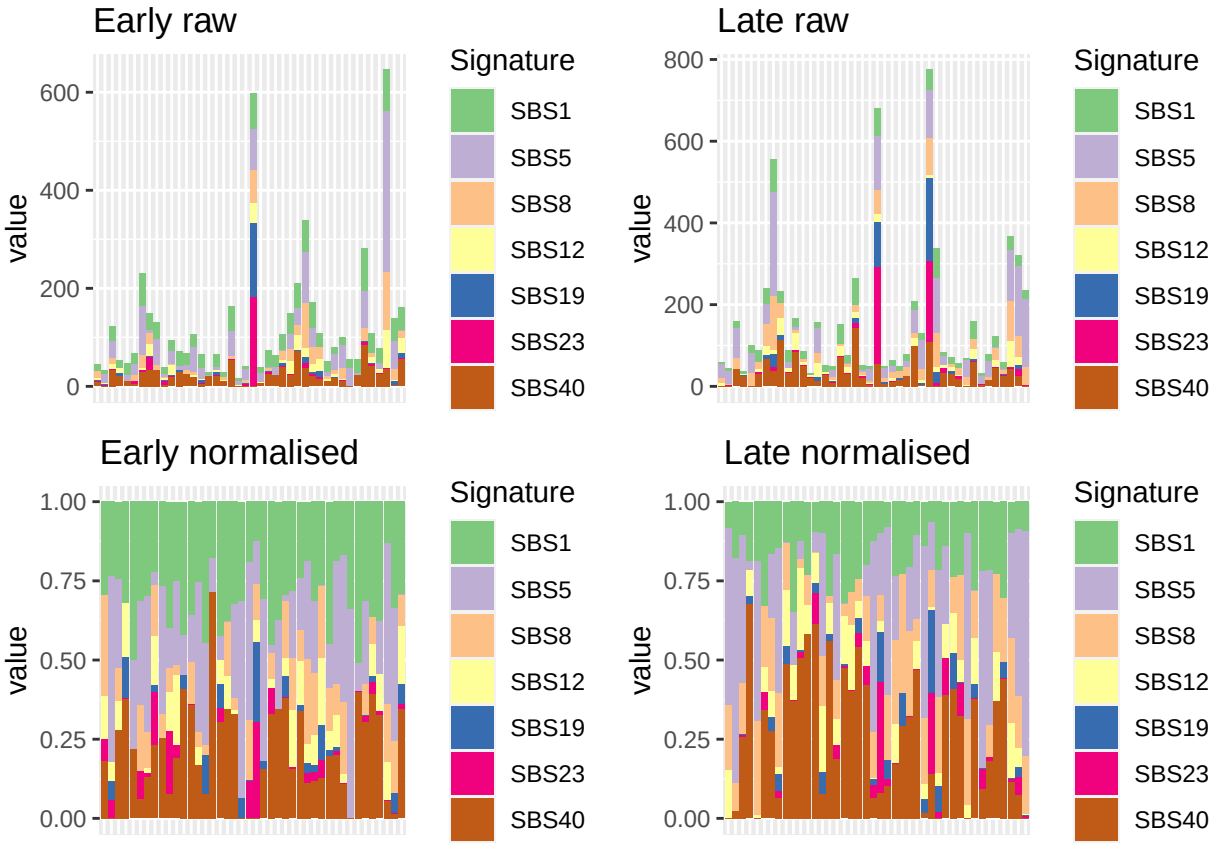
CNS-PiloAstro

CNS-PiloAstro

Barplot and general statistics

```
## [1] 42
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 42
## Creating plot... it might take some time if the data are large. Number of samples: 42
## Creating plot... it might take some time if the data are large. Number of samples: 42
## Creating plot... it might take some time if the data are large. Number of samples: 42
```



The number of samples and signatures is:

```
## [1] 84  7
```

The signatures are:

```
## [1] "SBS1"  "SBS5"  "SBS8"  "SBS12" "SBS19" "SBS23" "SBS40"
```

Convergence table

We have converged results for everything except for full RE DM, in the case of all signatures (with only nonexo everything has).

```
##            value                                L2                 L1
## 1  CNS-PiloAstro  hessian_positivedefinite_bool          diagRE_M
## 2  CNS-PiloAstro  hessian_positivedefinite_bool          fullRE_M
```

```
## 3  CNS-PiloAstro    hessian_positivedefinite_bool             diagRE_DMDL
## 4  CNS-PiloAstro hessian_nonpositivedefinite_bool           fullRE_halfDM
## 5  CNS-PiloAstro hessian_nonpositivedefinite_bool             fullRE_DMDL
## 6  CNS-PiloAstro    hessian_positivedefinite_bool             diagRE_DMSL
## 7  CNS-PiloAstro    hessian_positivedefinite_bool           sparseRE_DMSL
## 8  CNS-PiloAstro hessian_nonpositivedefinite_bool             fullRE_DMSL
## 9  CNS-PiloAstro hessian_nonpositivedefinite_bool        fullRE_DMSL_SBS1
## 10 CNS-PiloAstro    hessian_positivedefinite_bool         fullRE_M_nonexo
## 11 CNS-PiloAstro    hessian_positivedefinite_bool       diagRE_DMSL_nonexo
## 12 CNS-PiloAstro    hessian_positivedefinite_bool     sparseRE_DMSL_nonexo
## 13 CNS-PiloAstro    hessian_positivedefinite_bool       fullRE_DMSL_nonexo
## 14 CNS-PiloAstro hessian_nonpositivedefinite_bool       fullRE_DMDL_nonexo
## 15 CNS-PiloAstro    hessian_positivedefinite_bool fullRE_DMDL_sortednonexo
```

Re-running of fitting

Using fullRE_M to fit fullRE_DMSL (all sigs, as the one with nonexo has already converged)

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

If we use the values of the fullRE M as initial values for the fullRE DMSL still do not converge:

```
## [1] FALSE
```

Potentially problematic signatures

We notice that there are no truly problematic signatures (SBS15 has the most zeros; 50%).

```
colSums(obj_CNS_PiloAstro$Y == 0)/nrow(obj_CNS_PiloAstro$Y)
```

```
##      SBS1      SBS5      SBS8     SBS12     SBS19     SBS23     SBS40
## 0.0000000 0.2261905 0.2023810 0.2857143 0.5119048 0.5000000 0.1190476
```

```
colSums(obj_CNS_PiloAstro$Y)/sum(obj_CNS_PiloAstro$Y)
```

```
##       SBS1       SBS5       SBS8      SBS12      SBS19      SBS23      SBS40
## 0.19840611 0.26357297 0.14212187 0.07313631 0.05894073 0.06749128 0.19633073
```

SBS19 and SBS23 are quite sparse.

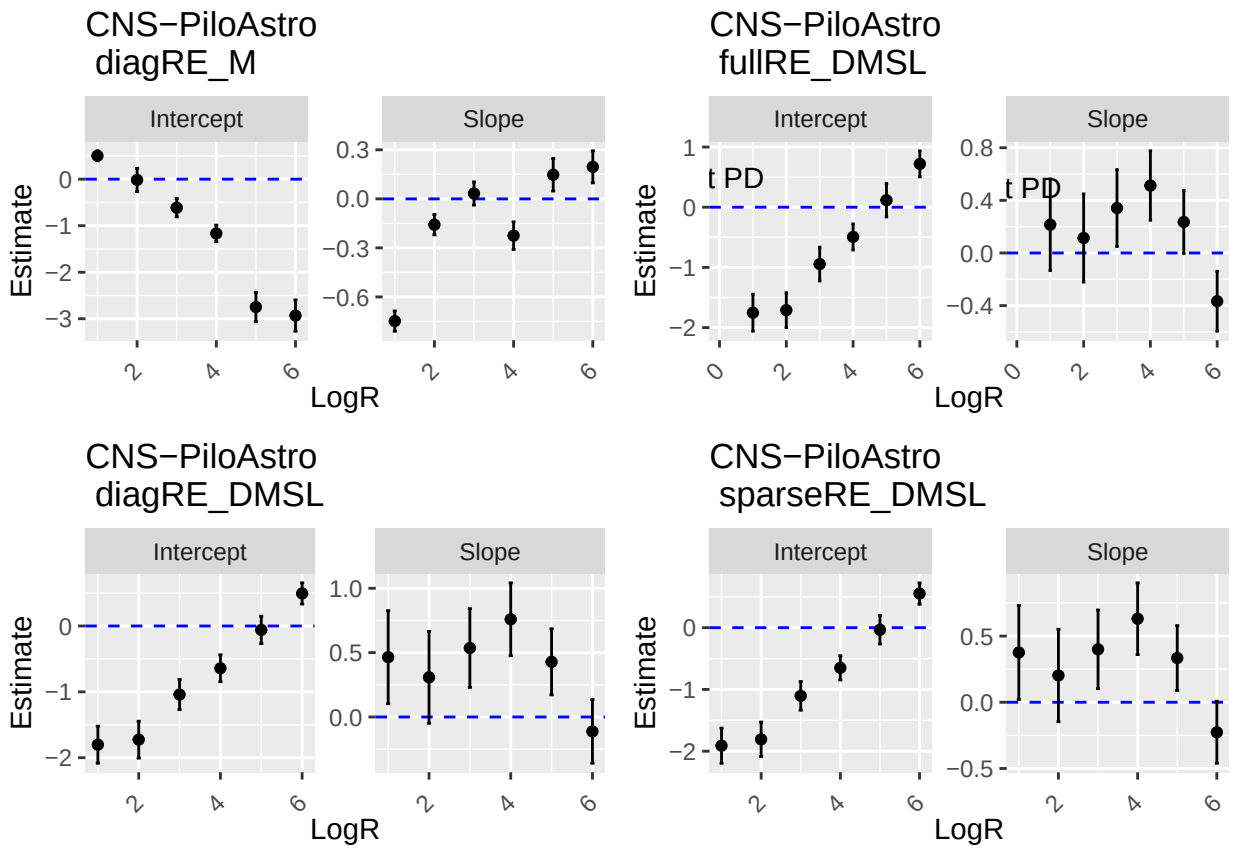
```
additional_sortedMnonexo[["CNS-PiloAstro"]] <- sortedM_CNSPiloAstro
additional_sortedDMSLnonexo[["CNS-PiloAstro"]] <- sortedDM_CNSPiloAstro
```

Betas

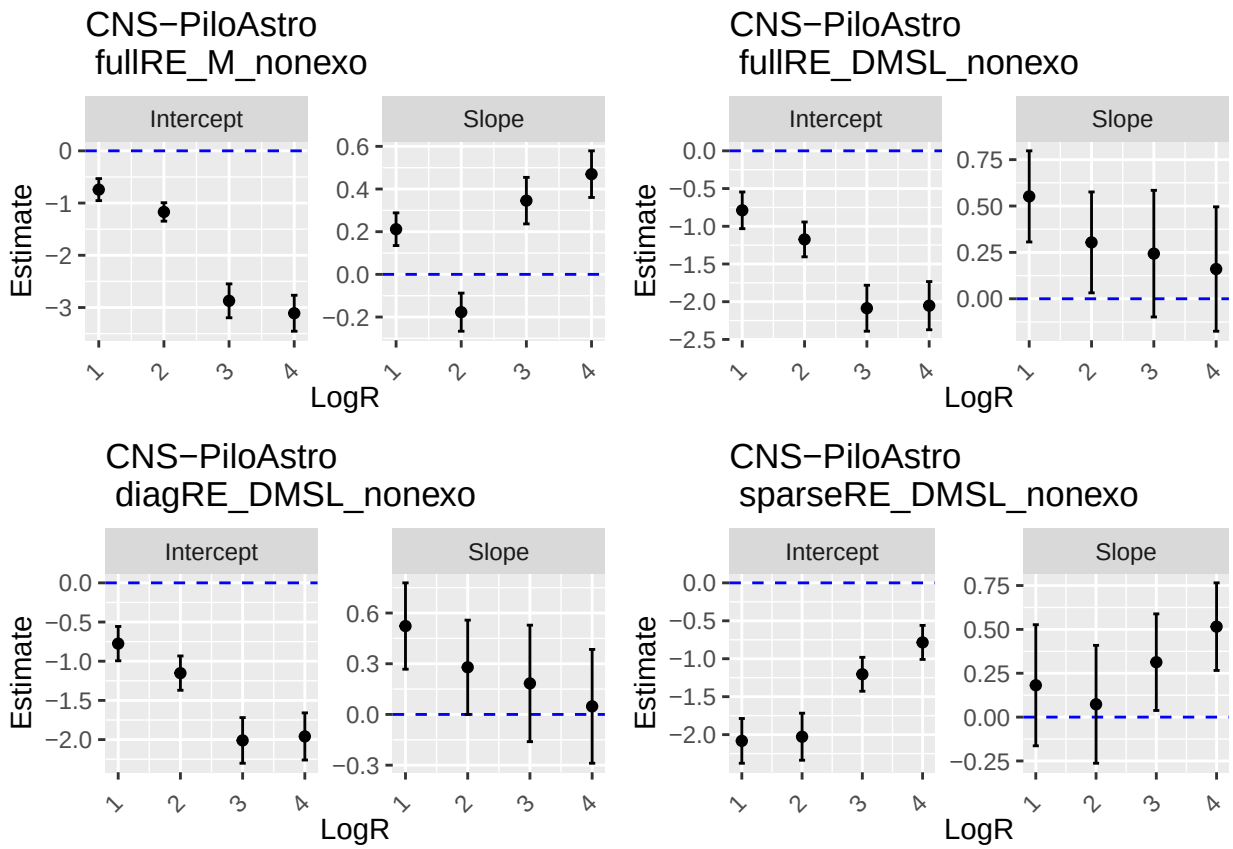
```
ct <- "CNS-PiloAstro"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

```
## Warning in sqrt(as.numeric(object$diag.cov.random)): NaNs produced
```



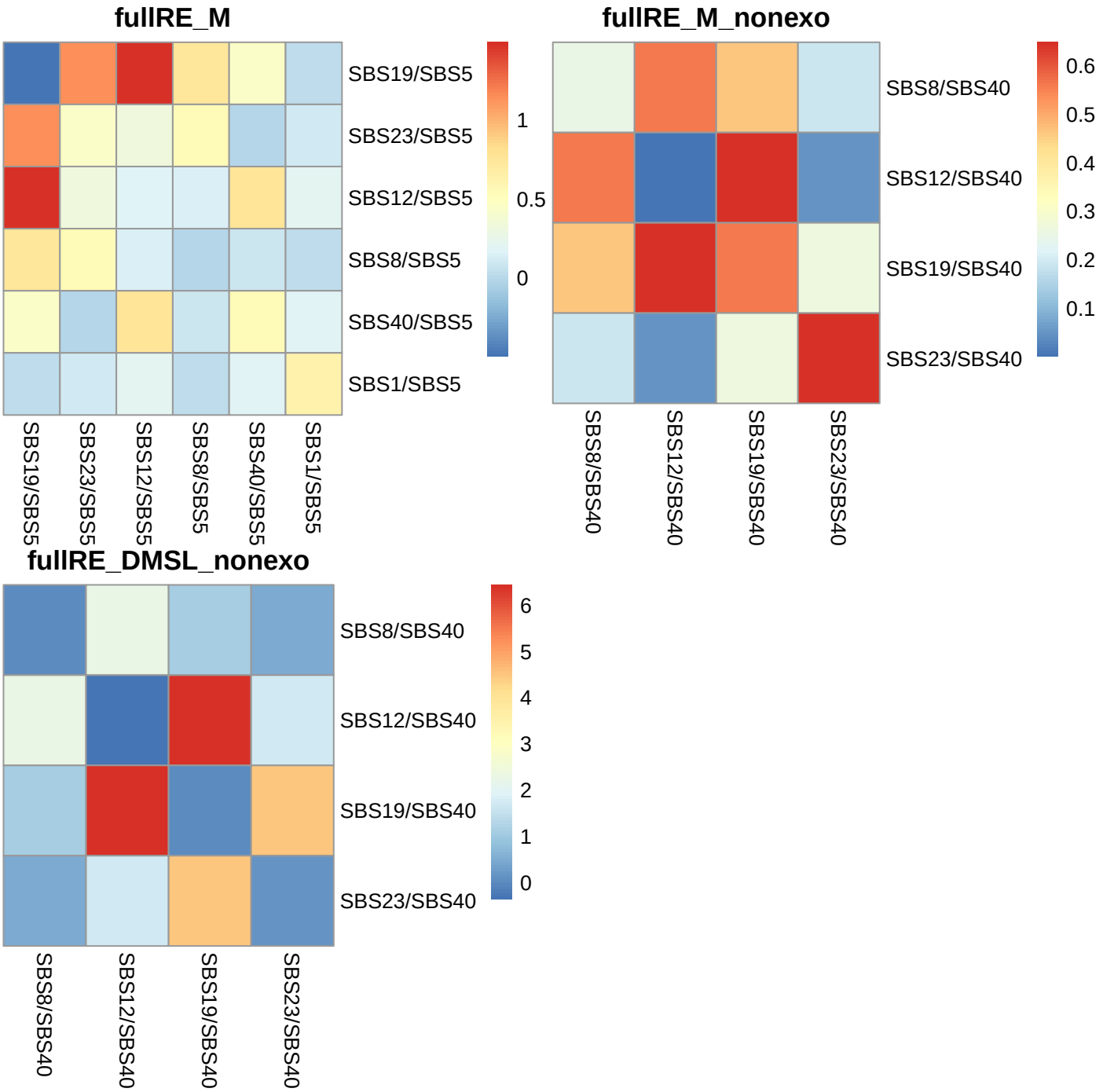

```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(fullRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
  plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
  plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct

## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used

## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 0.2632004.

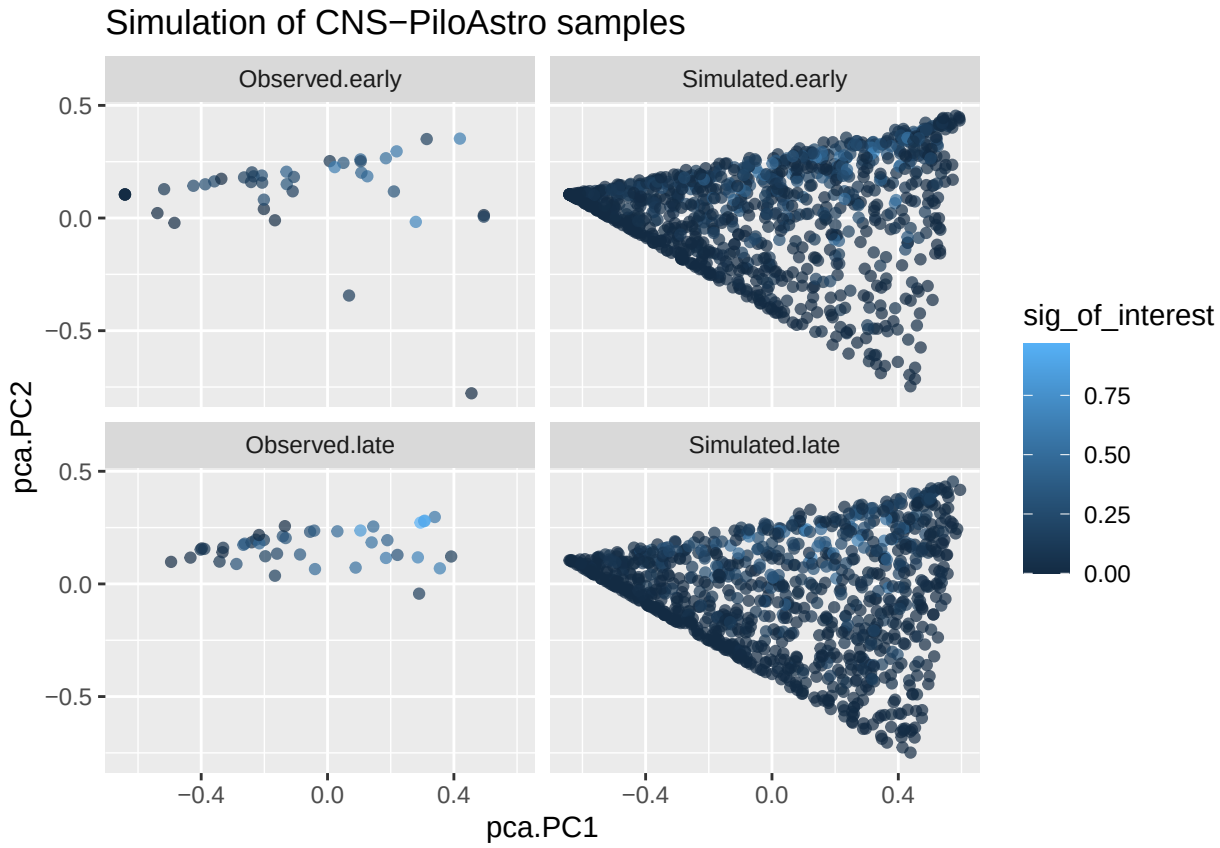
Covariance matrices



Simulation under inferred data

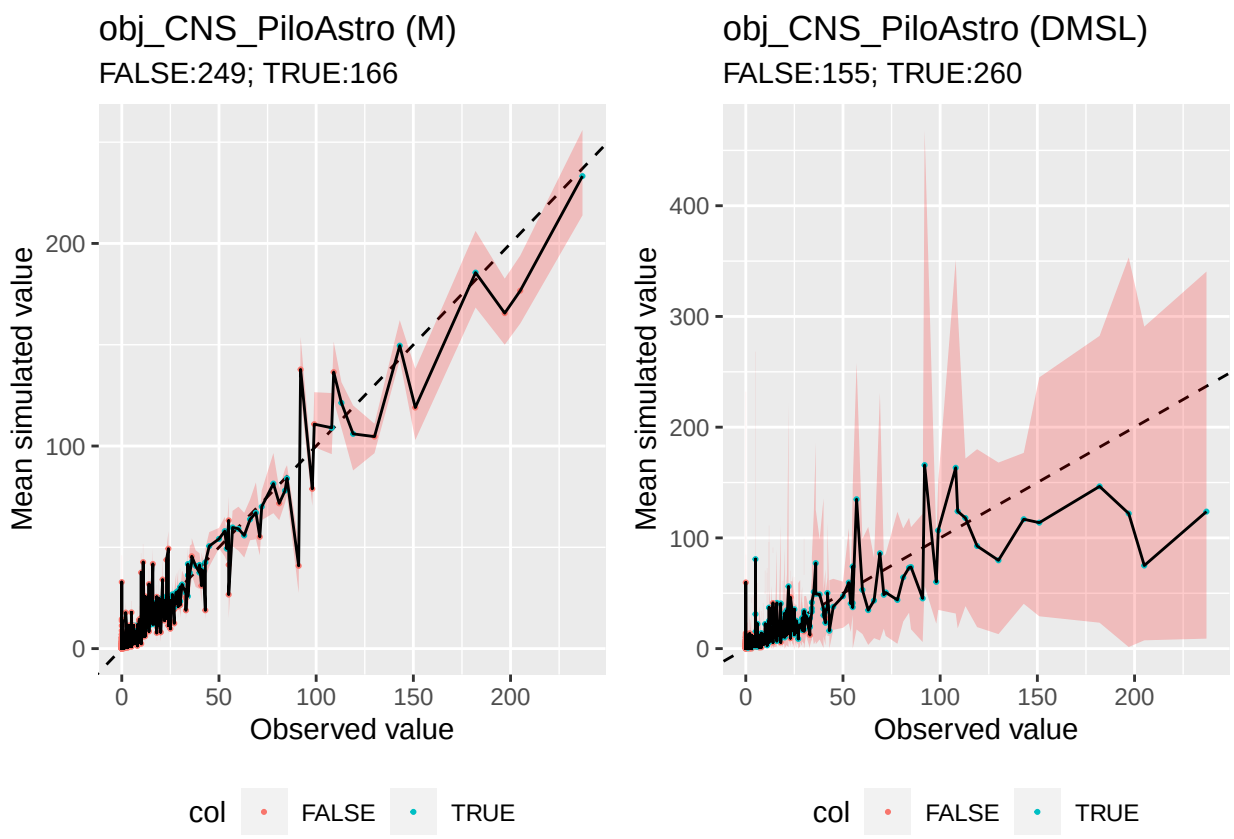
```
## [1] 42
```

```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```



Ranked plot for coverage

```
ct <- "CNS-PiloAstro"
integer_overdispersion_param_DMSL <- 1
obj_CNS_PiloAstro_nonexo <- give_subset_sigs_TMBobj(obj_CNS_PiloAstro, sigs_to_remove = nonexogenous$V1)
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                data_object = obj_CNS_PiloAstro_nonexo,
                print_plot = F, nreps = 20, model = "M")), function(i){
                  lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                         rank_number=1:length(j)) )})[[1]],
                data_object = obj_CNS_PiloAstro_nonexo,
                loglog = F, title = 'obj_CNS_PiloAstro (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = fullRE_DMSL_nor
                data_object = obj_CNS_PiloAstro_nonexo,
                print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                  lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                         rank_number=1:length(j)) )})[[1]],
                data_object = obj_CNS_PiloAstro_nonexo,
           loglog = F, title = 'obj_CNS_PiloAstro (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are a bit more chaotic:

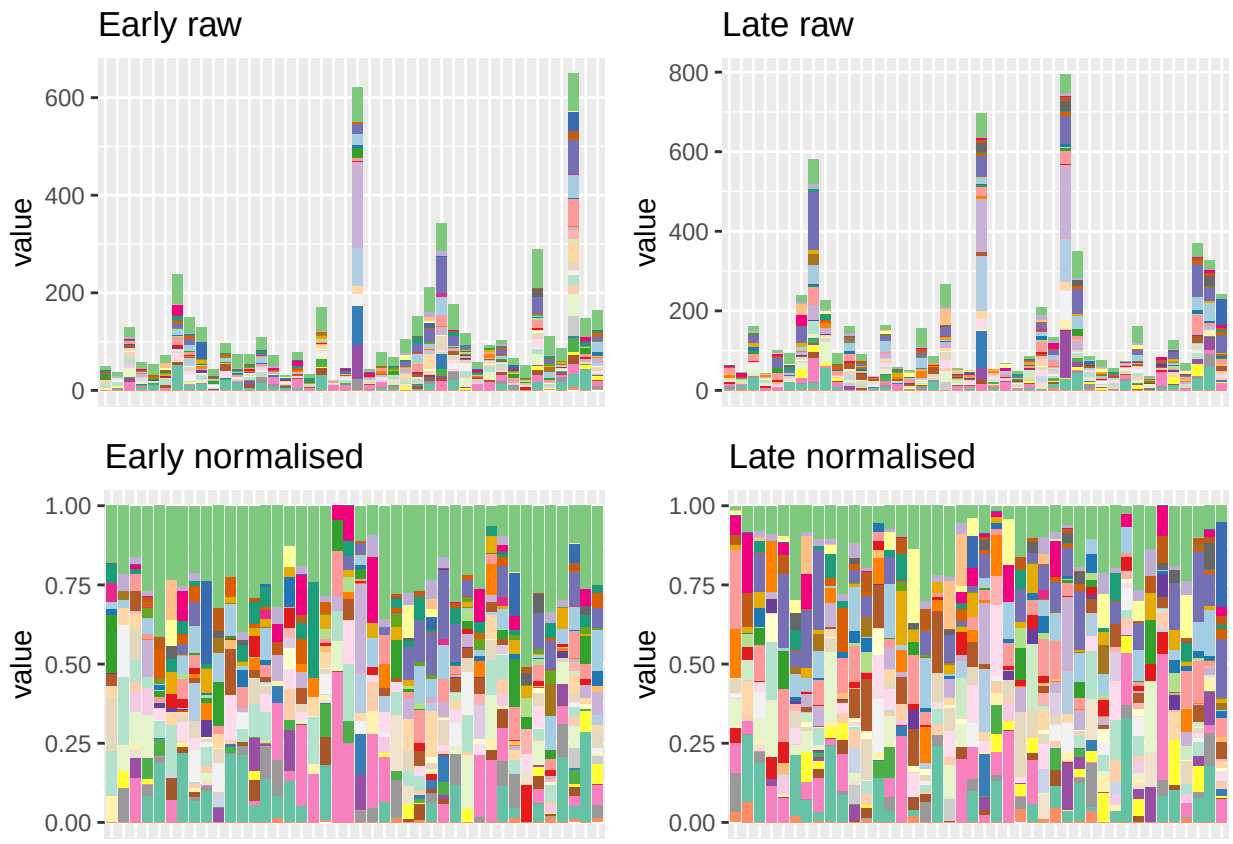
```
obj_CNS_PiloAstro_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

```
## [1] 42
```

```
give_barplot_from_obj(obj = obj_CNS_PiloAstro_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 42
## Creating plot... it might take some time if the data are large. Number of samples: 42
## Creating plot... it might take some time if the data are large. Number of samples: 42
## Creating plot... it might take some time if the data are large. Number of samples: 42
```

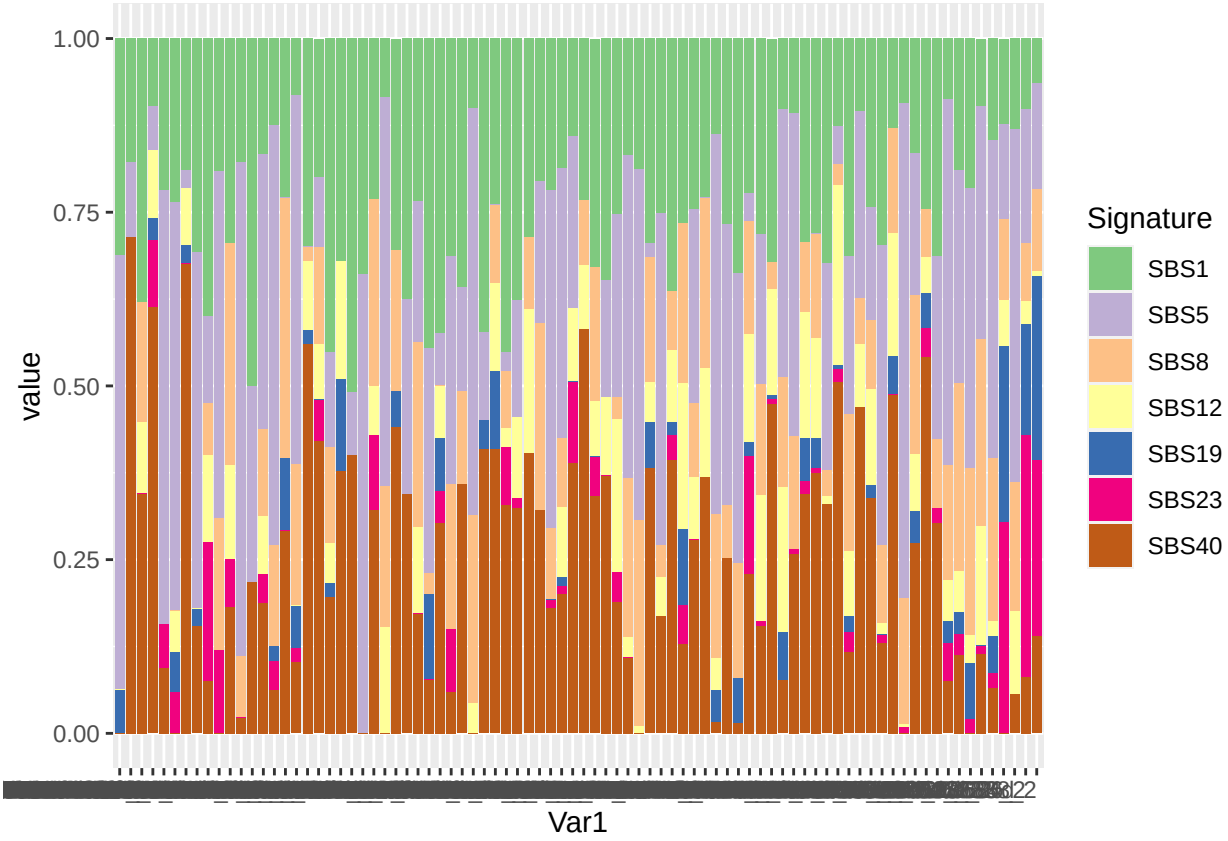
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations, with perhaps SBS9 being slightly found in the rightmost side preferentially.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_CNS_PiloAstro$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_CNS_PiloAstro$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 84
```



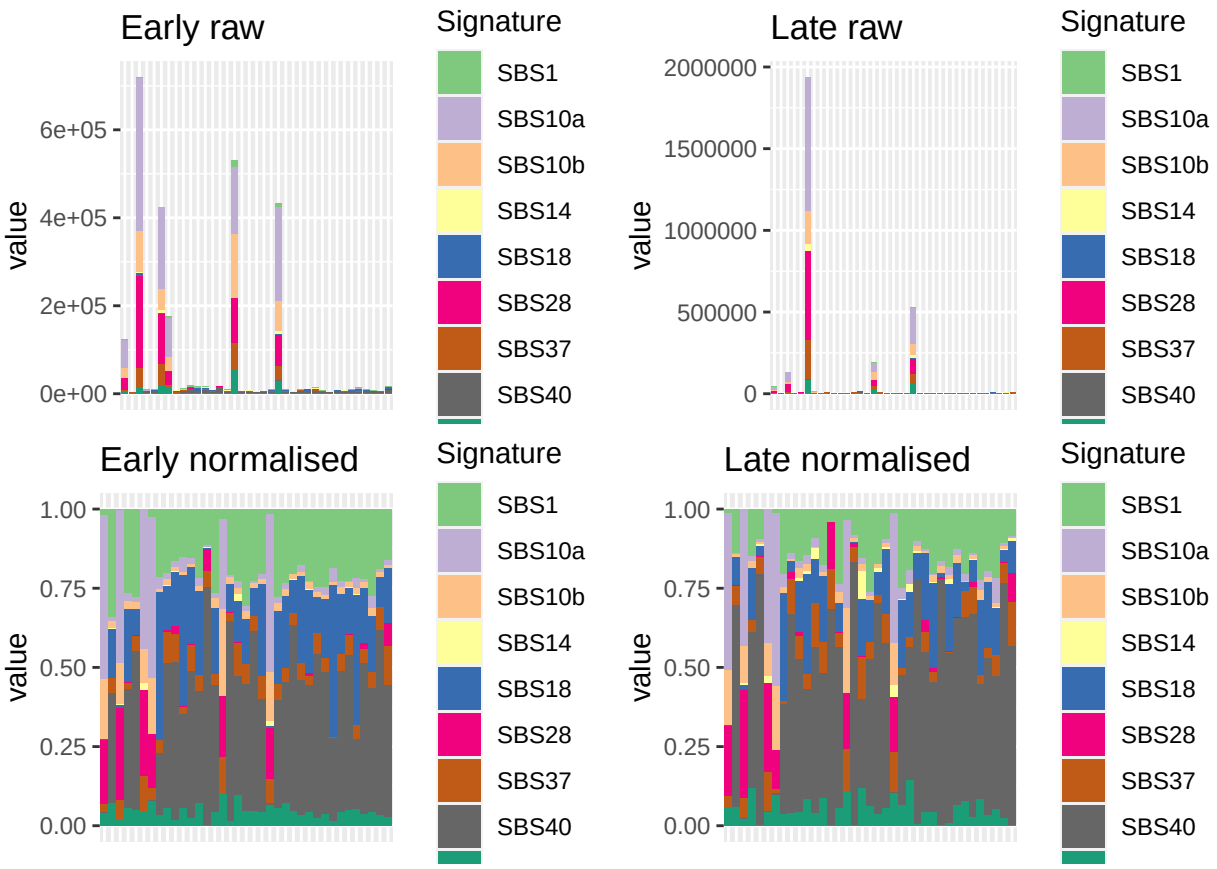
ColoRect-AdenoCA

ColoRect-AdenoCA

Barplot and general statistics

```
## [1] 37
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 37
## Creating plot... it might take some time if the data are large. Number of samples: 37
## Creating plot... it might take some time if the data are large. Number of samples: 37
## Creating plot... it might take some time if the data are large. Number of samples: 37
```



The number of samples and signatures is:

```
## [1] 74  9
```

The signatures are:

```
## [1] "SBS1"   "SBS10a" "SBS10b" "SBS14"  "SBS18"  "SBS28"  "SBS37"  "SBS40"
## [9] "SBS44"
```

Convergence table

We only have converged results for the multinomial with diag RE, when including all mutations. For exogenous mutations, full DMSL is has not converged.

```
##                value                                L2                  L1
## 1  ColoRect-AdenoCA    hessian_positivedefinite_bool          diagRE_M
## 2  ColoRect-AdenoCA hessian_nonpositivedefinite_bool          fullRE_M
## 3  ColoRect-AdenoCA hessian_nonpositivedefinite_bool       diagRE_DMDL
## 4  ColoRect-AdenoCA hessian_nonpositivedefinite_bool     fullRE_halfDM
## 5  ColoRect-AdenoCA hessian_nonpositivedefinite_bool       fullRE_DMDL
## 6  ColoRect-AdenoCA    hessian_positivedefinite_bool       diagRE_DMSL
## 7  ColoRect-AdenoCA    hessian_positivedefinite_bool     sparseRE_DMSL
## 8  ColoRect-AdenoCA hessian_nonpositivedefinite_bool       fullRE_DMSL
## 9  ColoRect-AdenoCA hessian_nonpositivedefinite_bool  fullRE_DMSL_SBS1
## 10 ColoRect-AdenoCA    hessian_positivedefinite_bool    fullRE_M_nonexo
## 11 ColoRect-AdenoCA    hessian_positivedefinite_bool diagRE_DMSL_nonexo
```

```
## 12 ColoRect-AdenoCA    hessian_positivedefinite_bool     sparseRE_DMSL_nonexo
## 13 ColoRect-AdenoCA hessian_nonpositivedefinite_bool       fullRE_DMSL_nonexo
## 14 ColoRect-AdenoCA hessian_nonpositivedefinite_bool       fullRE_DMDL_nonexo
## 15 ColoRect-AdenoCA                          Timeout fullRE_DMDL_sortednonexo
```

Re-running of fitting

Using fullRE_M_nonexo to fit fullRE_DMSL_nonexo

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

Now the fullM doesn't converge (even though the original fullRE M nonexo did converge?), so I cannot use all the parameters to find the starting parameters of the DM, as some are NA. I can however use some, such as beta.

What parameters are NA?

```
##         beta         beta         beta         beta         beta         beta
##  -2.54404819   0.59706447   0.63355077  -0.46879338   4.20343871   0.18574156
##         beta         beta         beta         beta         beta         beta
## -19.99432403   0.29636775   3.02975360   0.28475722  -1.60129347   0.01913378
##         beta         beta   cov_par_RE   cov_par_RE   cov_par_RE   cov_par_RE
##   5.93971517   0.15499188 -12.04185894 -16.74375580   7.37447864   9.17341782
##   cov_par_RE   cov_par_RE   cov_par_RE   cov_par_RE   cov_par_RE   cov_par_RE
## -17.09070185  -8.65885911   6.41420768 -10.90041616 -20.09373728   4.61570780
##   cov_par_RE   cov_par_RE   cov_par_RE   cov_par_RE   cov_par_RE   cov_par_RE
##   7.72147141 -12.99908453  -4.22783276   9.21589607  -2.22915894  -0.93447317
##   cov_par_RE   cov_par_RE   cov_par_RE   cov_par_RE   cov_par_RE   logs_sd_RE
##  10.83144466   9.10923370  -7.69300283 -16.65325966  -2.26097772  18.34680278
##   logs_sd_RE   logs_sd_RE   logs_sd_RE   logs_sd_RE   logs_sd_RE   logs_sd_RE
##  10.36960317   9.28298541  27.22237889   5.86088489   3.32760927   5.93365712
```

Betas, logsd and covariances are not NA. Therefore, we use these values as starting values, and give an empty random effects matrix.

I get the error "gradient function must rerurn a number vector of length 43" for some reason I don't understand - it's as though the initial values I am giving are not correct.

Potentially problematic signatures

```
colSums(obj_ColoRect_AdenoCA$Y == 0)/nrow(obj_ColoRect_AdenoCA$Y)
```

```
##       SBS1     SBS10a     SBS10b      SBS14      SBS18      SBS28      SBS37
## 0.02702703 0.04054054 0.02702703 0.68918919 0.13513514 0.52702703 0.04054054
##      SBS40      SBS44
## 0.09459459 0.05405405
```

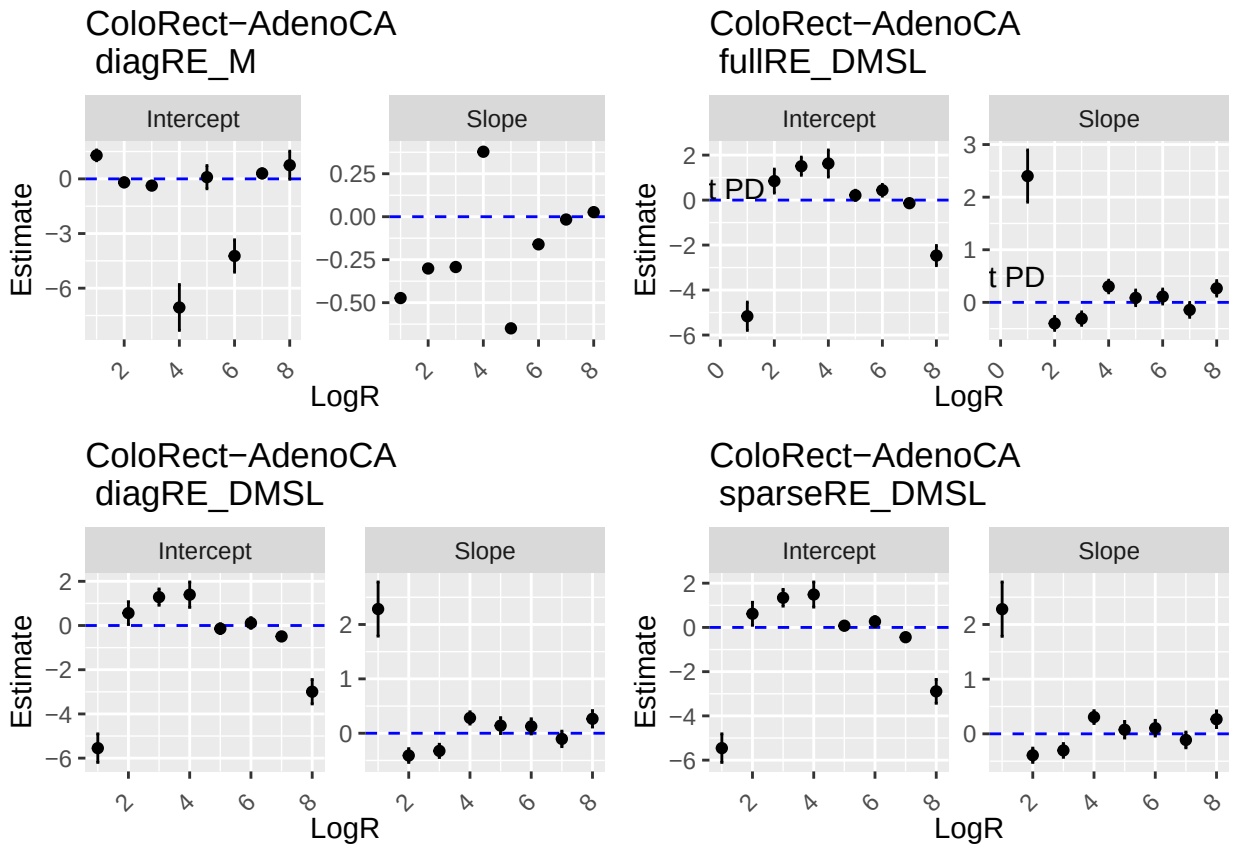
```
colSums(obj_ColoRect_AdenoCA$Y)/sum(obj_ColoRect_AdenoCA$Y)
```

```
##       SBS1     SBS10a     SBS10b      SBS14      SBS18      SBS28      SBS37
## 0.02342633 0.39302667 0.13415977 0.01502674 0.01674129 0.22524153 0.09998130
##      SBS40      SBS44
## 0.03731777 0.05507859
```

Betas

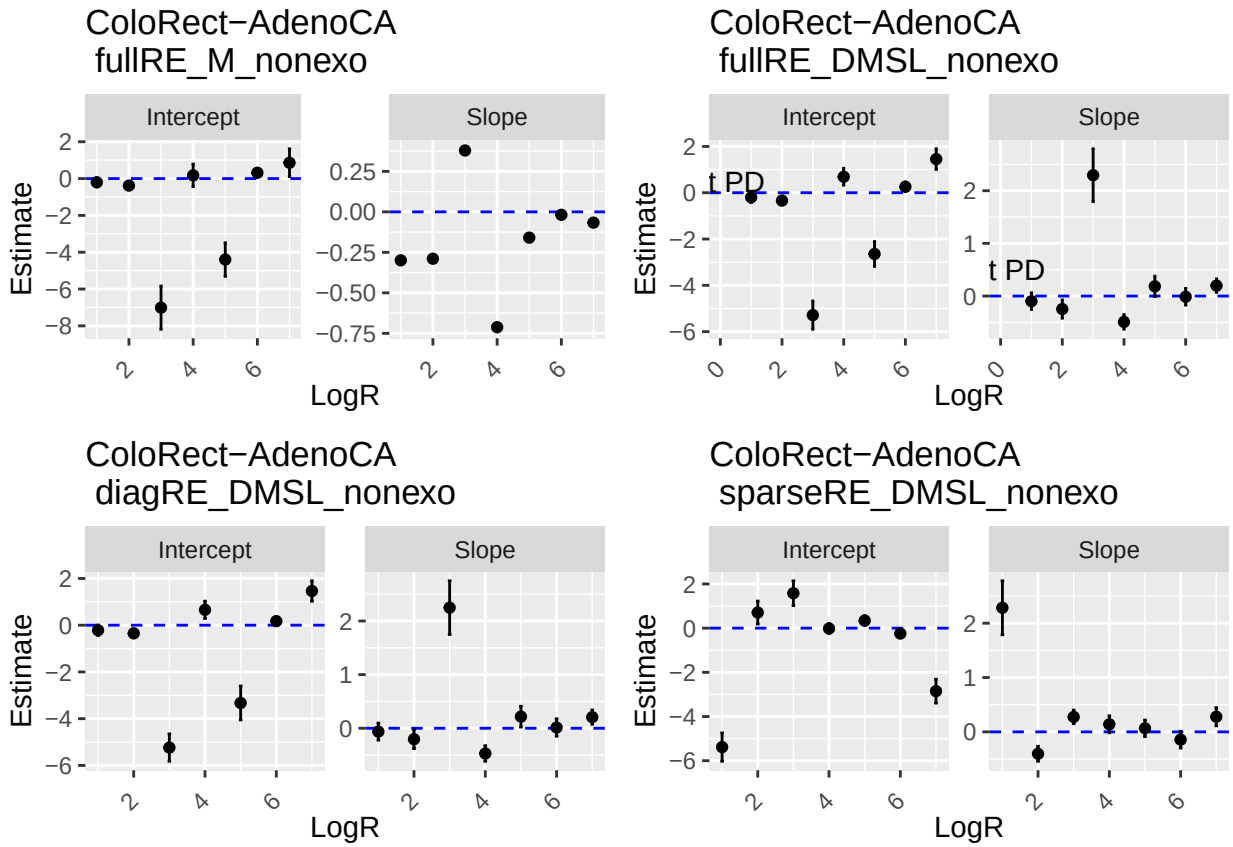
```
ct <- "ColoRect-AdenoCA"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```




```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(fullRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
  plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
  plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')
                                                 ), nrow=2)
```

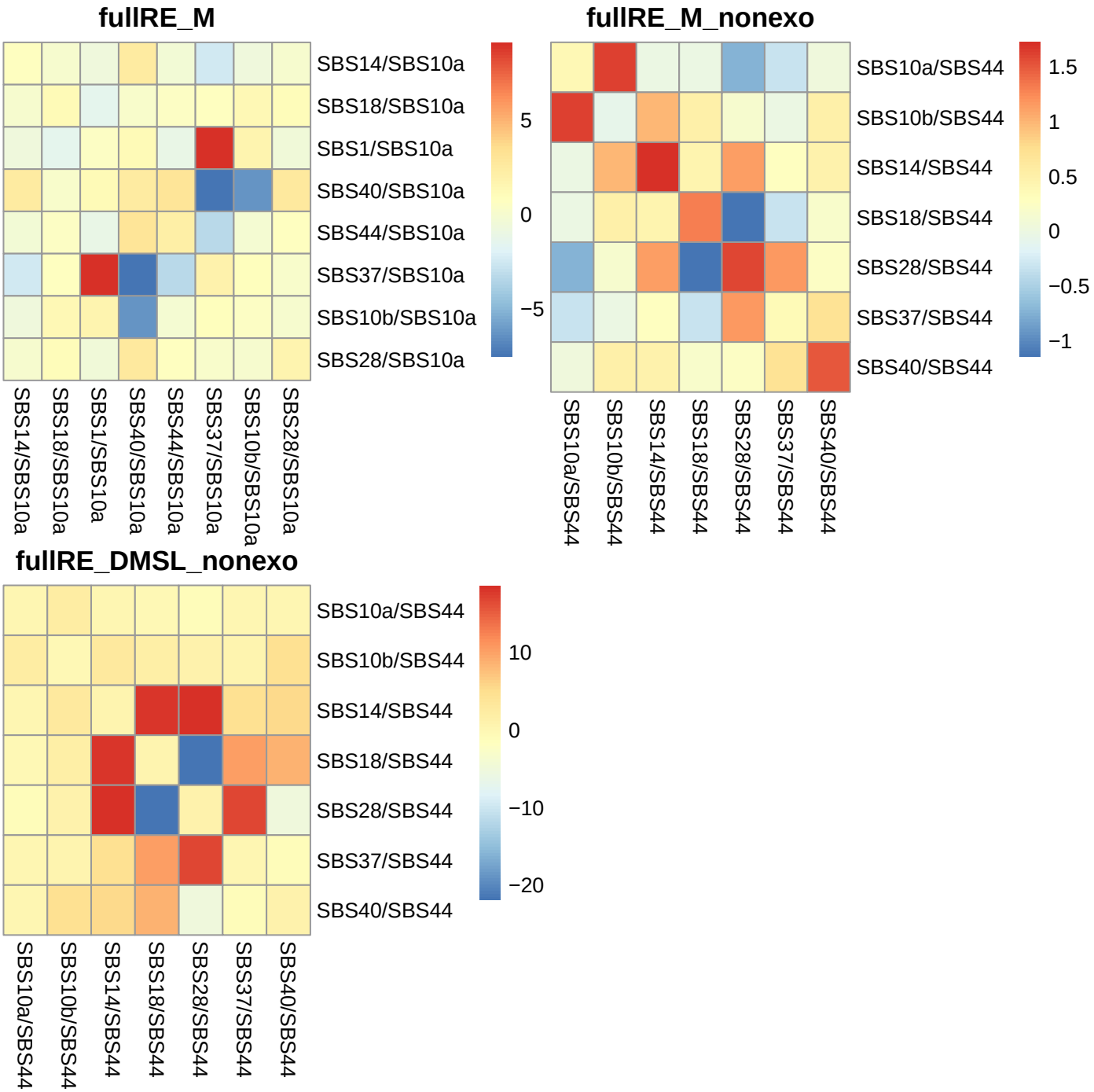
```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct

## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used

## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the diagonal RE single lambda DM nonexo to test for differential abundance, giving a p-value of $8.8714208 \times 10^{-16}$.

Covariance matrices



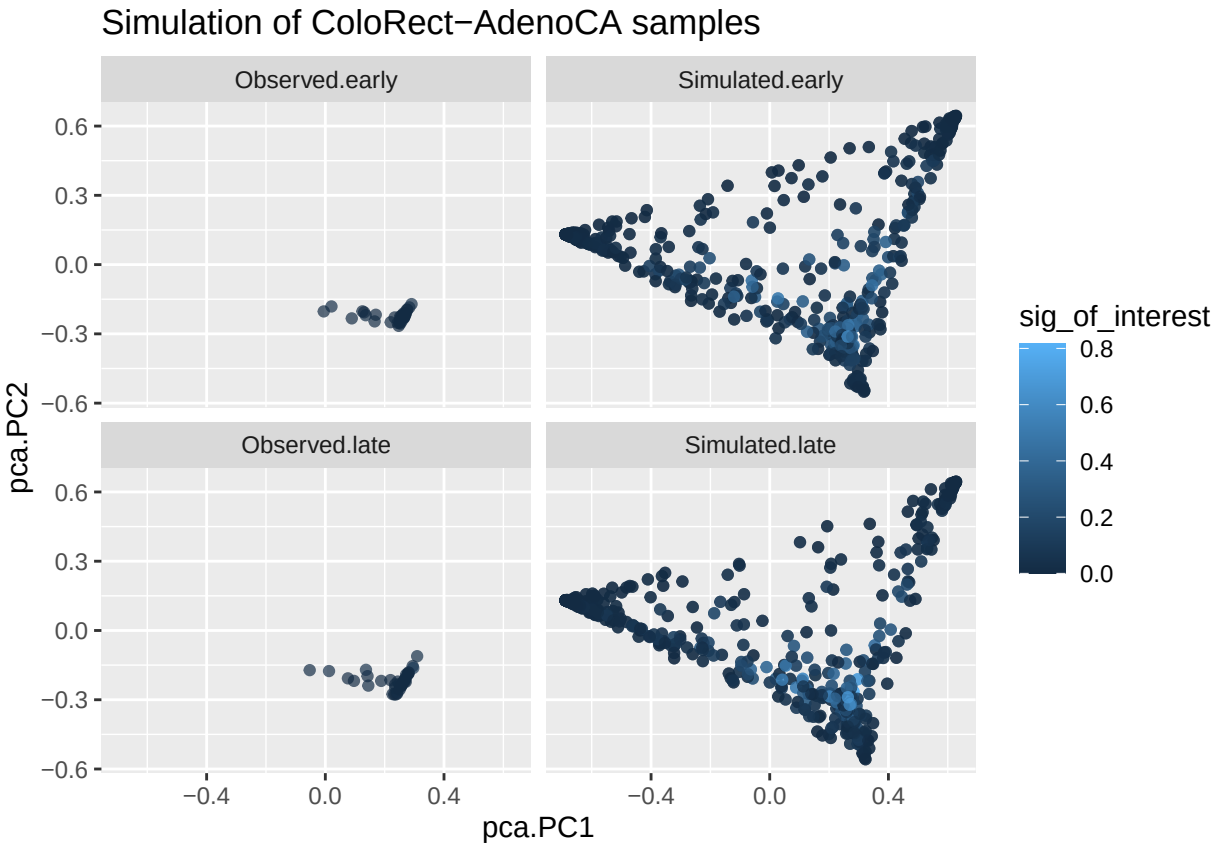
Simulation under inferred data

I am simulating using the full effects multinomial, because the function needs to be adapted to diagDMSL.

```
## [1] 37
```

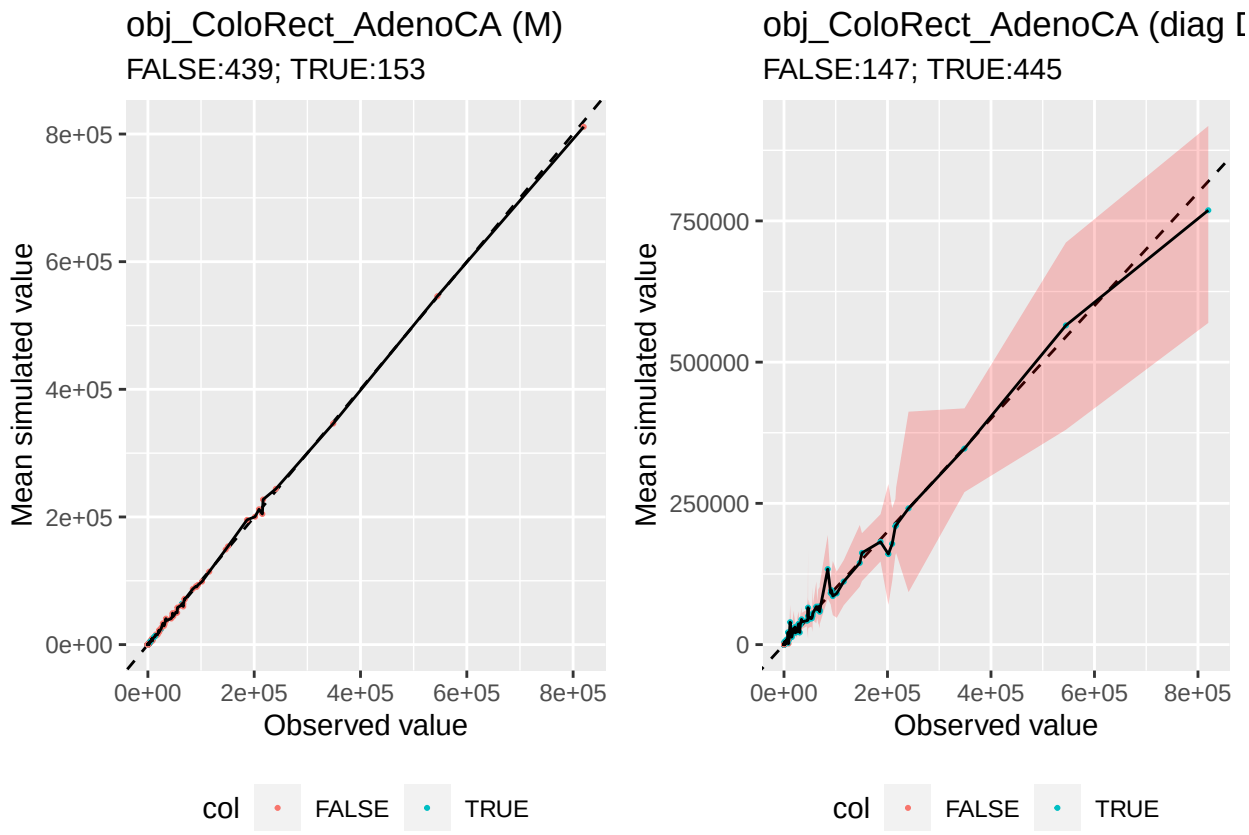
```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
```

```
## sigma is numerically not positive semidefinite
```



Ranked plot for coverage

```
ct <- "ColoRect-AdenoCA"
integer_overdispersion_param_DMSL <- 1
obj_ColoRect_AdenoCA_nonexo <- give_subset_sigs_TMBobj(obj_ColoRect_AdenoCA, sigs_to_remove = nonexogenou
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                  data_object = obj_ColoRect_AdenoCA_nonexo,
                  print_plot = F, nreps = 20, model = "M")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_ColoRect_AdenoCA_nonexo,
                  loglog = F, title = 'obj_ColoRect_AdenoCA (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = diagRE_DMSL_nor
                  data_object = obj_ColoRect_AdenoCA_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_ColoRect_AdenoCA_nonexo,
            loglog = F, title = 'obj_ColoRect_AdenoCA (diag DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

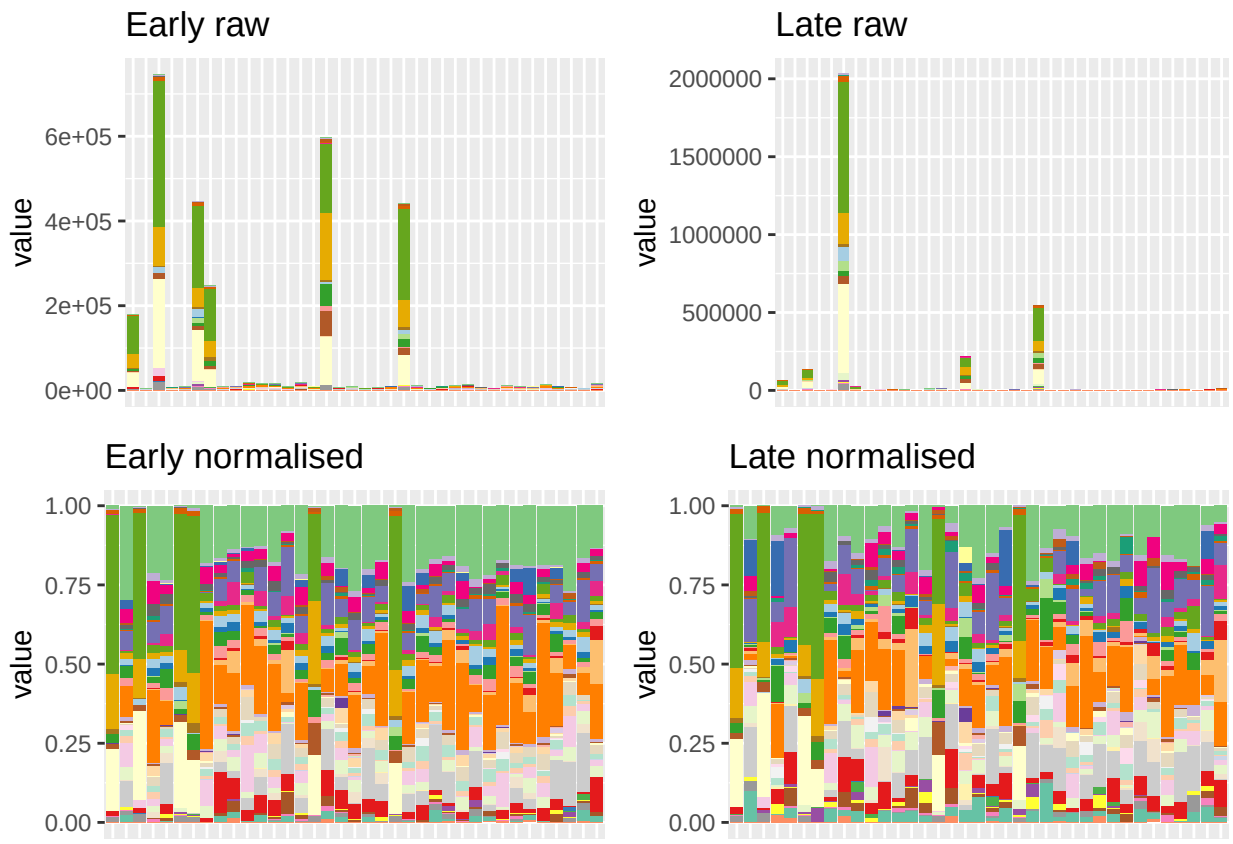
```
obj_ColoRect_AdenoCA_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

```
## [1] 37
```

```
give_barplot_from_obj(obj = obj_ColoRect_AdenoCA_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 37
## Creating plot... it might take some time if the data are large. Number of samples: 37
## Creating plot... it might take some time if the data are large. Number of samples: 37
## Creating plot... it might take some time if the data are large. Number of samples: 37
```

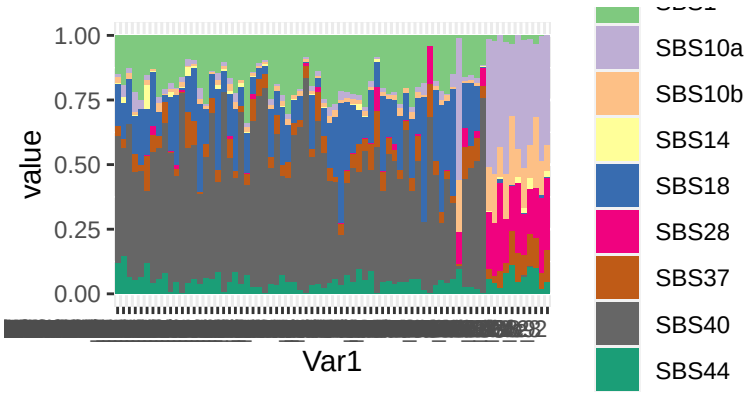
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: very clearly there are a few samples with very high number of mutations that also have a completely different mutational signature exposure.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_ColoRect_AdenoCA$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_ColoRect_AdenoCA$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 74
```

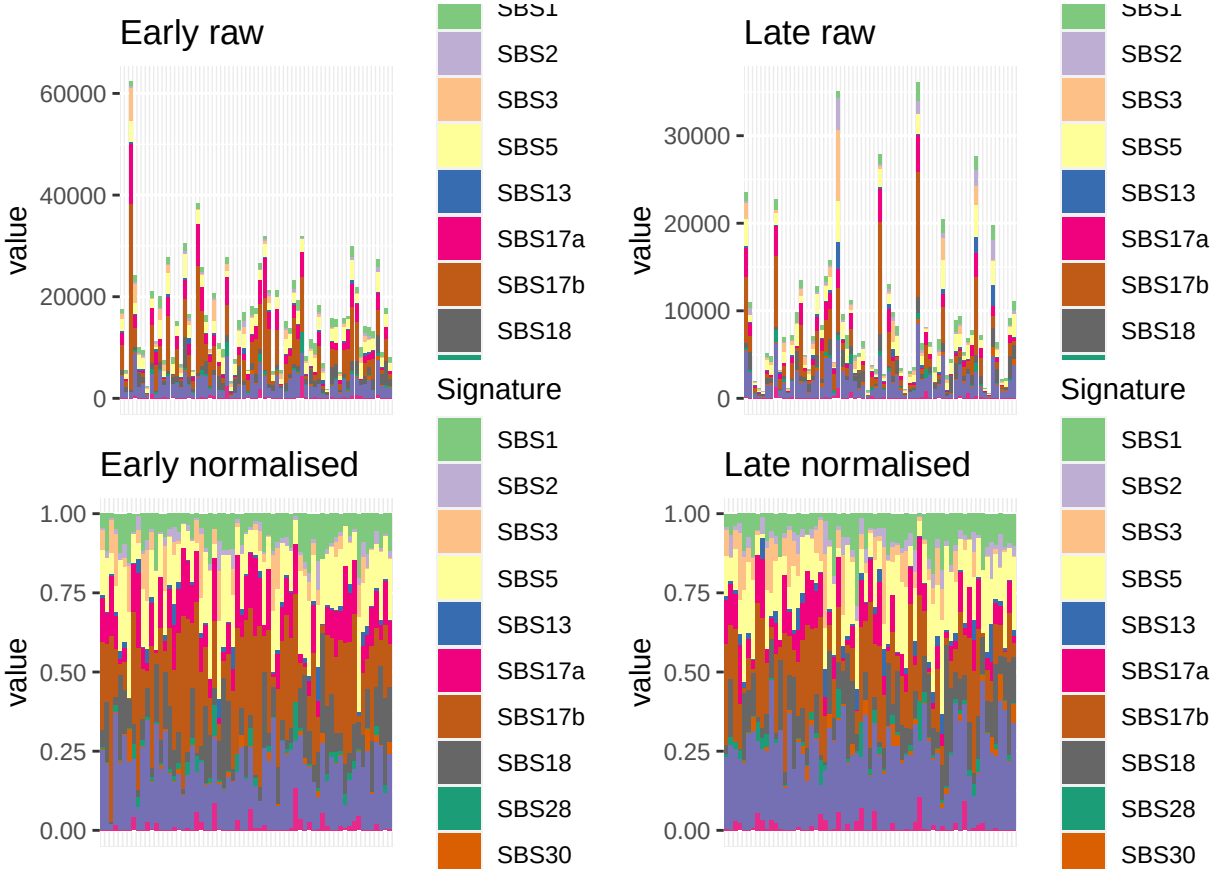


Eso-AdenoCA

Barplot and general statistics

```
## [1] 65
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 65
## Creating plot... it might take some time if the data are large. Number of samples: 65
## Creating plot... it might take some time if the data are large. Number of samples: 65
## Creating plot... it might take some time if the data are large. Number of samples: 65
```



The number of samples and signatures is:

```
## [1] 130  12
```

The signatures are:

```
##  [1] "SBS1"   "SBS2"   "SBS3"   "SBS5"   "SBS13"  "SBS17a" "SBS17b" "SBS18"
##  [9] "SBS28"  "SBS30"  "SBS40"  "SBS46"
```

Convergence table

None of the fullRE have converged when including all signatures. When including nonexo, all but fullRE_DMSL_nonexo (using either the highest absolute signature or SBS1) have converged.

```
##          value                                 L2                 L1
## 1  Eso-AdenoCA    hessian_positivedefinite_bool          diagRE_M
## 2  Eso-AdenoCA hessian_nonpositivedefinite_bool          fullRE_M
```

```
## 3  Eso-AdenoCA hessian_nonpositivedefinite_bool             diagRE_DMDL
## 4  Eso-AdenoCA hessian_nonpositivedefinite_bool            fullRE_halfDM
## 5  Eso-AdenoCA hessian_nonpositivedefinite_bool             fullRE_DMDL
## 6  Eso-AdenoCA    hessian_positivedefinite_bool             diagRE_DMSL
## 7  Eso-AdenoCA    hessian_positivedefinite_bool            sparseRE_DMSL
## 8  Eso-AdenoCA hessian_nonpositivedefinite_bool             fullRE_DMSL
## 9  Eso-AdenoCA hessian_nonpositivedefinite_bool         fullRE_DMSL_SBS1
## 10 Eso-AdenoCA    hessian_positivedefinite_bool          fullRE_M_nonexo
## 11 Eso-AdenoCA    hessian_positivedefinite_bool       diagRE_DMSL_nonexo
## 12 Eso-AdenoCA    hessian_positivedefinite_bool     sparseRE_DMSL_nonexo
## 13 Eso-AdenoCA hessian_nonpositivedefinite_bool       fullRE_DMSL_nonexo
## 14 Eso-AdenoCA    hessian_positivedefinite_bool       fullRE_DMDL_nonexo
## 15 Eso-AdenoCA    hessian_positivedefinite_bool fullRE_DMDL_sortednonexo
```

Re-running of fitting

Using fullRE_M_nonexo to fit fullRE_DMSL_nonexo

which has a positive-semidefinite covariance matrix, i.e. has converged

```
## [1] TRUE
```

The fullRE DMSL hasn't, though:

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

```
## [1] FALSE
```

Potentially problematic signatures

We notice that there are no truly problematic signatures (SBS30 has the most zeros; 54.6%).

```
colSums(obj_Eso_AdenoCA$Y == 0)/nrow(obj_Eso_AdenoCA$Y)
```

```
##        SBS1        SBS2        SBS3        SBS5       SBS13      SBS17a
## 0.000000000 0.023076923 0.392307692 0.000000000 0.215384615 0.038461538
##      SBS17b       SBS18       SBS28       SBS30       SBS40       SBS46
## 0.007692308 0.038461538 0.238461538 0.546153846 0.000000000 0.476923077
```

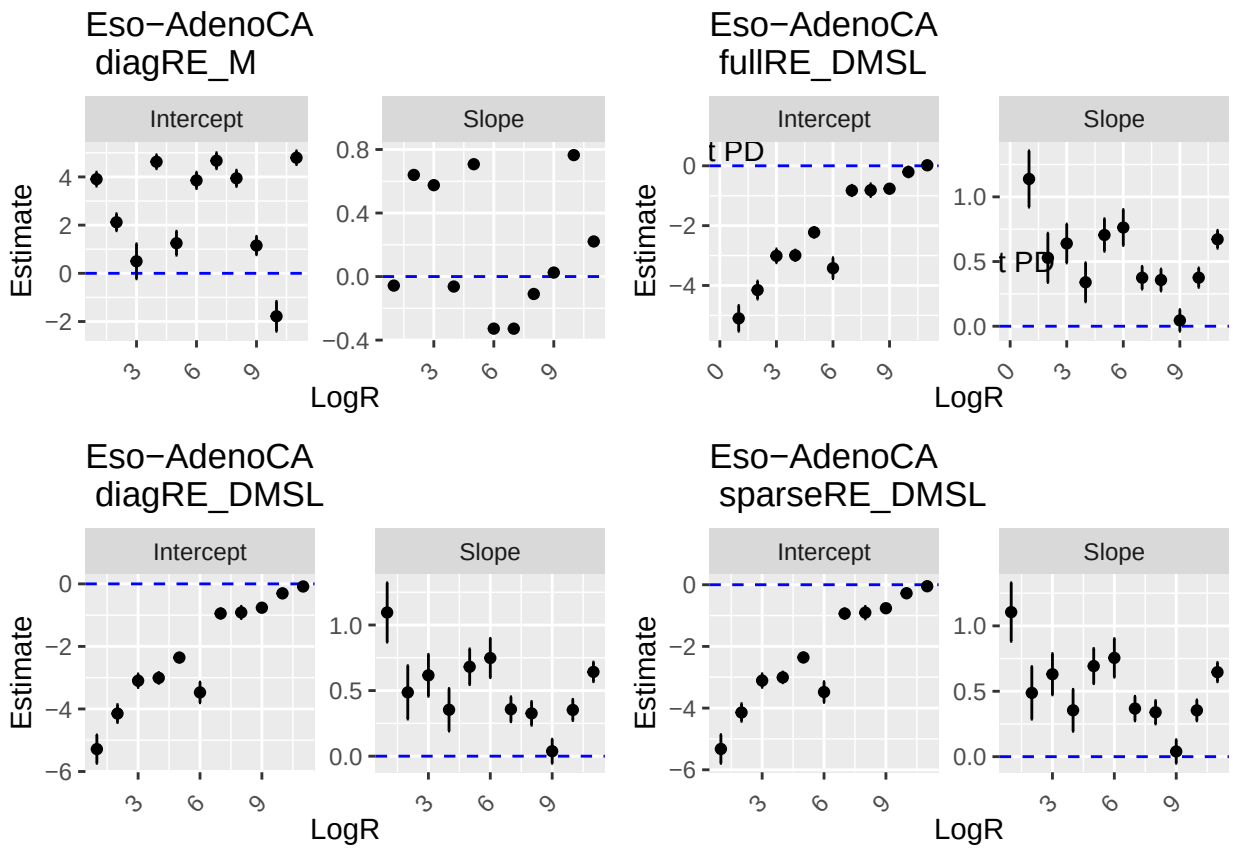
```
colSums(obj_Eso_AdenoCA$Y)/sum(obj_Eso_AdenoCA$Y)
```

```
##        SBS1        SBS2        SBS3        SBS5       SBS13      SBS17a
## 0.069743929 0.022981455 0.042124010 0.135767687 0.017294837 0.118553858
##      SBS17b       SBS18       SBS28       SBS30       SBS40       SBS46
## 0.265599550 0.088385597 0.020133817 0.006873288 0.198223396 0.014318577
```

Betas

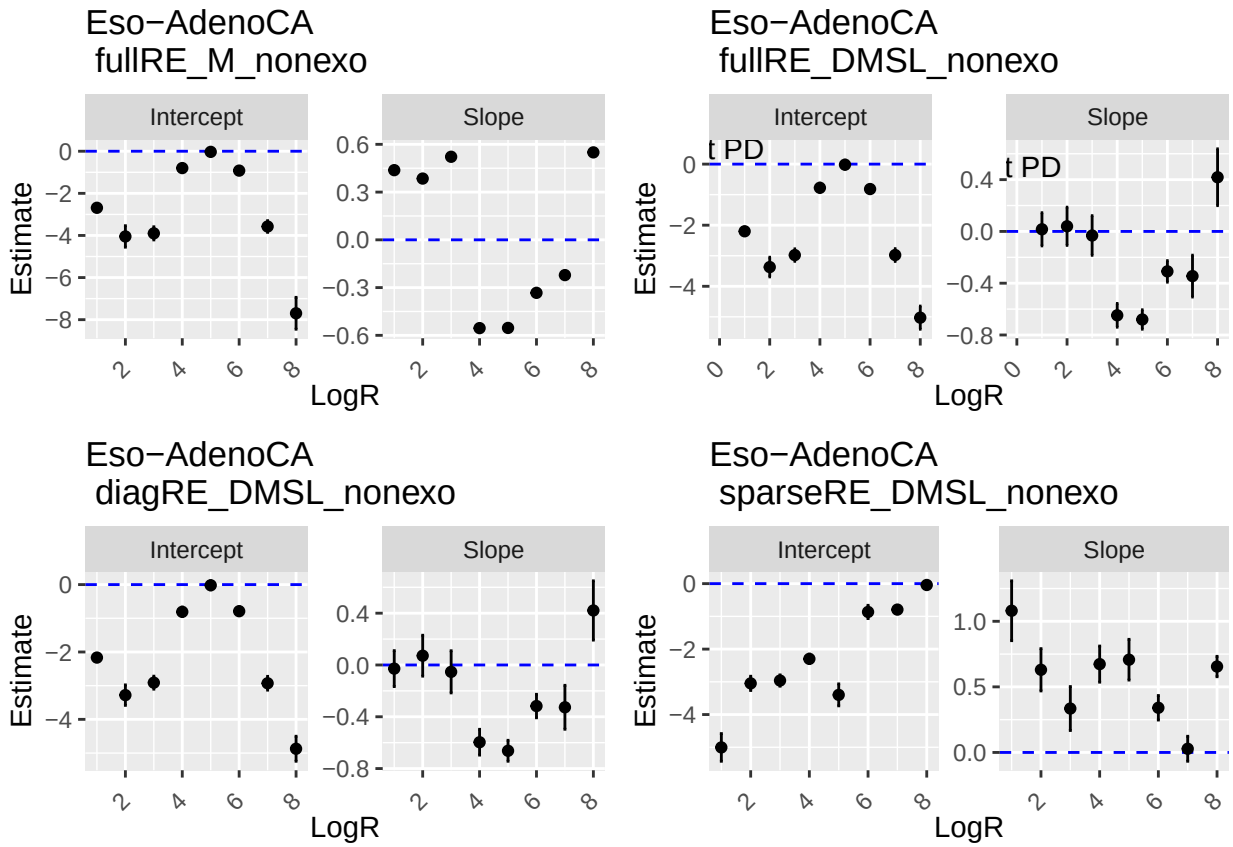
```
ct <- "Eso-AdenoCA"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```




```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(fullRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```

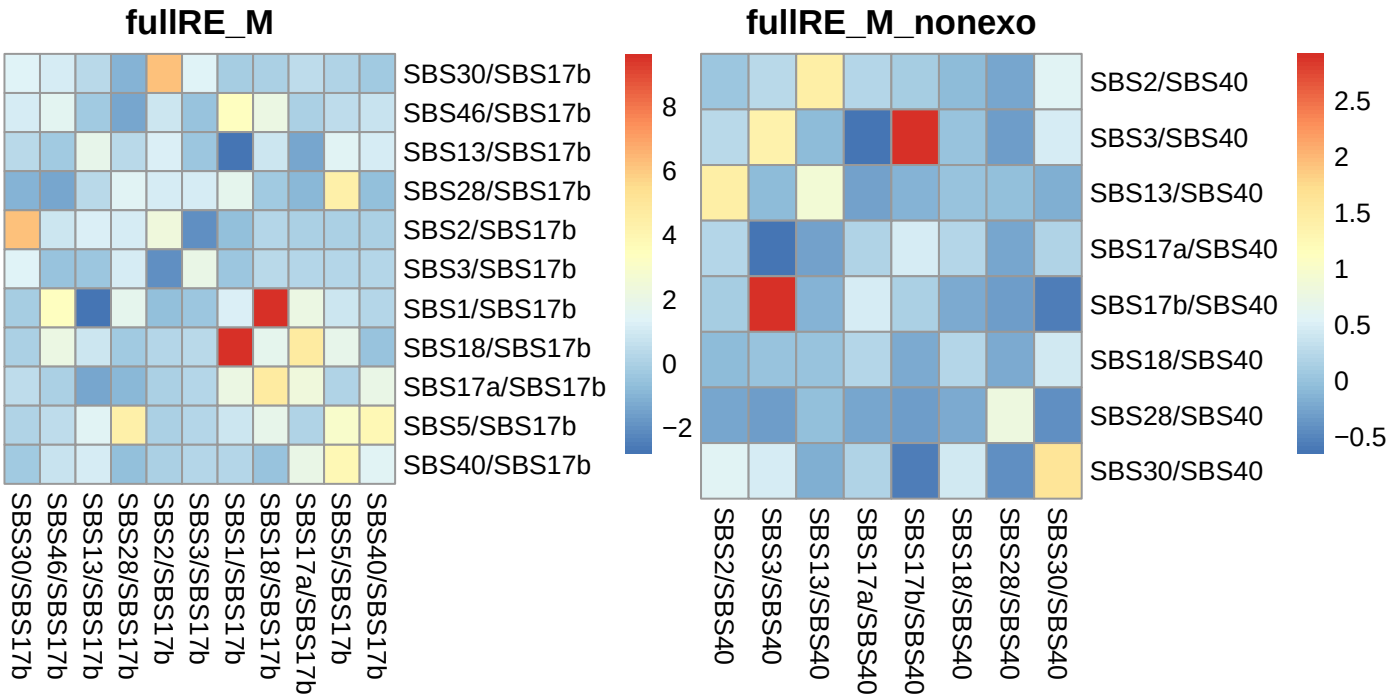
```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct

## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used

## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of $2.4465743 \times 10^{-18}$.

Covariance matrices



Simulation under inferred data

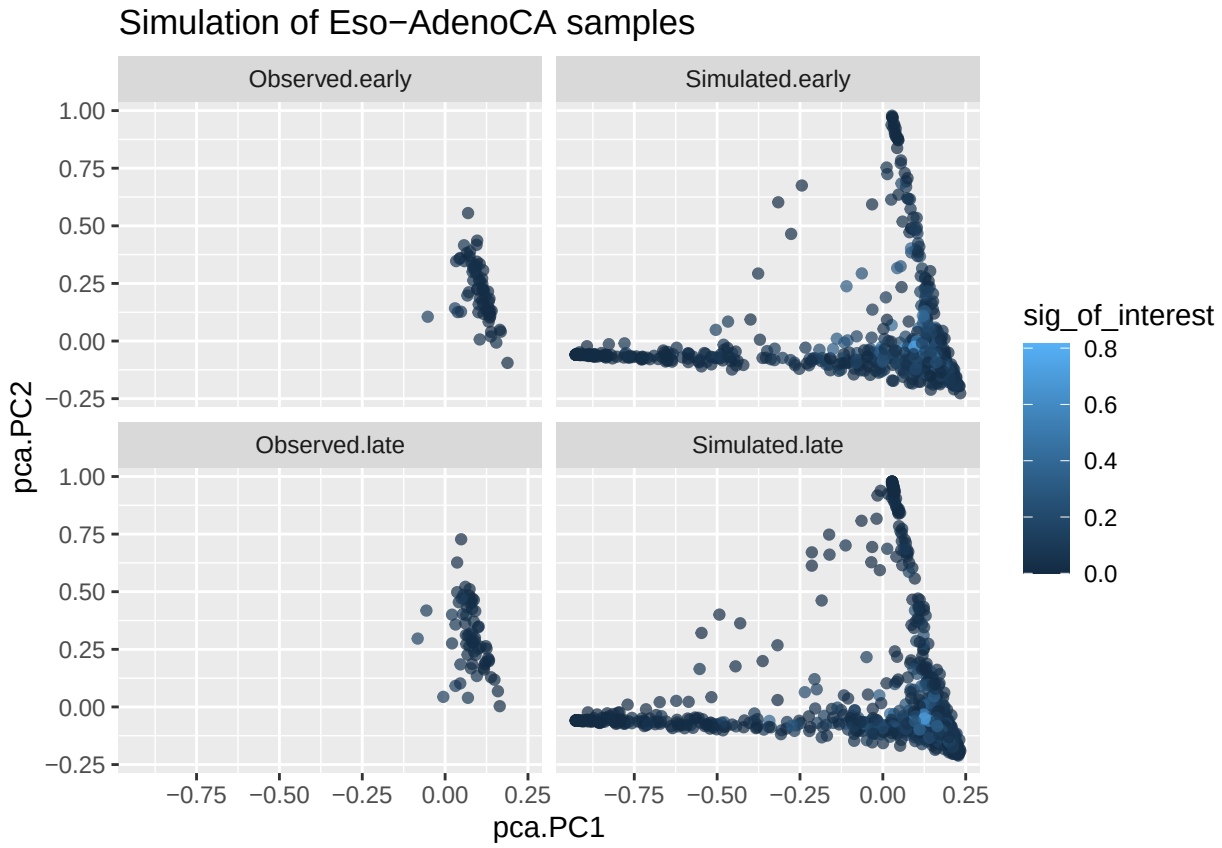
```
## [1] 65
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```

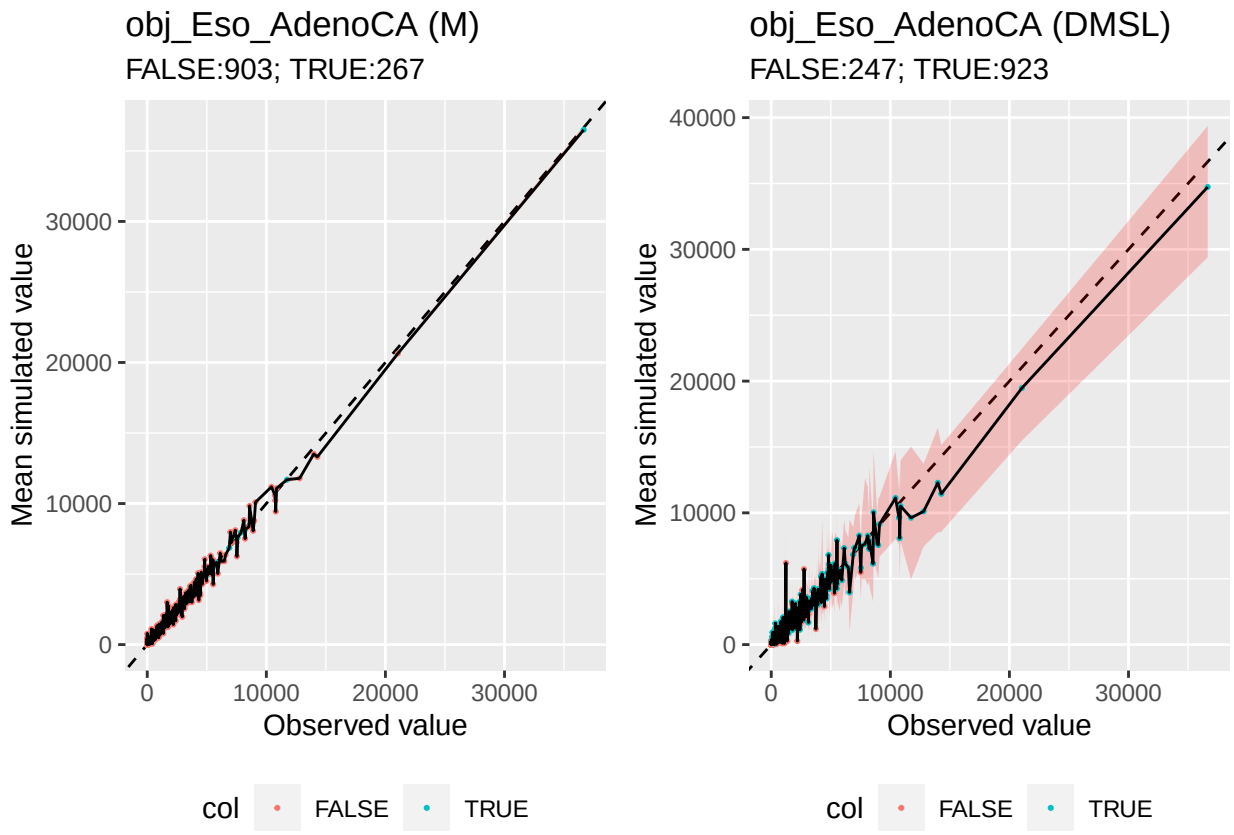
```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```



Ranked plot for coverage

```
ct <- "Eso-AdenoCA"
integer_overdispersion_param_DMSL <- 1
obj_Eso_AdenoCA_nonexo <- give_subset_sigs_TMBobj(obj_Eso_AdenoCA, sigs_to_remove = nonexogenous$V1)
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                  data_object = obj_Eso_AdenoCA_nonexo,
                  print_plot = F, nreps = 20, model = "M")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Eso_AdenoCA_nonexo,
                  loglog = F, title = 'obj_Eso_AdenoCA (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = diagRE_DMSL_nor
                  data_object = obj_Eso_AdenoCA_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Eso_AdenoCA_nonexo,
            loglog = F, title = 'obj_Eso_AdenoCA (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

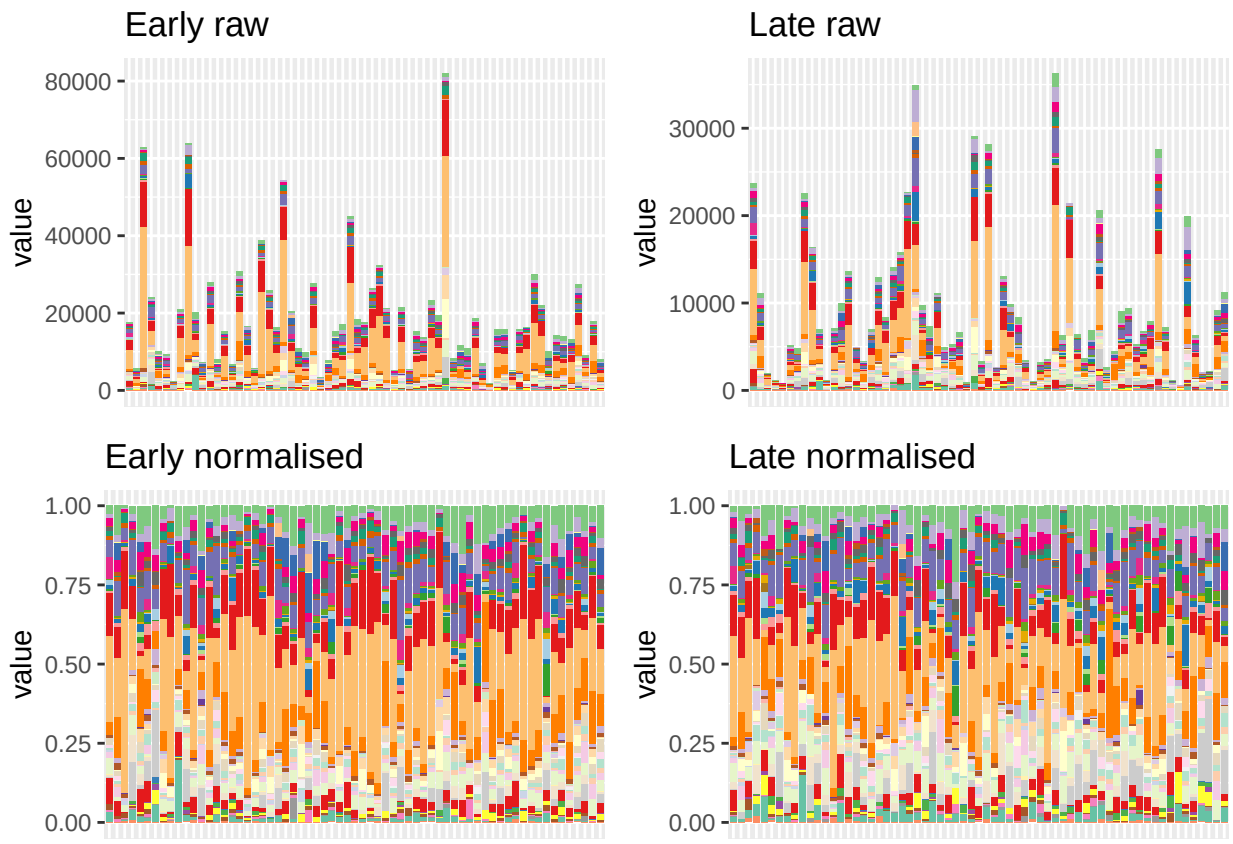
```
obj_Eso_AdenoCA_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                   path_to_data = "../../data/")
```

```
## [1] 65
```

```
give_barplot_from_obj(obj = obj_Eso_AdenoCA_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 65
## Creating plot... it might take some time if the data are large. Number of samples: 65
## Creating plot... it might take some time if the data are large. Number of samples: 65
## Creating plot... it might take some time if the data are large. Number of samples: 65
```

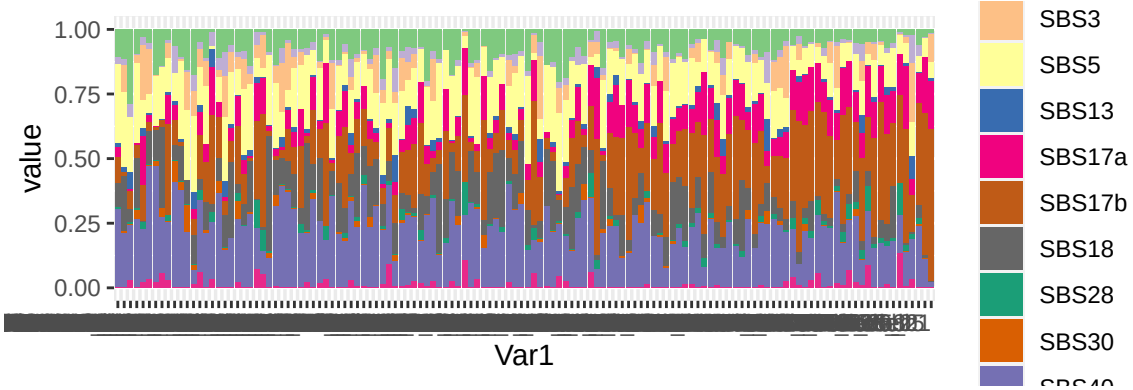
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: there is a trend of samples with more mutations having more SBS17b and less SBS5, relatively.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Eso_AdenoCA$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Eso_AdenoCA$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 130
```

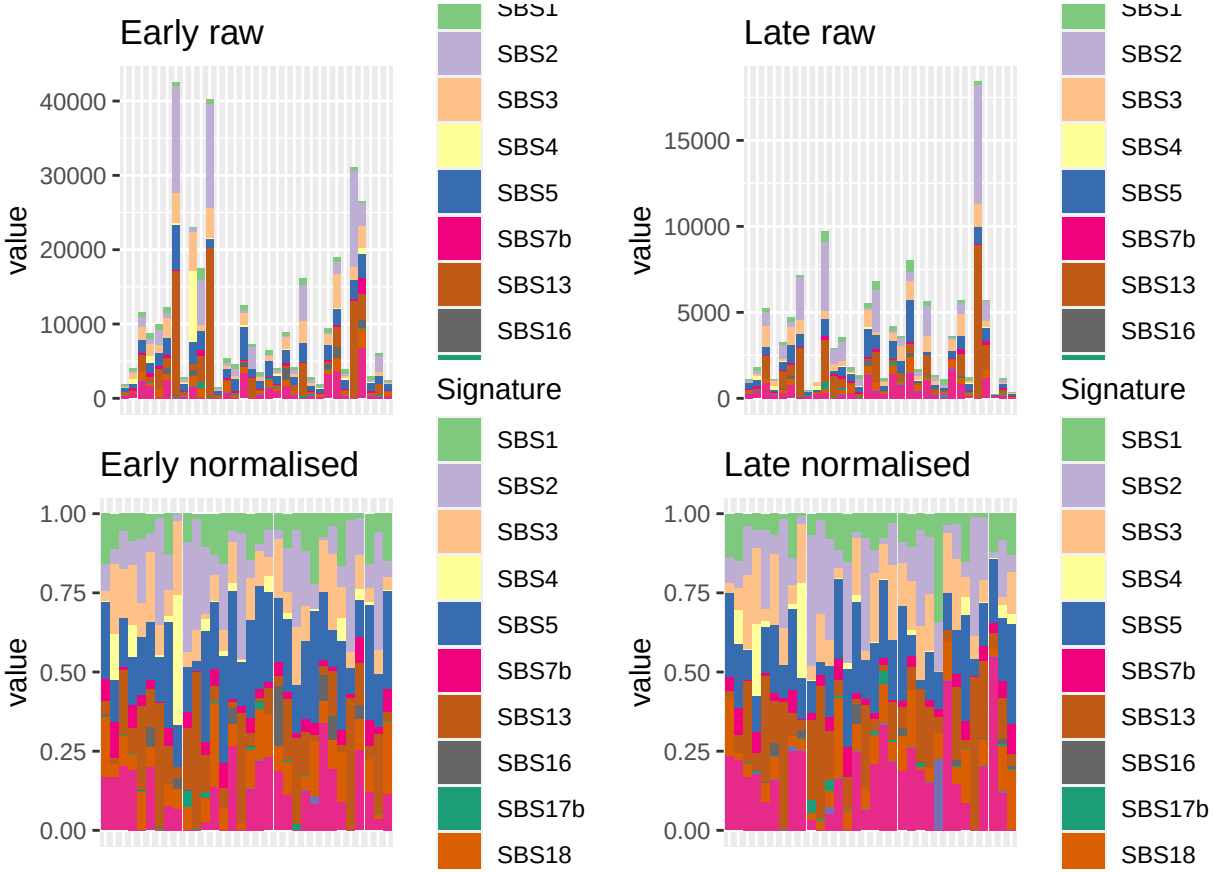


Head-SCC

Barplot and general statistics

```
## [1] 32
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 32
## Creating plot... it might take some time if the data are large. Number of samples: 32
## Creating plot... it might take some time if the data are large. Number of samples: 32
## Creating plot... it might take some time if the data are large. Number of samples: 32
```



The number of samples and signatures is:

```
## [1] 64 12
```

The signatures are:

```
##  [1] "SBS1"   "SBS2"   "SBS3"   "SBS4"   "SBS5"   "SBS7b"  "SBS13"  "SBS16"
##  [9] "SBS17b" "SBS18"  "SBS33"  "SBS40"
```

Convergence table

We don't have converged results for the multinomial with full RE, but for nonexogenous signatures everything has.

```
##       value                                 L2                  L1
## 1  Head-SCC    hessian_positivedefinite_bool          diagRE_M
## 2  Head-SCC hessian_nonpositivedefinite_bool          fullRE_M
```

```
## 3  Head-SCC hessian_nonpositivedefinite_bool             diagRE_DMDL
## 4  Head-SCC hessian_nonpositivedefinite_bool            fullRE_halfDM
## 5  Head-SCC hessian_nonpositivedefinite_bool             fullRE_DMDL
## 6  Head-SCC    hessian_positivedefinite_bool             diagRE_DMSL
## 7  Head-SCC    hessian_positivedefinite_bool            sparseRE_DMSL
## 8  Head-SCC hessian_nonpositivedefinite_bool             fullRE_DMSL
## 9  Head-SCC hessian_nonpositivedefinite_bool         fullRE_DMSL_SBS1
## 10 Head-SCC    hessian_positivedefinite_bool          fullRE_M_nonexo
## 11 Head-SCC    hessian_positivedefinite_bool       diagRE_DMSL_nonexo
## 12 Head-SCC    hessian_positivedefinite_bool     sparseRE_DMSL_nonexo
## 13 Head-SCC    hessian_positivedefinite_bool       fullRE_DMSL_nonexo
## 14 Head-SCC hessian_nonpositivedefinite_bool       fullRE_DMDL_nonexo
## 15 Head-SCC                         Timeout fullRE_DMDL_sortednonexo
```

Re-running of fitting

We don't need refitting, as the results have already converged.

Potentially problematic signatures

SBS33 is likely to be problematic.

```
colSums(obj_Head_SCC$Y == 0)/nrow(obj_Head_SCC$Y)
```

```
##    SBS1    SBS2    SBS3    SBS4    SBS5   SBS7b   SBS13   SBS16  SBS17b   SBS18
## 0.00000 0.00000 0.06250 0.50000 0.00000 0.06250 0.00000 0.75000 0.40625 0.09375
##   SBS33   SBS40
## 0.81250 0.21875
```

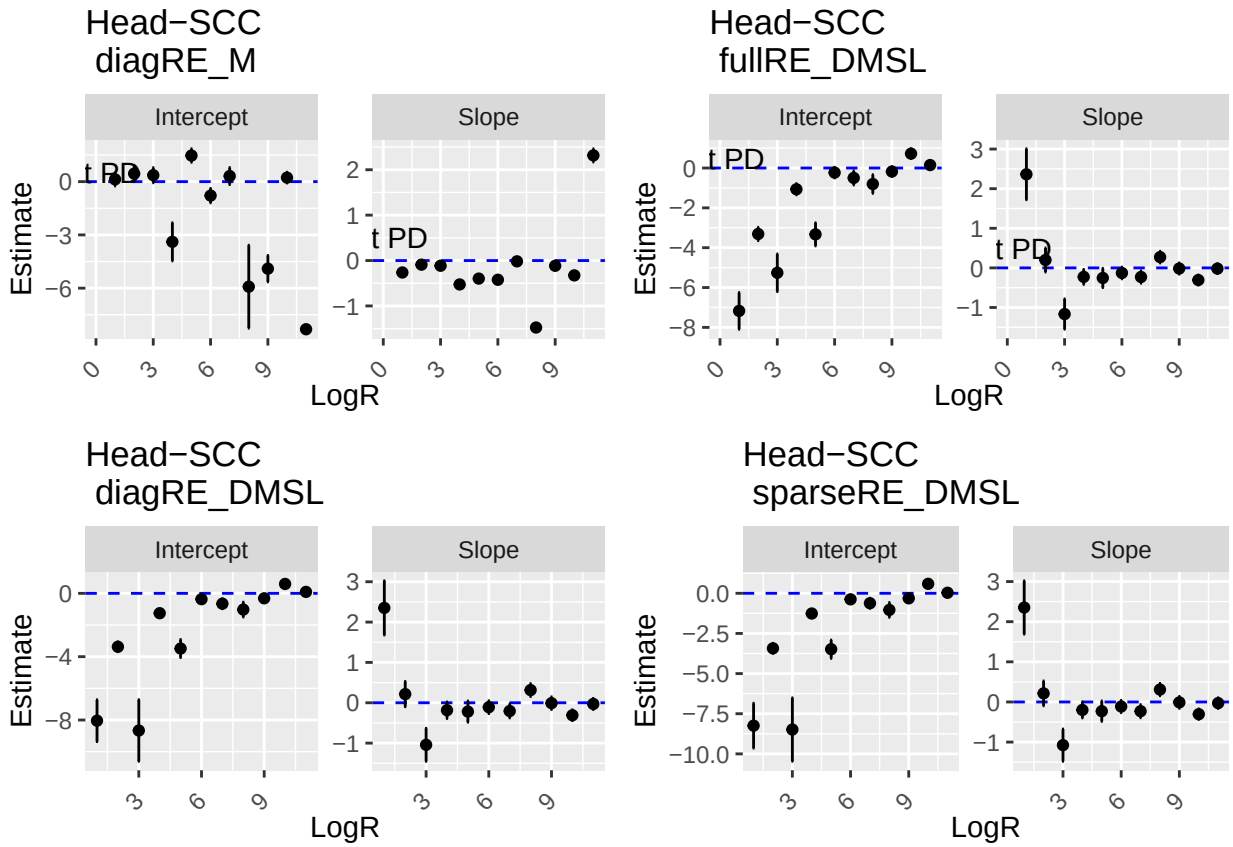
```
colSums(obj_Head_SCC$Y)/sum(obj_Head_SCC$Y)
```

```
##        SBS1        SBS2        SBS3        SBS4        SBS5       SBS7b
## 0.052157398 0.209133263 0.121874082 0.030243442 0.152377754 0.025011542
##       SBS13       SBS16      SBS17b       SBS18       SBS33       SBS40
## 0.225057712 0.017861490 0.005867786 0.056873033 0.001013641 0.102528856
```

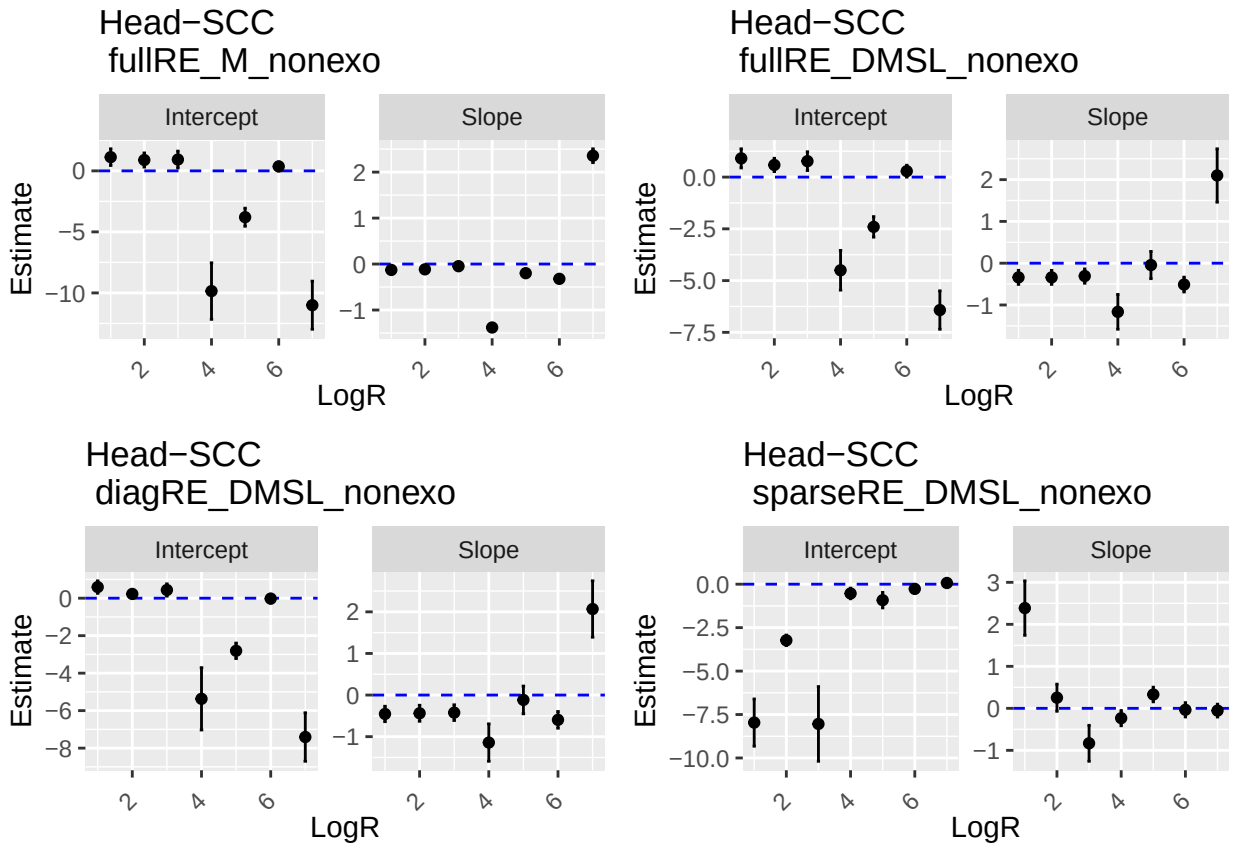
Betas

```
ct <- "Head-SCC"

grid.arrange(plot_betas(fullRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
             plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
             plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
             plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced

## Warning in sqrt(as.numeric(object$diag.cov.random)): NaNs produced

## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```



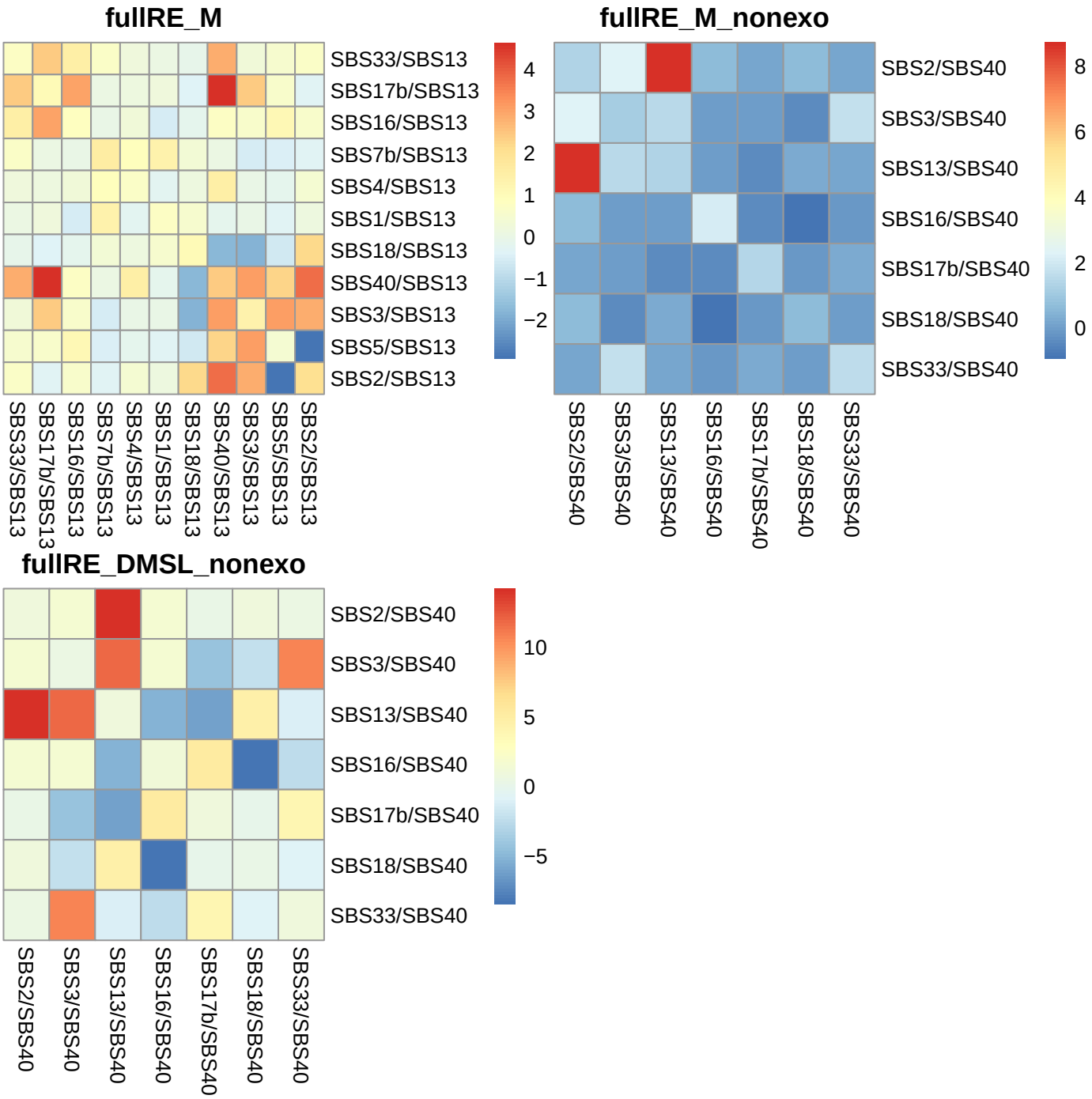

```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(fullRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
  plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
  plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct

## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used

## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 8.4420109×10^{-5}.

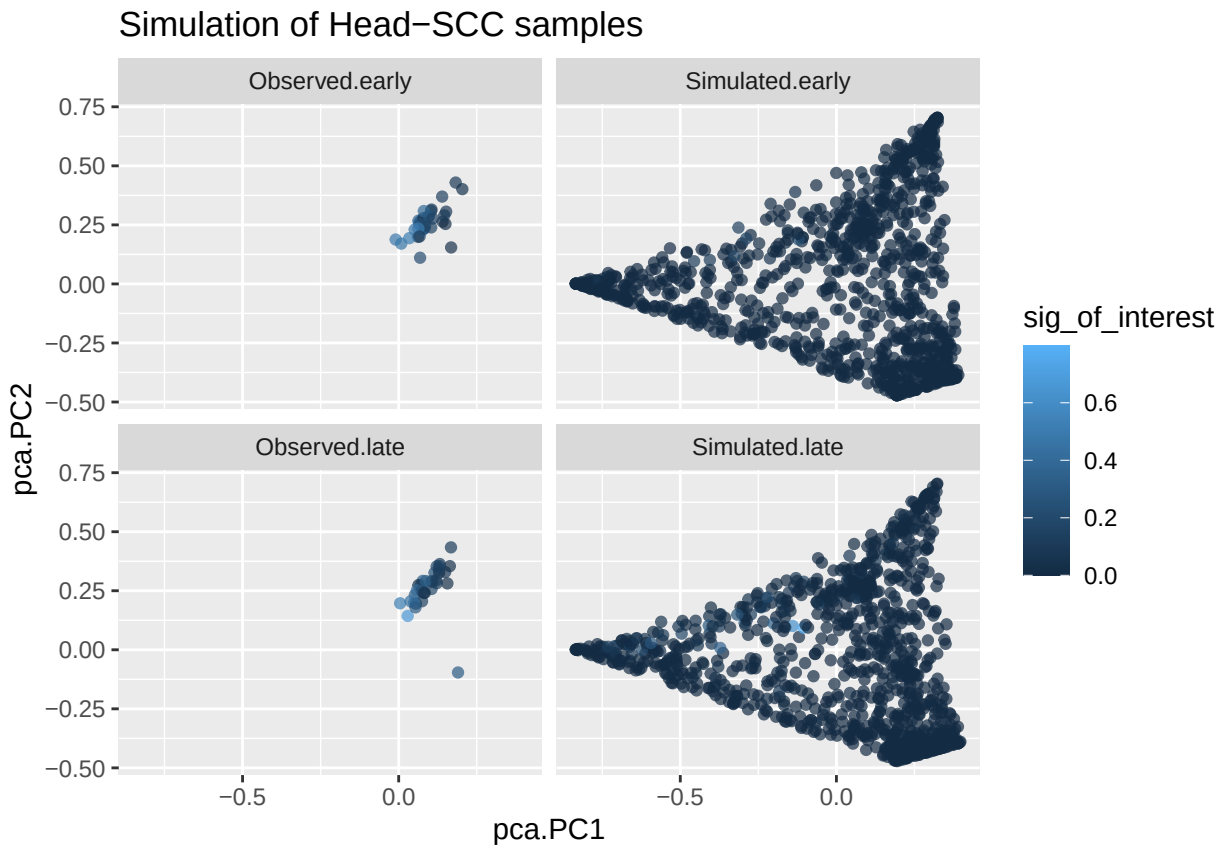
Covariance matrices



Simulation under inferred data

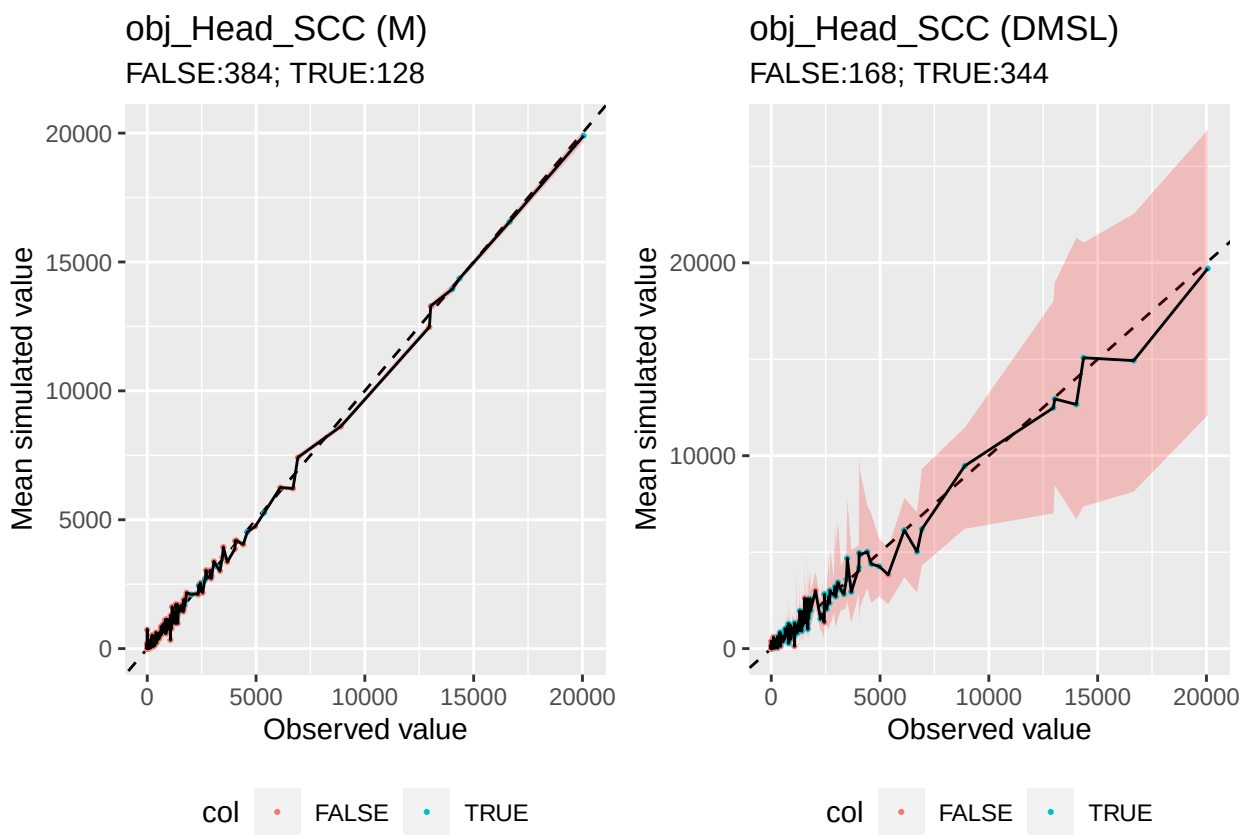
```
## [1] 32
```

```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```



Ranked plot for coverage

```
ct <- "Head-SCC"
integer_overdispersion_param_DMSL <- 1
obj_Head_SCC_nonexo <- give_subset_sigs_TMBobj(obj_Head_SCC, sigs_to_remove = nonexogenous$V1)
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                  data_object = obj_Head_SCC_nonexo,
                  print_plot = F, nreps = 20, model = "M")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Head_SCC_nonexo,
                  loglog = F, title = 'obj_Head_SCC (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = fullRE_DMSL_nor
                  data_object = obj_Head_SCC_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Head_SCC_nonexo,
           loglog = F, title = 'obj_Head_SCC (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

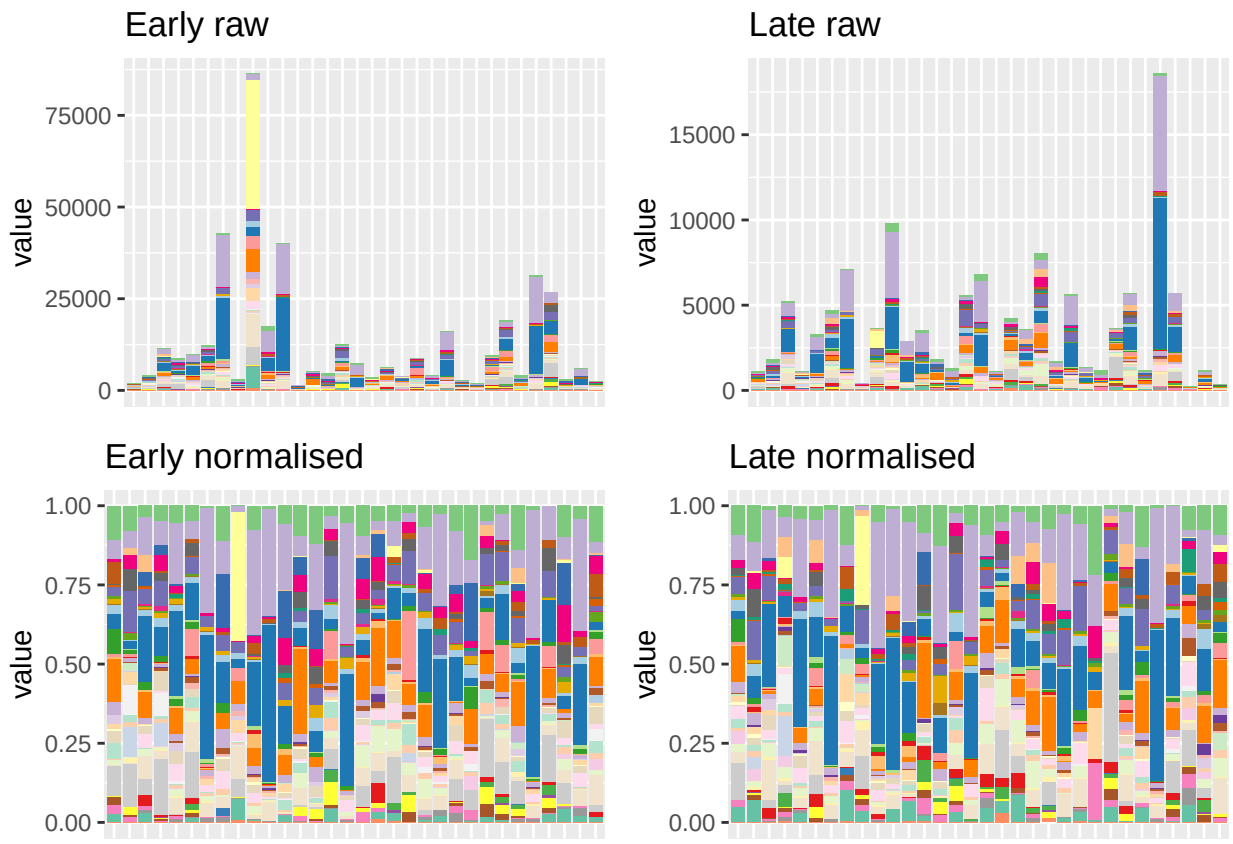
```
obj_Head_SCC_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                   path_to_data = "../../data/")
```

```
## [1] 32
```

```
give_barplot_from_obj(obj = obj_Head_SCC_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 32
## Creating plot... it might take some time if the data are large. Number of samples: 32
## Creating plot... it might take some time if the data are large. Number of samples: 32
## Creating plot... it might take some time if the data are large. Number of samples: 32
```

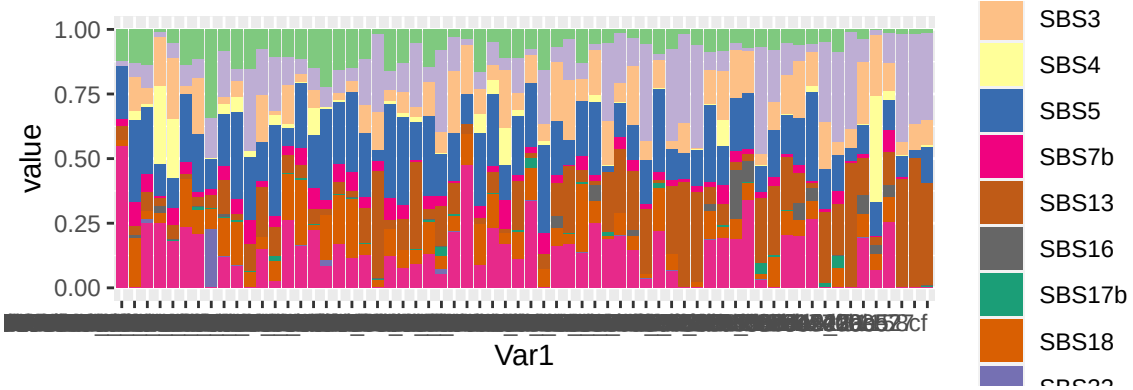
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Head_SCC$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Head_SCC$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 64
```

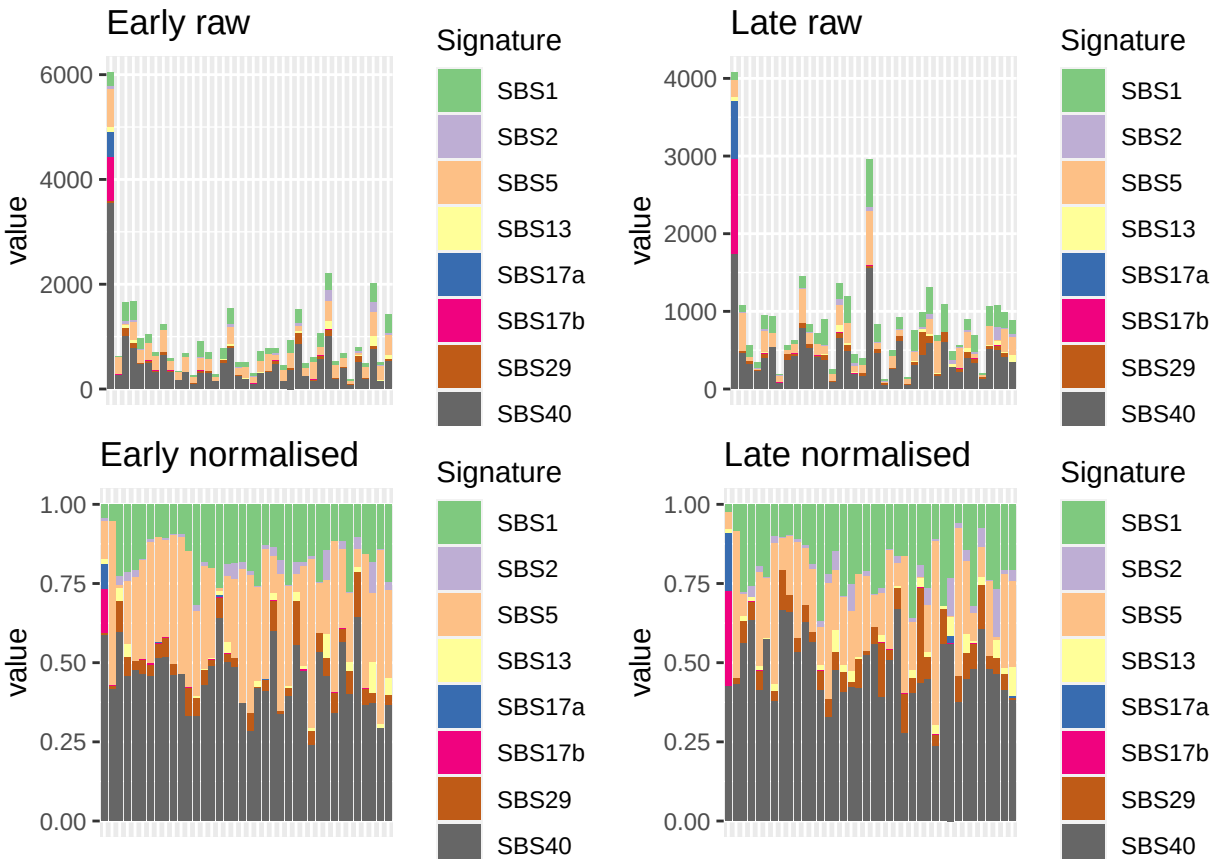


Kidney-ChRCC

Barplot and general statistics

```
## [1] 38
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 38
## Creating plot... it might take some time if the data are large. Number of samples: 38
## Creating plot... it might take some time if the data are large. Number of samples: 38
## Creating plot... it might take some time if the data are large. Number of samples: 38
```



The number of samples and signatures is:

```
## [1] 76  8
```

The signatures are:

```
## [1] "SBS1"   "SBS2"   "SBS5"   "SBS13"  "SBS17a" "SBS17b" "SBS29"  "SBS40"
```

Convergence table

For all signatures, no fullRE model has converged. For nonexogenous ones, all have.

```
##           value                                L2                  L1
## 1  Kidney-ChRCC hessian_nonpositivedefinite_bool             diagRE_M
## 2  Kidney-ChRCC hessian_nonpositivedefinite_bool             fullRE_M
## 3  Kidney-ChRCC hessian_nonpositivedefinite_bool           diagRE_DMDL
## 4  Kidney-ChRCC hessian_nonpositivedefinite_bool         fullRE_halfDM
```

```
## 5  Kidney-ChRCC hessian_nonpositivedefinite_bool             fullRE_DMDL
## 6  Kidney-ChRCC    hessian_positivedefinite_bool             diagRE_DMSL
## 7  Kidney-ChRCC    hessian_positivedefinite_bool           sparseRE_DMSL
## 8  Kidney-ChRCC hessian_nonpositivedefinite_bool             fullRE_DMSL
## 9  Kidney-ChRCC hessian_nonpositivedefinite_bool        fullRE_DMSL_SBS1
## 10 Kidney-ChRCC    hessian_positivedefinite_bool         fullRE_M_nonexo
## 11 Kidney-ChRCC    hessian_positivedefinite_bool      diagRE_DMSL_nonexo
## 12 Kidney-ChRCC    hessian_positivedefinite_bool    sparseRE_DMSL_nonexo
## 13 Kidney-ChRCC    hessian_positivedefinite_bool      fullRE_DMSL_nonexo
## 14 Kidney-ChRCC hessian_nonpositivedefinite_bool      fullRE_DMDL_nonexo
## 15 Kidney-ChRCC hessian_nonpositivedefinite_bool fullRE_DMDL_sortednonexo
```

Re-running of fitting

We do not need to re-run any model fitting.

Potentially problematic signatures

We notice that SBS17a and SBS17b are perhaps problematic.

```
colSums(obj_Kidney_ChRCC$Y == 0)/nrow(obj_Kidney_ChRCC$Y)
```

```
##       SBS1       SBS2       SBS5      SBS13     SBS17a     SBS17b      SBS29
## 0.00000000 0.23684211 0.05263158 0.35526316 0.89473684 0.89473684 0.09210526
##      SBS40
## 0.00000000
```

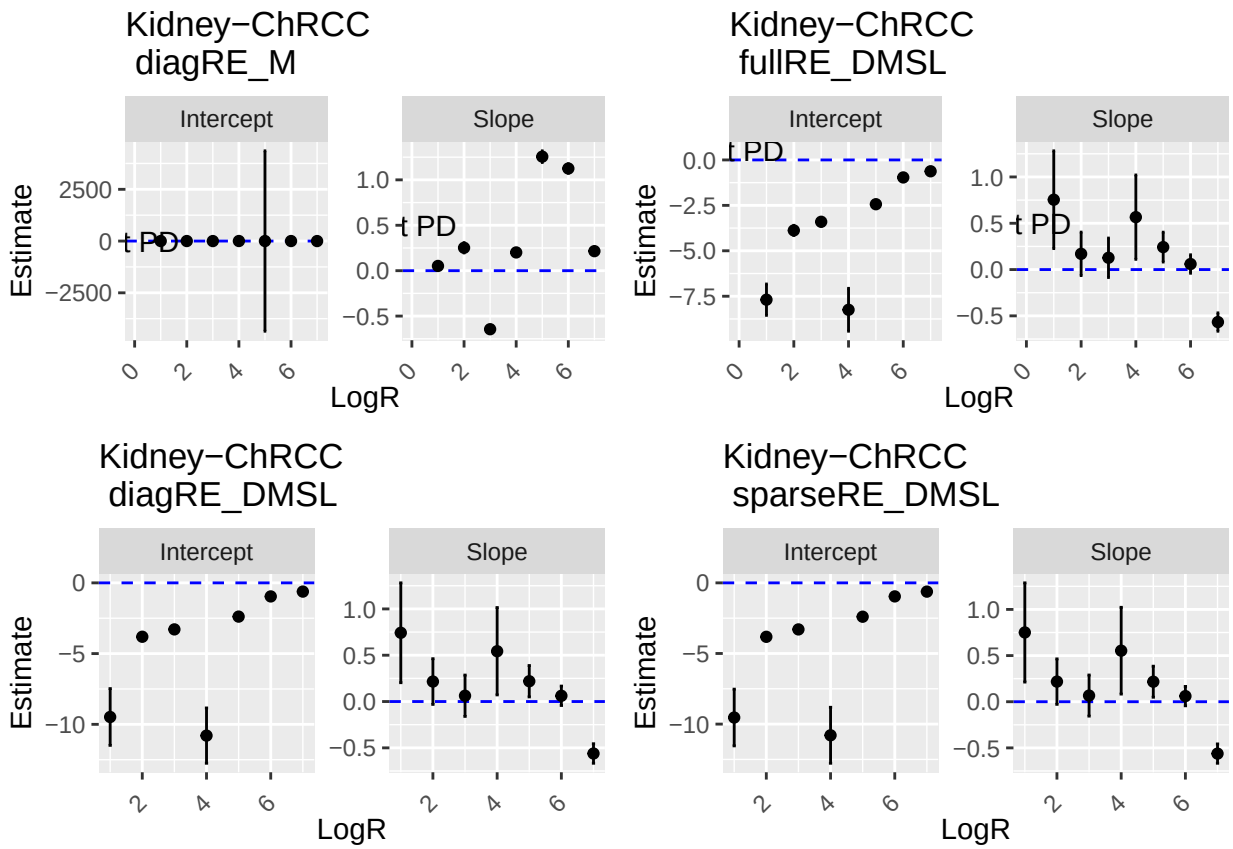
```
colSums(obj_Kidney_ChRCC$Y)/sum(obj_Kidney_ChRCC$Y)
```

```
##       SBS1       SBS2       SBS5      SBS13     SBS17a     SBS17b      SBS29
## 0.17183661 0.02350905 0.21046460 0.02066116 0.01747822 0.02920482 0.04789759
##      SBS40
## 0.47894796
```

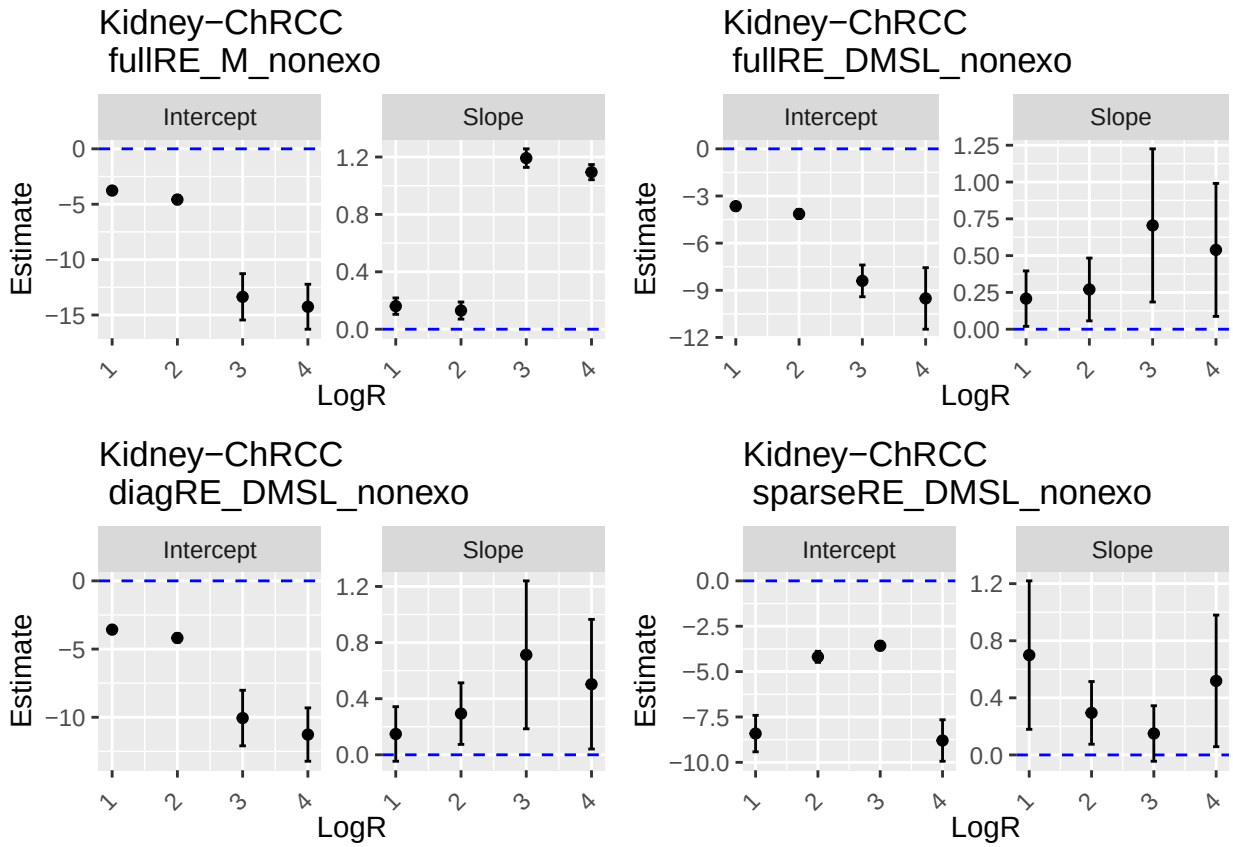
Betas

```
ct <- "Kidney-ChRCC"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced

## Warning in sqrt(as.numeric(object$diag.cov.random)): NaNs produced

## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```




```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(fullRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```



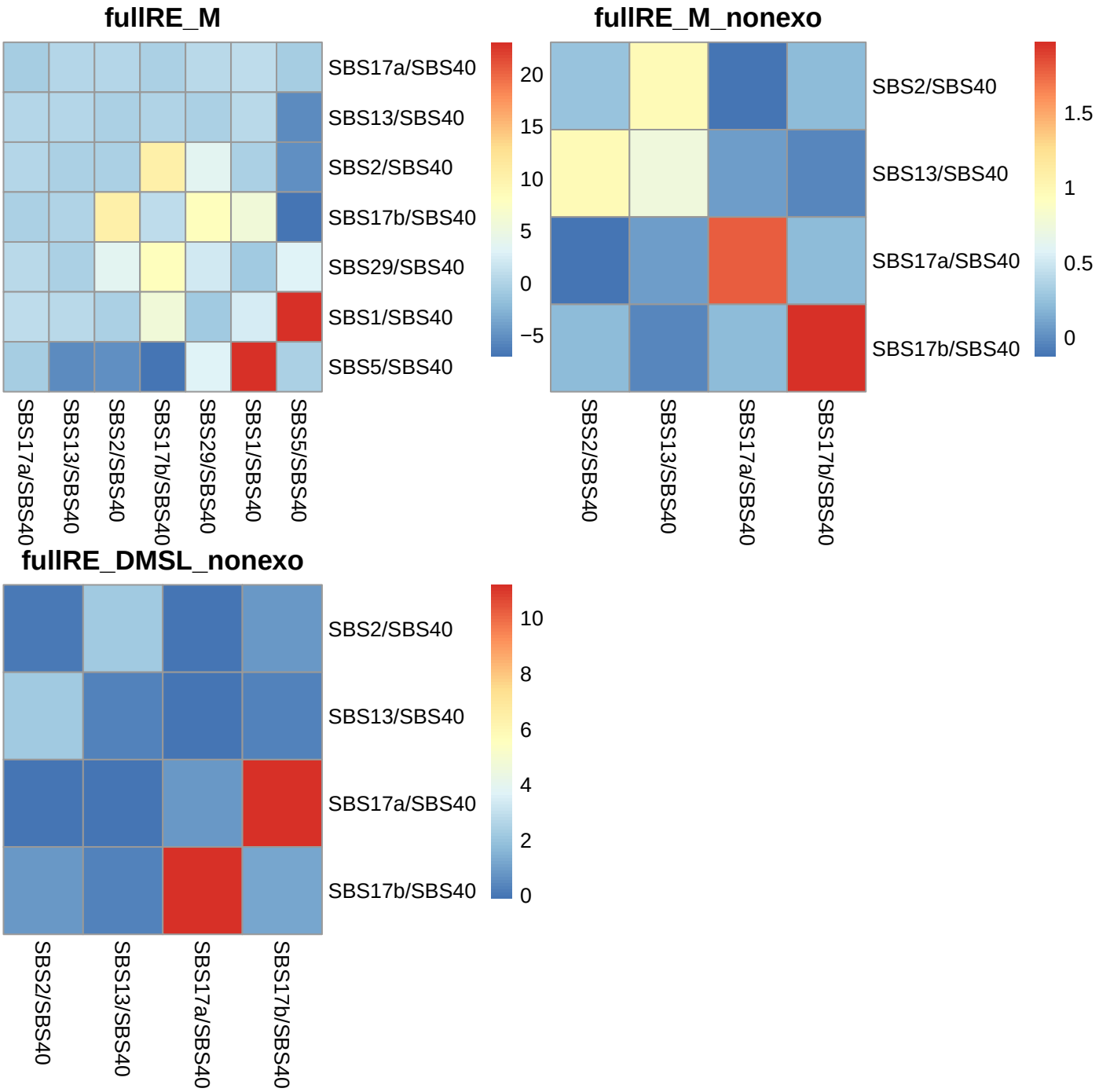

```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct
```

```
## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used
```

```
## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 0.2664763.

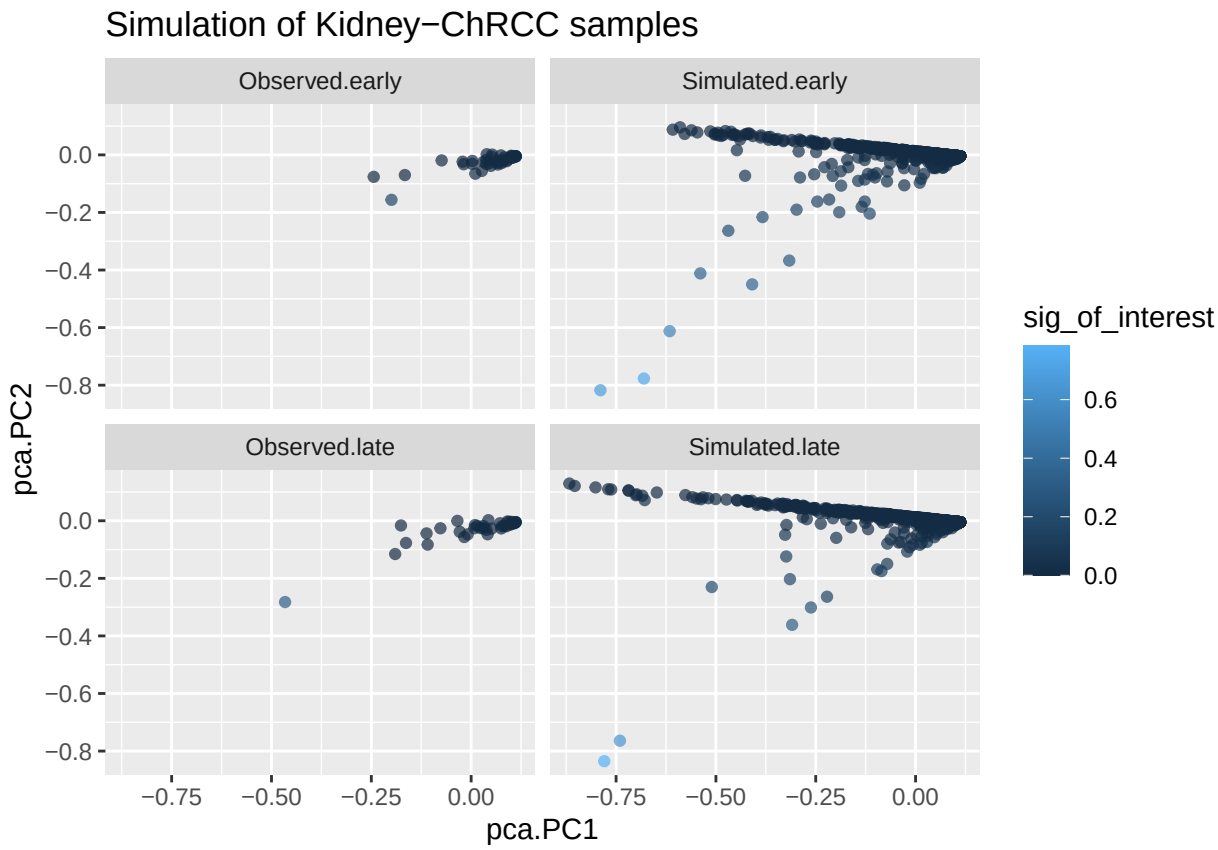
Covariance matrices



Simulation under inferred data

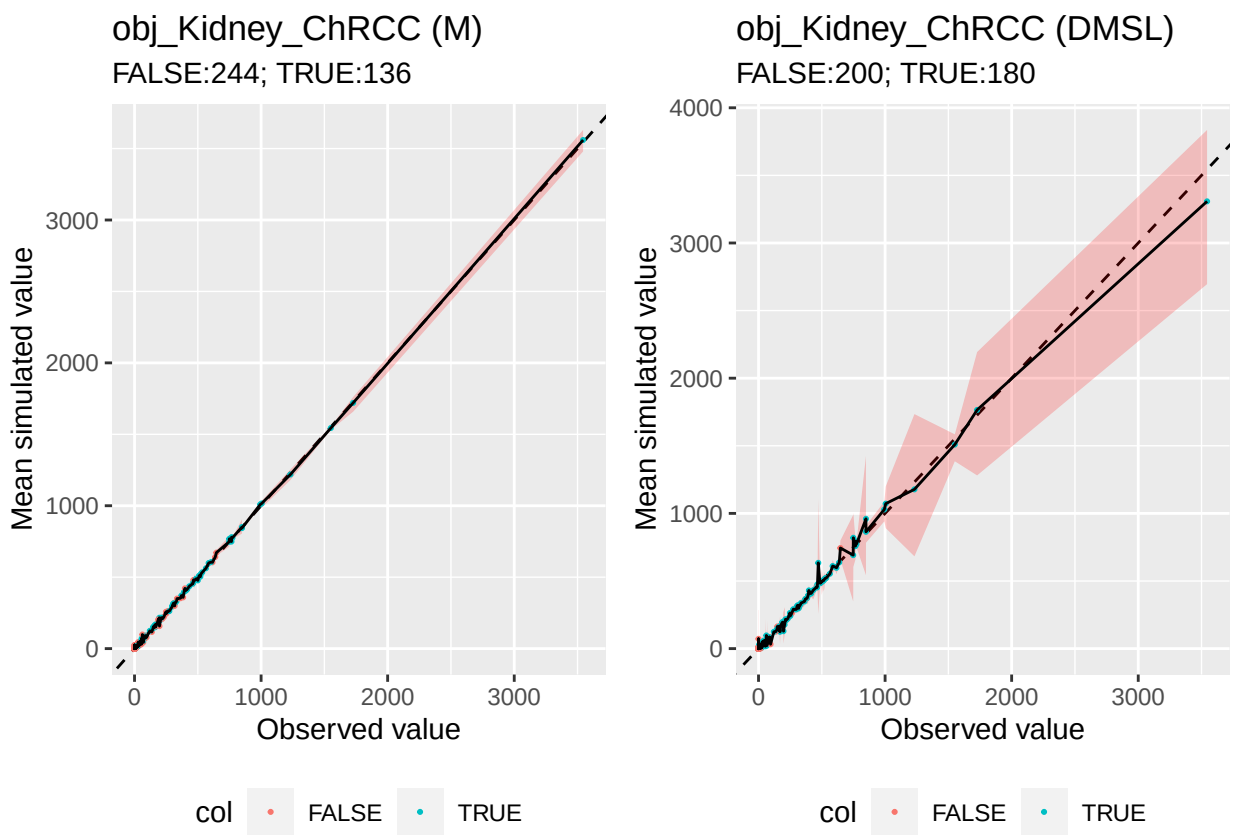
```
## [1] 38
```

```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```



Ranked plot for coverage

```
ct <- "Kidney-ChRCC"
integer_overdispersion_param_DMSL <- 1
obj_Kidney_ChRCC_nonexo <- give_subset_sigs_TMBobj(obj_Kidney_ChRCC, sigs_to_remove = nonexogenous$V1)
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                  data_object = obj_Kidney_ChRCC_nonexo,
                  print_plot = F, nreps = 20, model = "M")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Kidney_ChRCC_nonexo,
                  loglog = F, title = 'obj_Kidney_ChRCC (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = fullRE_DMSL_nor
                  data_object = obj_Kidney_ChRCC_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Kidney_ChRCC_nonexo,
            loglog = F, title = 'obj_Kidney_ChRCC (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

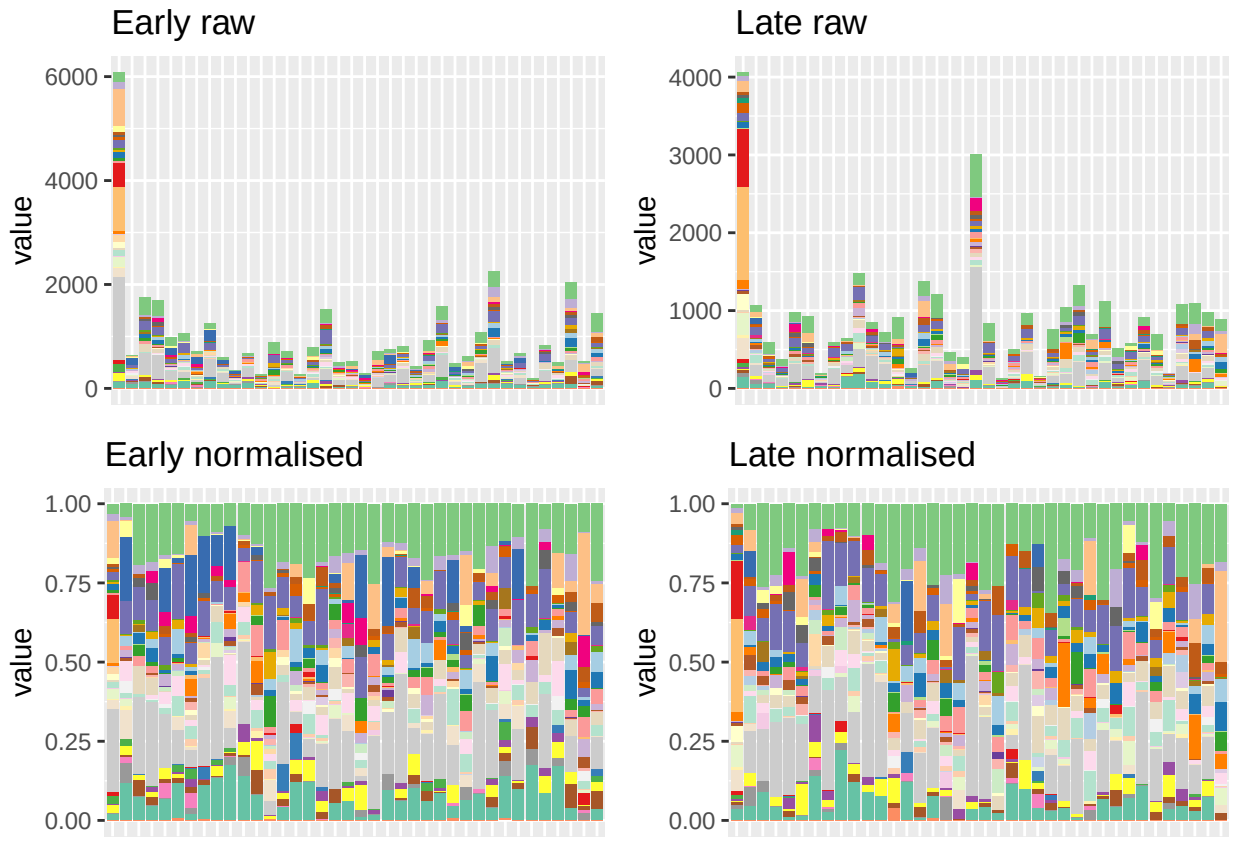
```
obj_Kidney_ChRCC_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

```
## [1] 38
```

```
give_barplot_from_obj(obj = obj_Kidney_ChRCC_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 38
## Creating plot... it might take some time if the data are large. Number of samples: 38
## Creating plot... it might take some time if the data are large. Number of samples: 38
## Creating plot... it might take some time if the data are large. Number of samples: 38
```

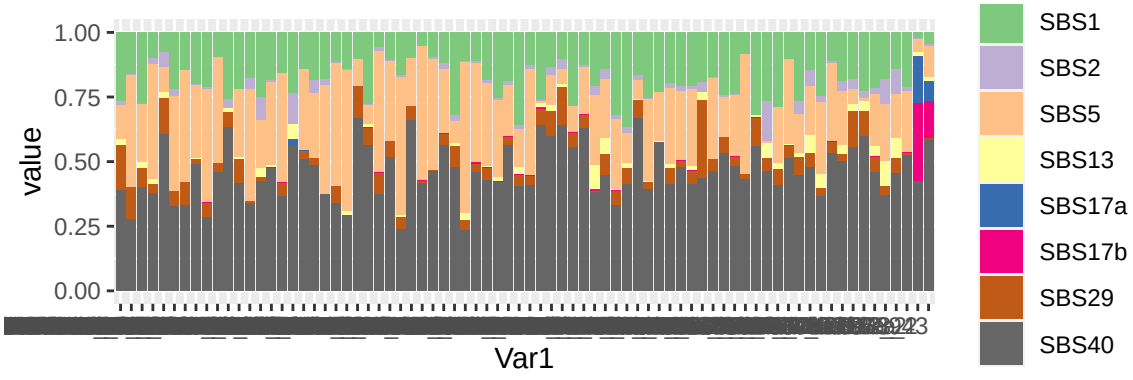
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Kidney_ChRCC$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Kidney_ChRCC$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 76
```

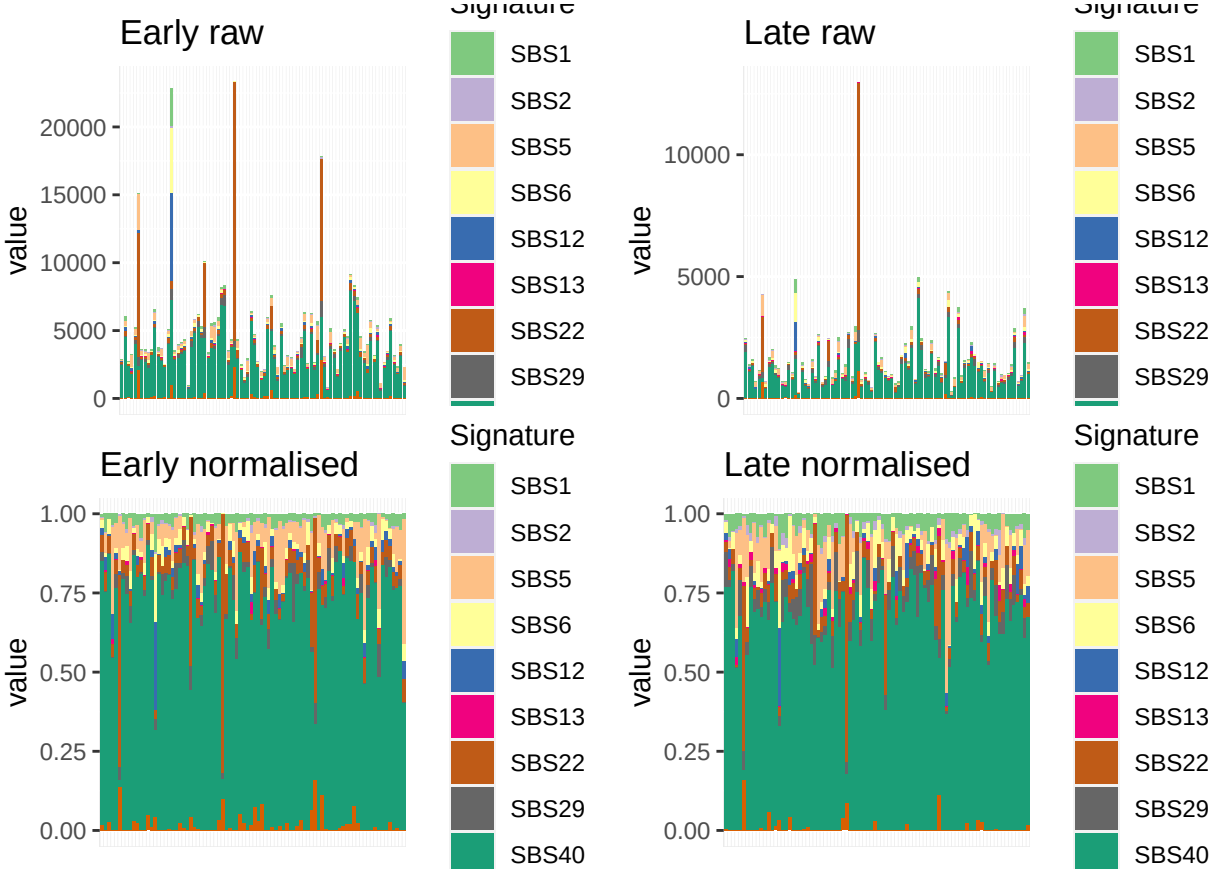


Kidney-RCC.clearcell

Barplot and general statistics

```
## [1] 86
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 86
## Creating plot... it might take some time if the data are large. Number of samples: 86
## Creating plot... it might take some time if the data are large. Number of samples: 86
## Creating plot... it might take some time if the data are large. Number of samples: 86
```



The number of samples and signatures is:

```
## [1] 172  10
```

The signatures are:

```
##  [1] "SBS1"  "SBS2"  "SBS5"  "SBS6"  "SBS12" "SBS13" "SBS22" "SBS29" "SBS40"
## [10] "SBS41"
```

Convergence table

Essentially, everything has converged.

```
##                   value                                L2
## 1  Kidney-RCC.clearcell    hessian_positivedefinite_bool
## 2  Kidney-RCC.clearcell    hessian_positivedefinite_bool
## 3  Kidney-RCC.clearcell hessian_nonpositivedefinite_bool
## 4  Kidney-RCC.clearcell                         Timeout
## 5  Kidney-RCC.clearcell hessian_nonpositivedefinite_bool
## 6  Kidney-RCC.clearcell    hessian_positivedefinite_bool
## 7  Kidney-RCC.clearcell    hessian_positivedefinite_bool
```

```
## 8  Kidney-RCC.clearcell    hessian_positivedefinite_bool
## 9  Kidney-RCC.clearcell    hessian_positivedefinite_bool
## 10 Kidney-RCC.clearcell    hessian_positivedefinite_bool
## 11 Kidney-RCC.clearcell    hessian_positivedefinite_bool
## 12 Kidney-RCC.clearcell    hessian_positivedefinite_bool
## 13 Kidney-RCC.clearcell    hessian_positivedefinite_bool
## 14 Kidney-RCC.clearcell    hessian_positivedefinite_bool
## 15 Kidney-RCC.clearcell                          Timeout
##                          L1
## 1                  diagRE_M
## 2                  fullRE_M
## 3                diagRE_DMDL
## 4              fullRE_halfDM
## 5                fullRE_DMDL
## 6                diagRE_DMSL
## 7              sparseRE_DMSL
## 8                fullRE_DMSL
## 9           fullRE_DMSL_SBS1
## 10           fullRE_M_nonexo
## 11        diagRE_DMSL_nonexo
## 12     sparseRE_DMSL_nonexo
## 13       fullRE_DMSL_nonexo
## 14       fullRE_DMDL_nonexo
## 15 fullRE_DMDL_sortednonexo
```

Potentially problematic signatures

There are no problematic signatures.

```
colSums(obj_Kidney_RCCclearcell$Y == 0)/nrow(obj_Kidney_RCCclearcell$Y)
```

```
##       SBS1       SBS2       SBS5       SBS6      SBS12      SBS13      SBS22
## 0.02906977 0.26744186 0.33139535 0.11627907 0.35465116 0.52325581 0.00000000
##      SBS29      SBS40      SBS41
## 0.13372093 0.00000000 0.58720930
```

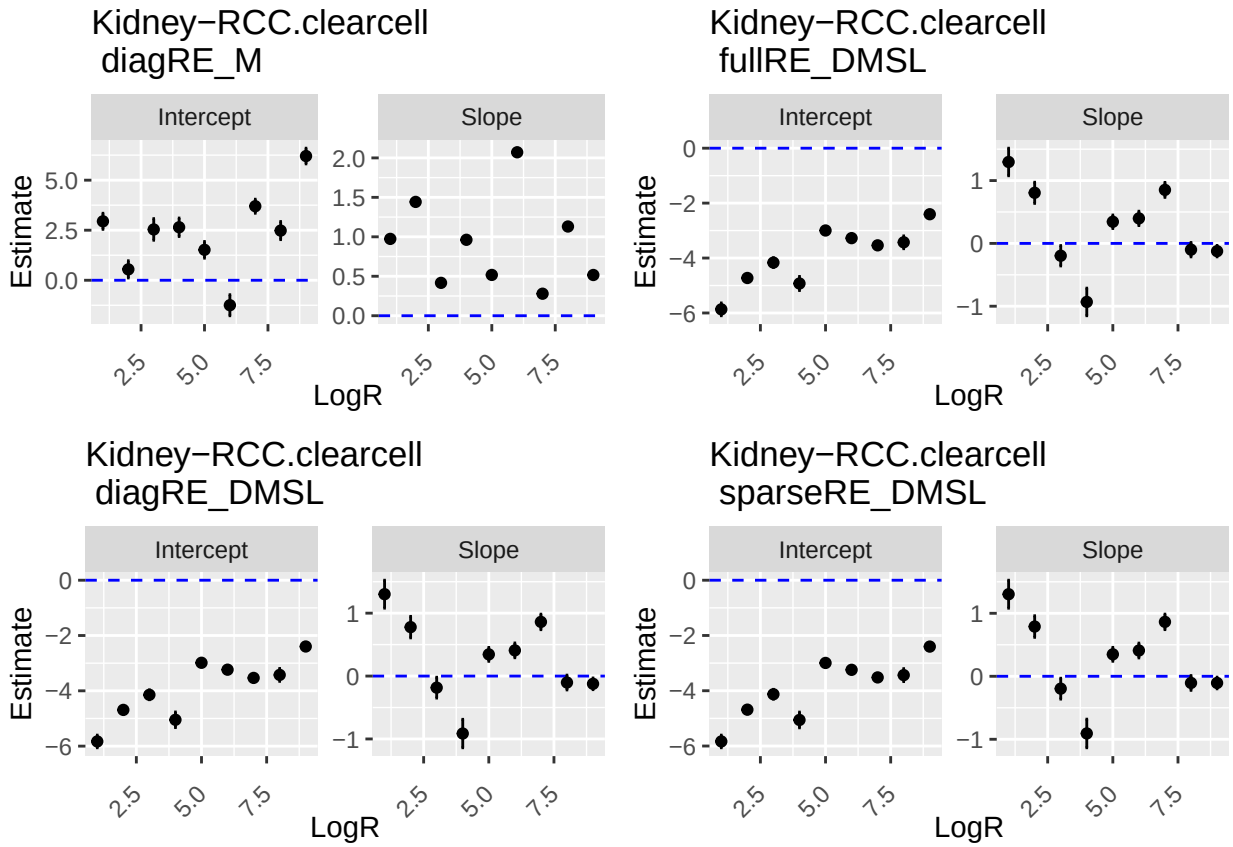
```
colSums(obj_Kidney_RCCclearcell$Y)/sum(obj_Kidney_RCCclearcell$Y)
```

```
##        SBS1        SBS2        SBS5        SBS6       SBS12       SBS13
## 0.033881764 0.005632854 0.060208144 0.036168761 0.026758216 0.003701688
##       SBS22       SBS29       SBS40       SBS41
## 0.140375696 0.036802695 0.629055577 0.027414605
```

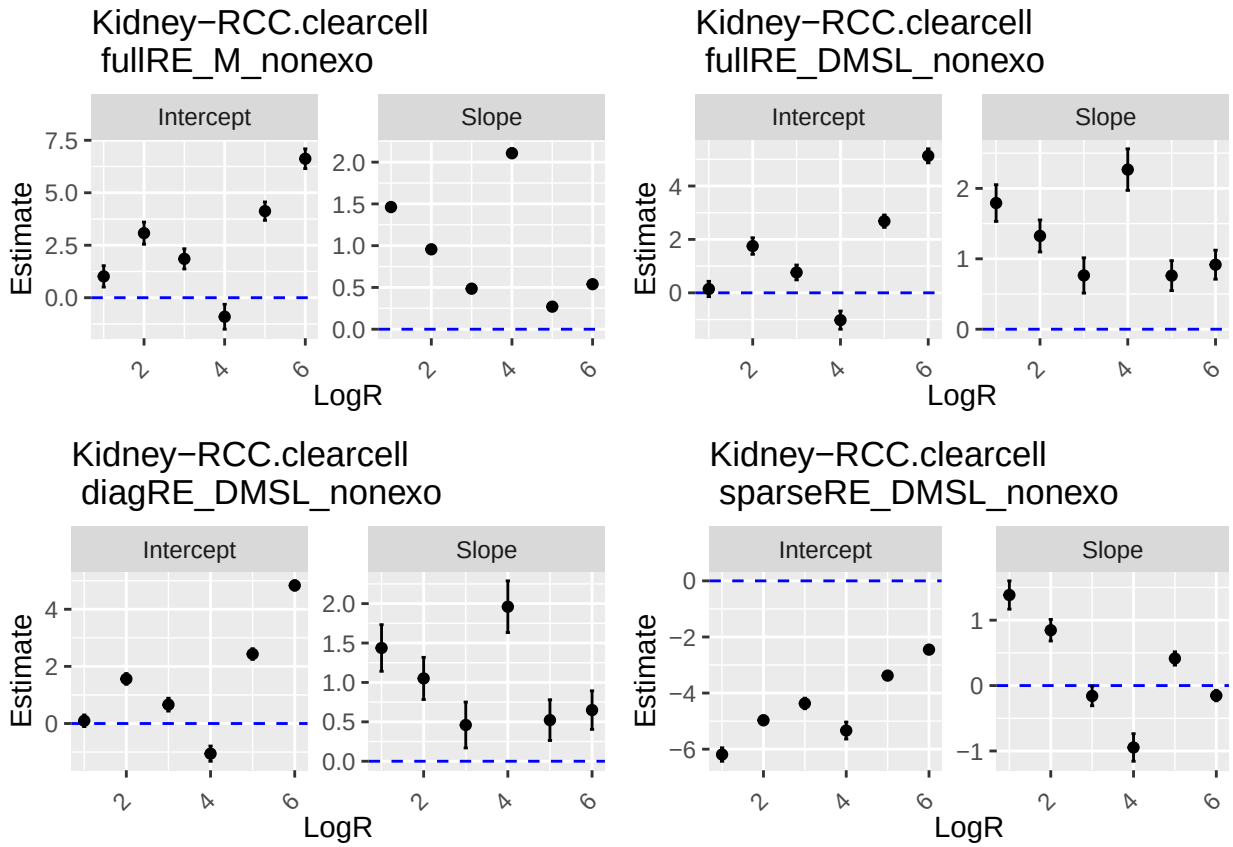
We would need to run `fullRE_DMSL`, because it timed out.

Betas

```
ct <- "Kidney-RCC.clearcell"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```



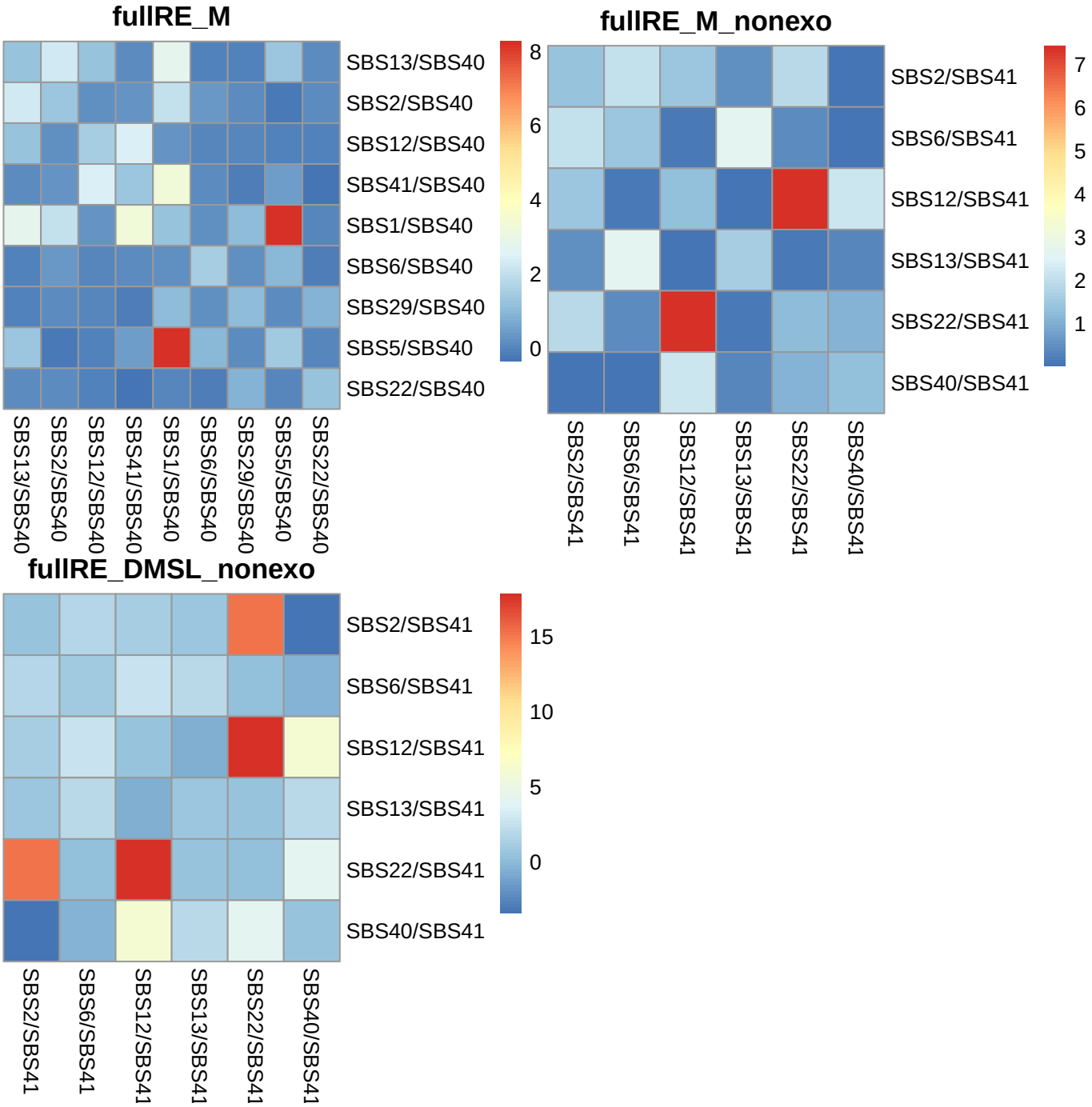

```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(fullRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct

## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used

## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of $3.2572102 \times 10^{-21}$.

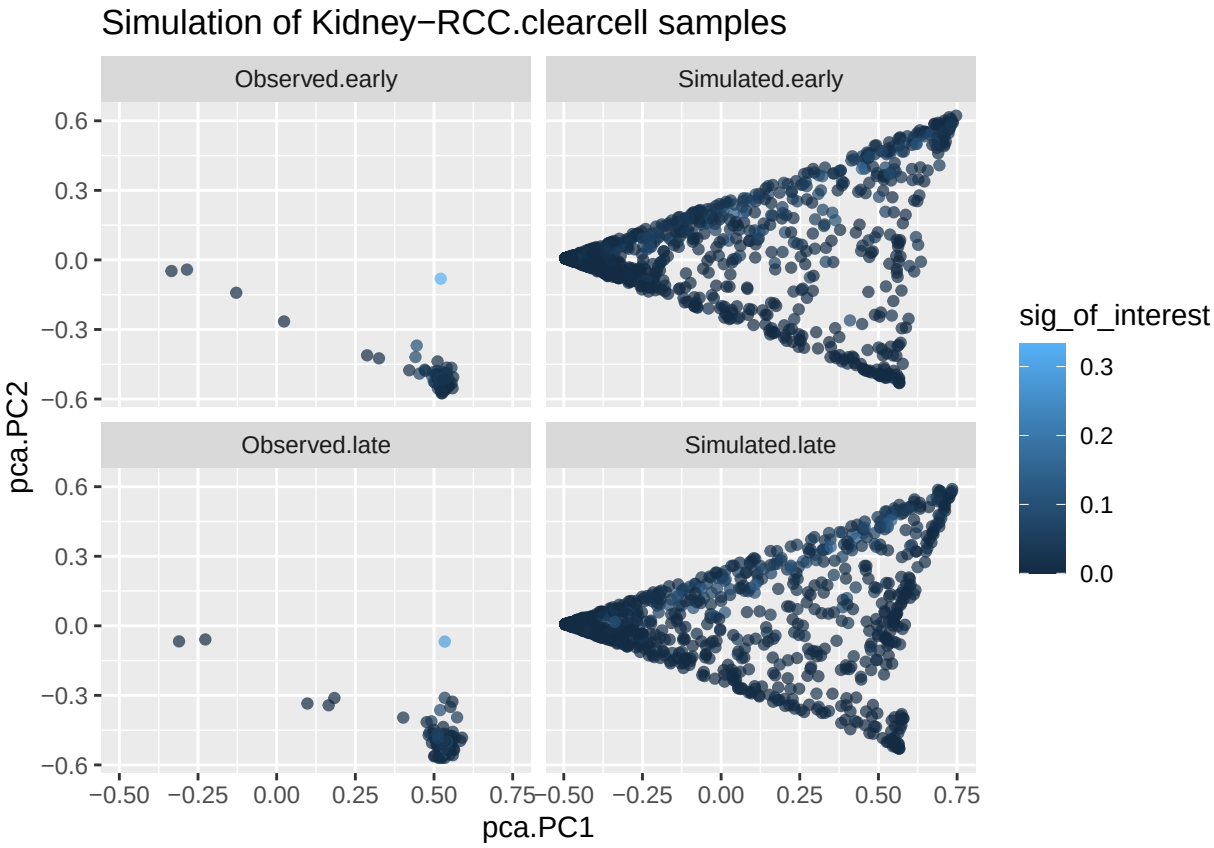
Covariance matrices



Simulation under inferred data

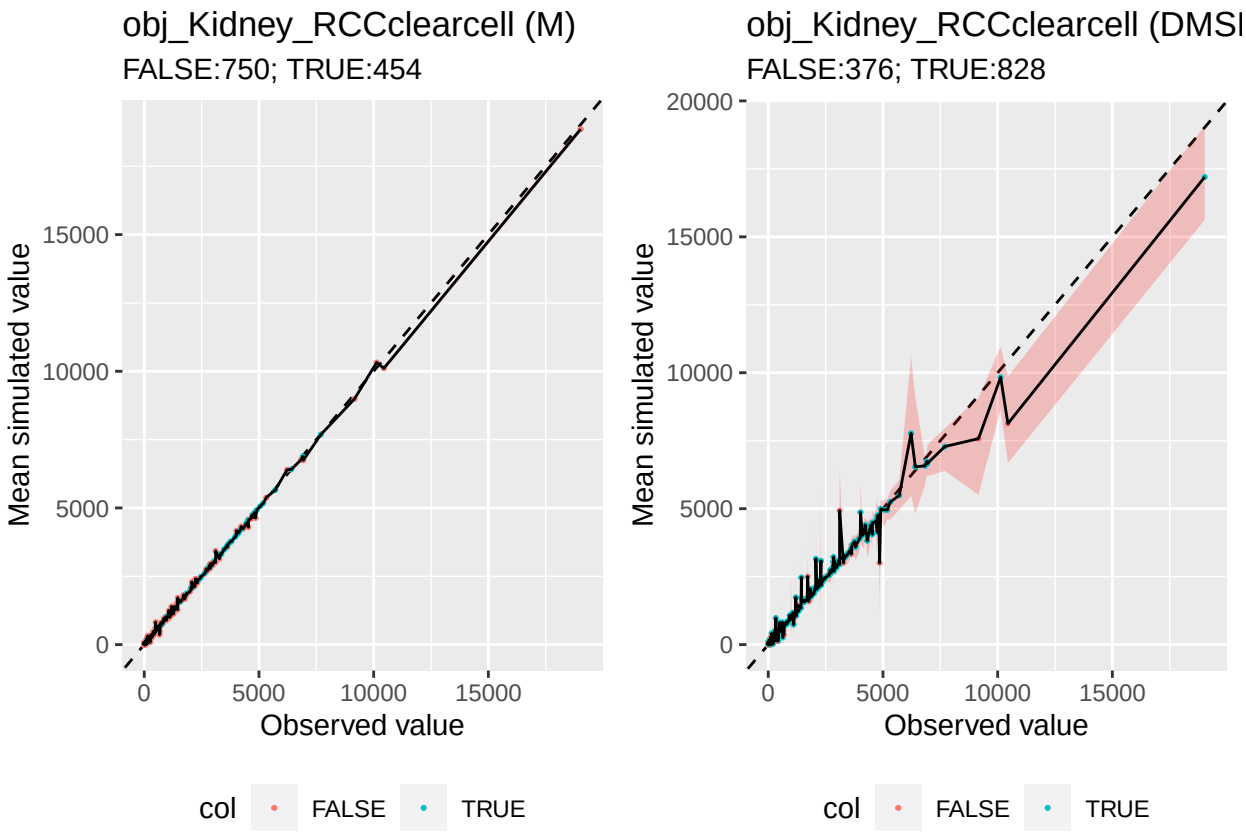
```
## [1] 86
```

```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```



Ranked plot for coverage

```
ct <- "Kidney-RCC.clearcell"
integer_overdispersion_param_DMSL <- 1
obj_Kidney_RCCclearcell_nonexo <- give_subset_sigs_TMBobj(obj_Kidney_RCCclearcell, sigs_to_remove = nonex
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                data_object = obj_Kidney_RCCclearcell_nonexo,
                print_plot = F, nreps = 20, model = "M")), function(i){
                  lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                         rank_number=1:length(j)) )})[[1]],
                data_object = obj_Kidney_RCCclearcell_nonexo,
                loglog = F, title = 'obj_Kidney_RCCclearcell (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = fullRE_DMSL_nor
                data_object = obj_Kidney_RCCclearcell_nonexo,
                print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                  lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                         rank_number=1:length(j)) )})[[1]],
                data_object = obj_Kidney_RCCclearcell_nonexo,
           loglog = F, title = 'obj_Kidney_RCCclearcell (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

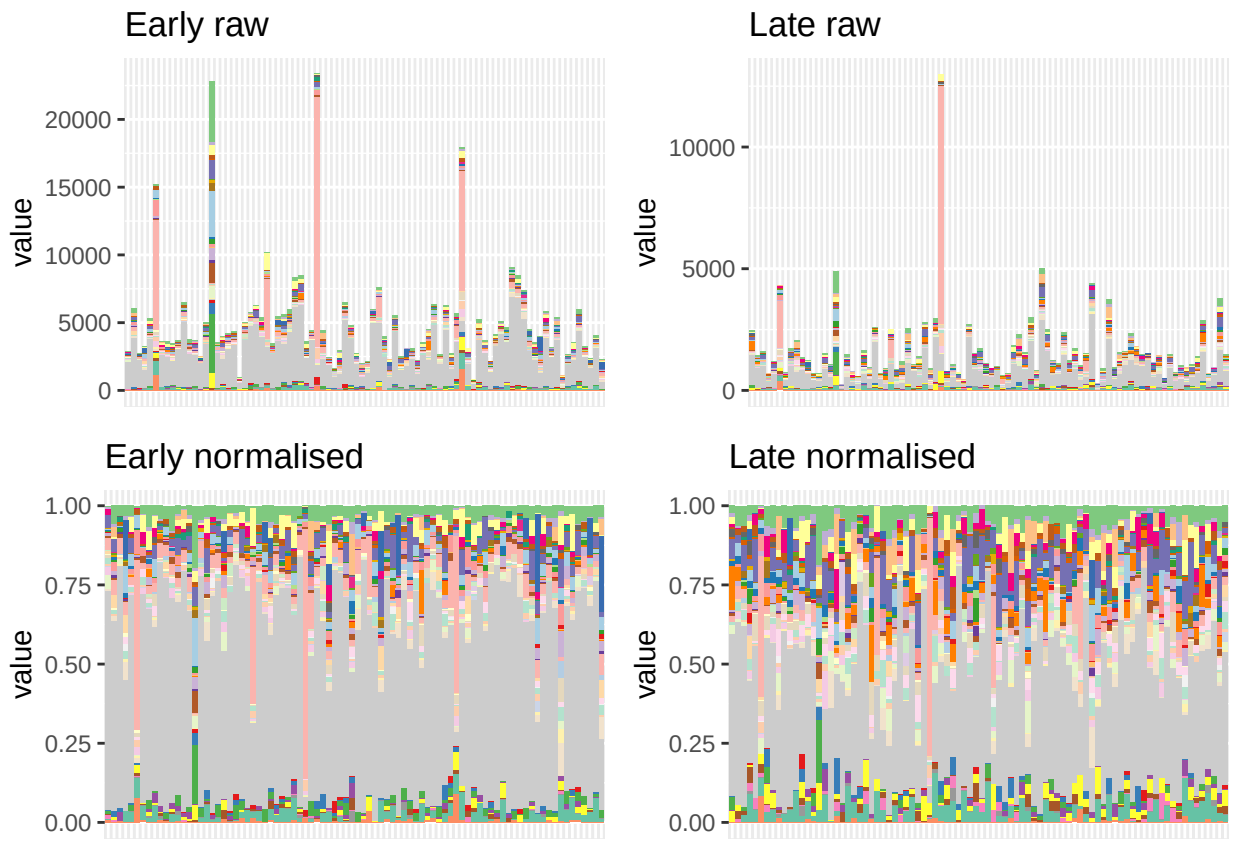
```
obj_Kidney_RCCclearcell_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

```
## [1] 86
```

```
give_barplot_from_obj(obj = obj_Kidney_RCCclearcell_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 86
## Creating plot... it might take some time if the data are large. Number of samples: 86
## Creating plot... it might take some time if the data are large. Number of samples: 86
## Creating plot... it might take some time if the data are large. Number of samples: 86
```

```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```

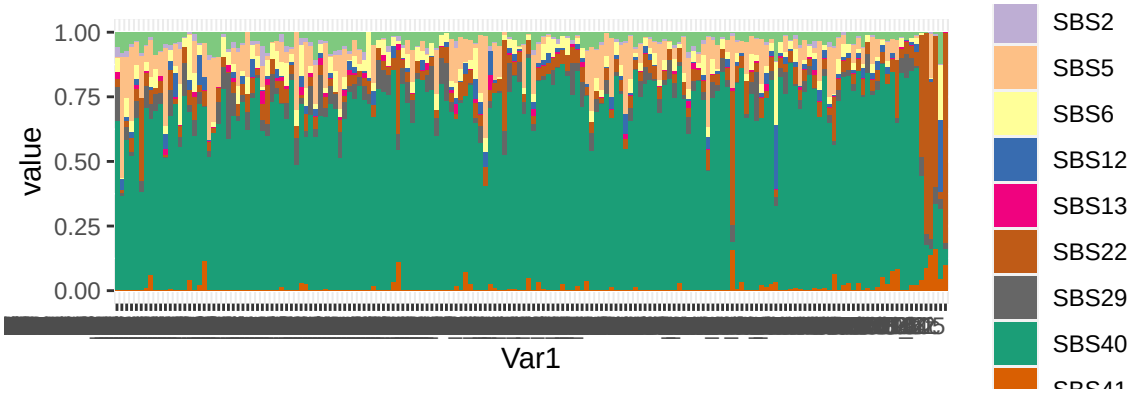


I should check if this grey exposure corresponds to SBS40.

Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations except for perhaps the very few with highest exposure.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Kidney_RCCclearcell$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Kidney_RCCclearcell$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 172
```



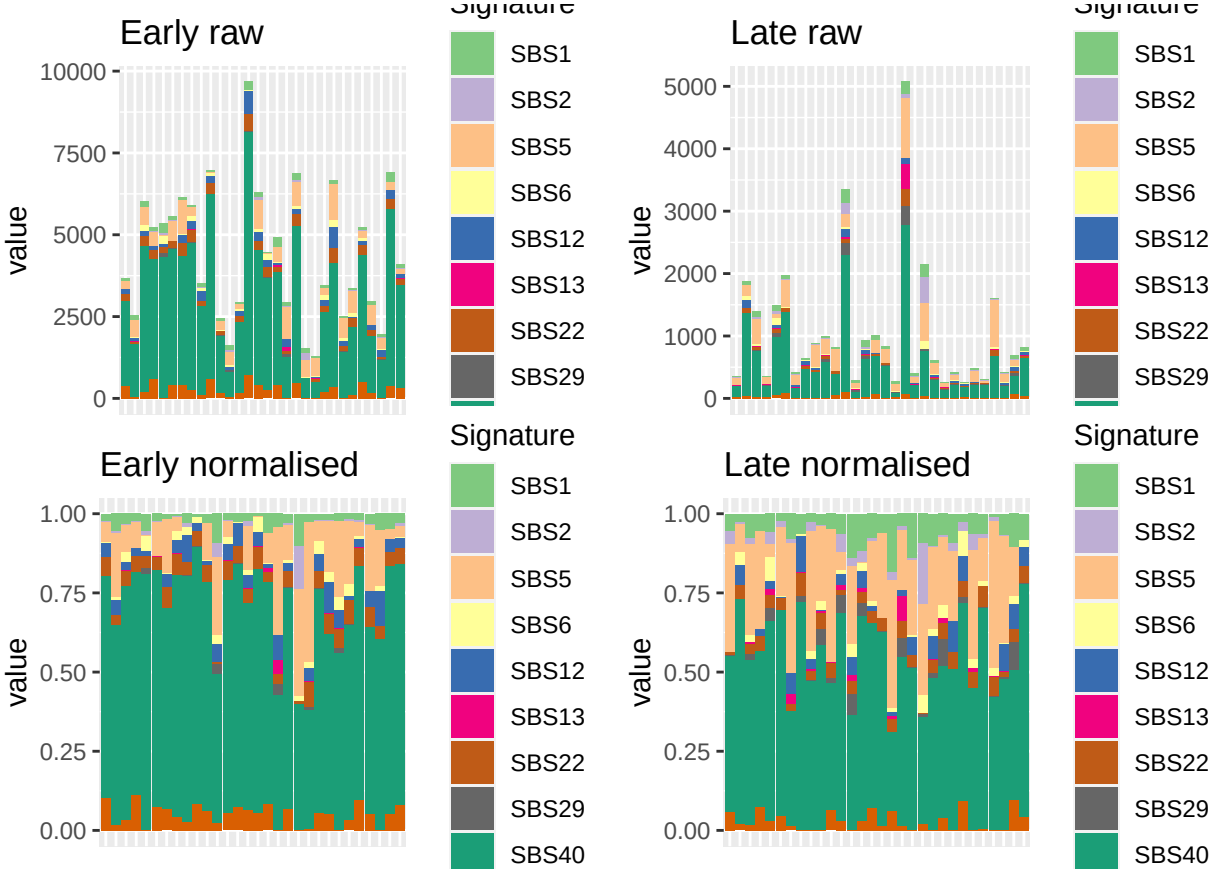
Kidney-RCC.papillary

It looks very similar to clear cell, looking generally at the signatures.

Barplot and general statistics

```
## [1] 30
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
```



The number of samples and signatures is:

```
## [1] 60 10
```

The signatures are:

```
##  [1] "SBS1"  "SBS2"  "SBS5"  "SBS6"  "SBS12" "SBS13" "SBS22" "SBS29" "SBS40"
## [10] "SBS41"
```

Convergence table

Although fulLRE DMSL has in one case converged, it hasn't when using SBS1 as baseline. The nonexogenous version has not converged, but M has.

```
##                  value                              L2
```

```
## 1  Kidney-RCC.papillary    hessian_positivedefinite_bool
## 2  Kidney-RCC.papillary    hessian_positivedefinite_bool
## 3  Kidney-RCC.papillary hessian_nonpositivedefinite_bool
## 4  Kidney-RCC.papillary hessian_nonpositivedefinite_bool
## 5  Kidney-RCC.papillary hessian_nonpositivedefinite_bool
## 6  Kidney-RCC.papillary    hessian_positivedefinite_bool
## 7  Kidney-RCC.papillary    hessian_positivedefinite_bool
## 8  Kidney-RCC.papillary    hessian_positivedefinite_bool
## 9  Kidney-RCC.papillary hessian_nonpositivedefinite_bool
## 10 Kidney-RCC.papillary    hessian_positivedefinite_bool
## 11 Kidney-RCC.papillary    hessian_positivedefinite_bool
## 12 Kidney-RCC.papillary    hessian_positivedefinite_bool
## 13 Kidney-RCC.papillary hessian_nonpositivedefinite_bool
## 14 Kidney-RCC.papillary hessian_nonpositivedefinite_bool
## 15 Kidney-RCC.papillary hessian_nonpositivedefinite_bool
##                            L1
## 1                   diagRE_M
## 2                   fullRE_M
## 3                 diagRE_DMDL
## 4               fullRE_halfDM
## 5                 fullRE_DMDL
## 6                 diagRE_DMSL
## 7               sparseRE_DMSL
## 8                 fullRE_DMSL
## 9            fullRE_DMSL_SBS1
## 10            fullRE_M_nonexo
## 11        diagRE_DMSL_nonexo
## 12      sparseRE_DMSL_nonexo
## 13        fullRE_DMSL_nonexo
## 14        fullRE_DMDL_nonexo
## 15 fullRE_DMDL_sortednonexo
```

Re-running of fitting

Using fullRE_M_nonexo to fit fullRE_DMSL_nonexo. We first re-run M.

The we use it to re-run DM.

If we use the values of the fullRE M exo as initial values for the fullRE DMSL exo do converge:

```
## [1] TRUE
```

Potentially problematic signatures

We explore whether there are problematic signatures:

```
colSums(obj_Kidney_RCCpapillary$Y == 0)/nrow(obj_Kidney_RCCpapillary$Y)
```

```
##      SBS1      SBS2      SBS5      SBS6     SBS12     SBS13     SBS22     SBS29
## 0.0000000 0.2333333 0.1000000 0.2666667 0.1833333 0.6500000 0.0000000 0.6333333
##     SBS40     SBS41
## 0.0000000 0.2166667
```

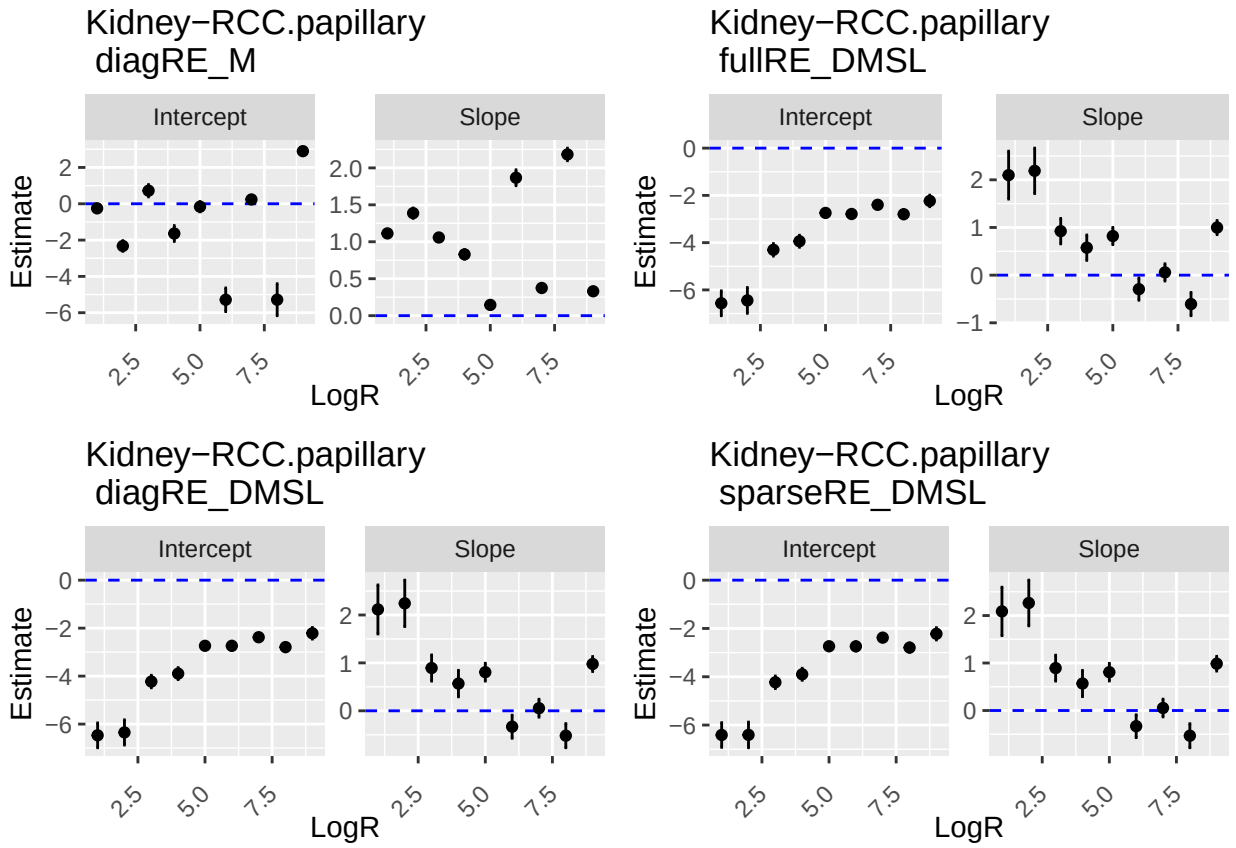
```
colSums(obj_Kidney_RCCpapillary$Y)/sum(obj_Kidney_RCCpapillary$Y)
```

```
##         SBS1         SBS2         SBS5         SBS6        SBS12        SBS13
## 0.035736437 0.010720323 0.116403371 0.016521337 0.039719314 0.004438931
##        SBS22        SBS29        SBS40        SBS41
## 0.049284298 0.007187420 0.669488124 0.050500444
```

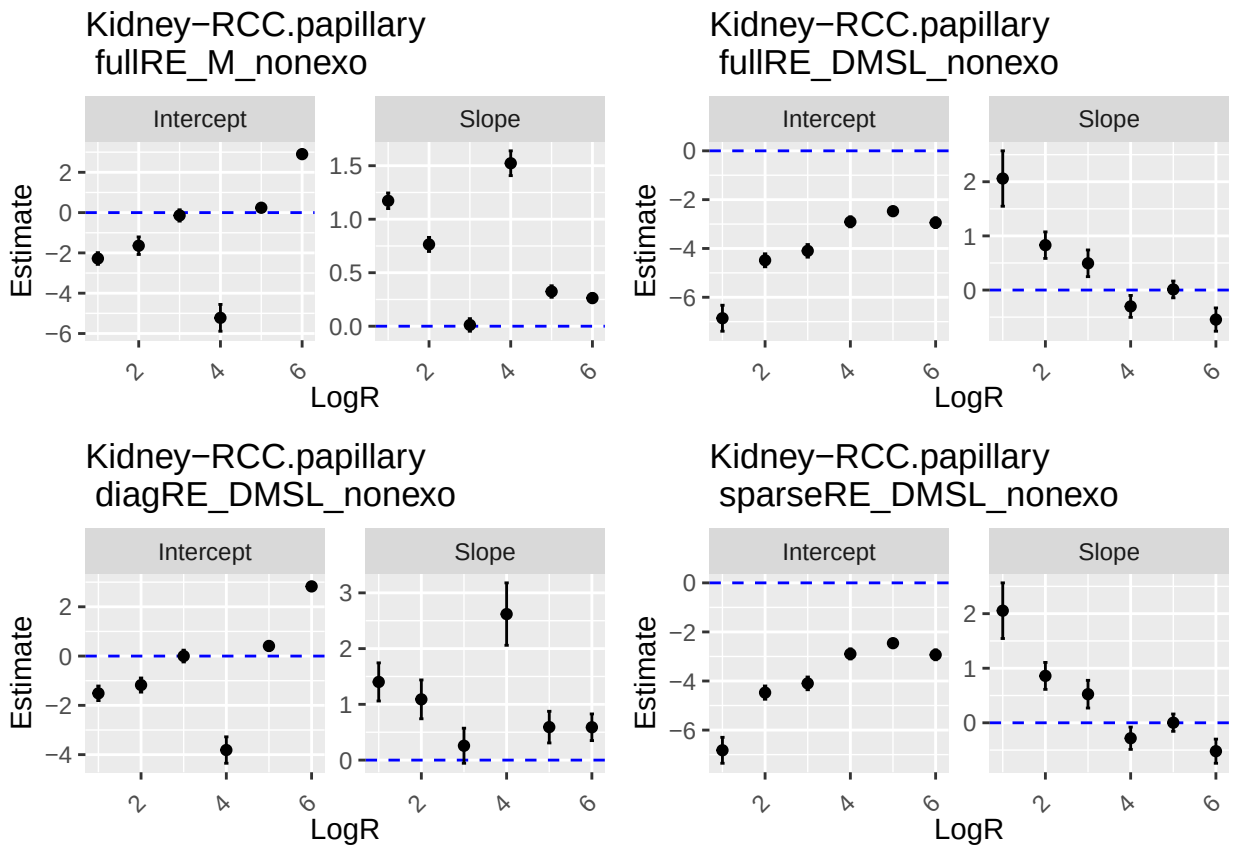
SBS29 is found in relatively small quantities.

Betas

```
ct <- "Kidney-RCC.papillary"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```



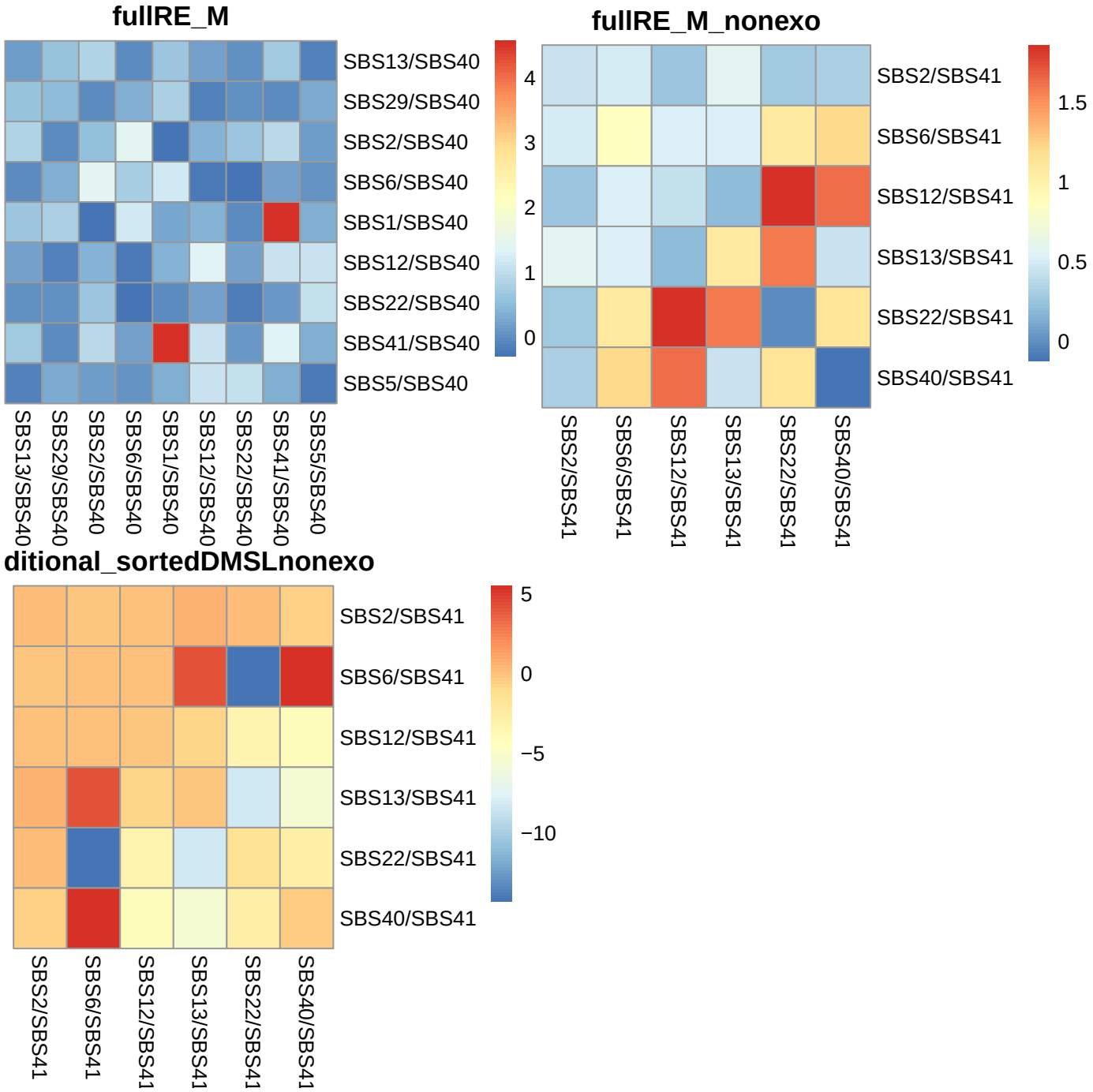

```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(sortedDM_KidneyRCCpapillary)+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct

## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used

## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 2.591235×10^{-7}.

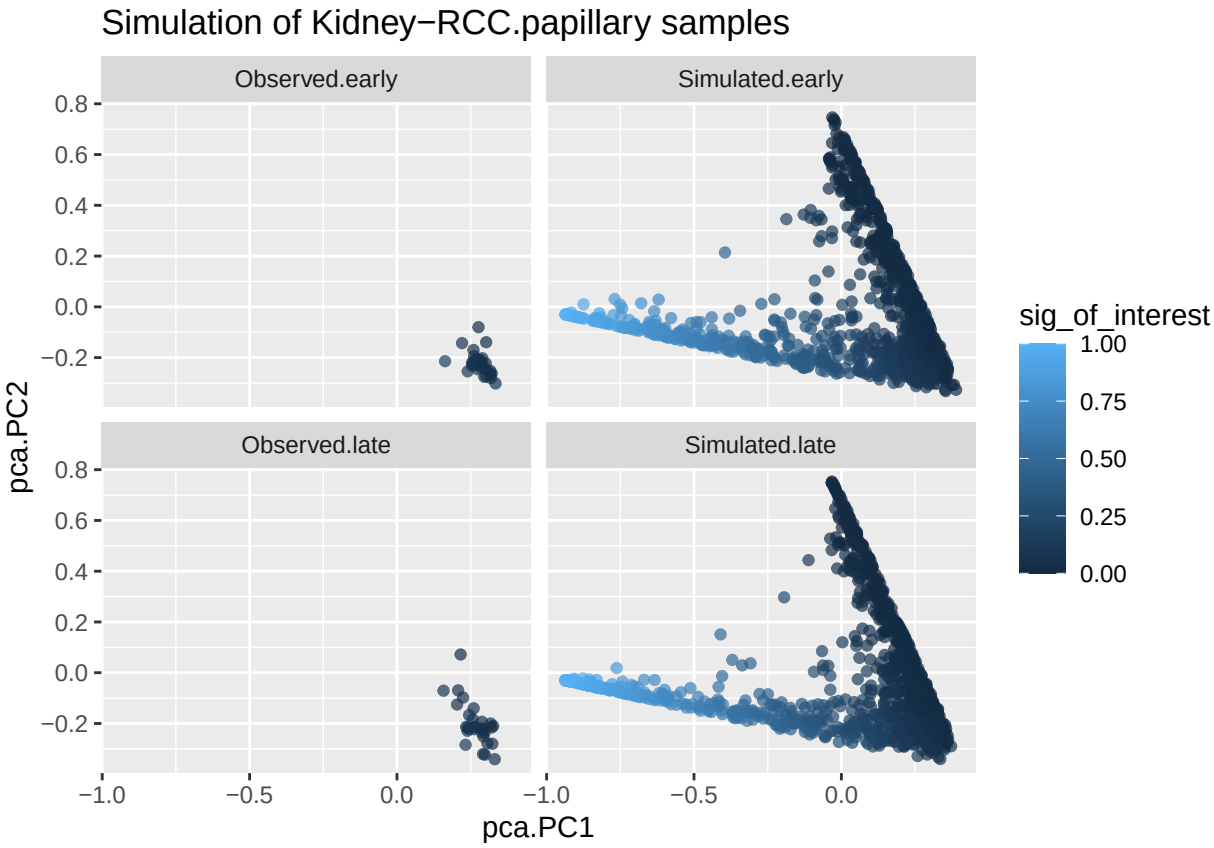
Covariance matrices



Simulation under inferred data

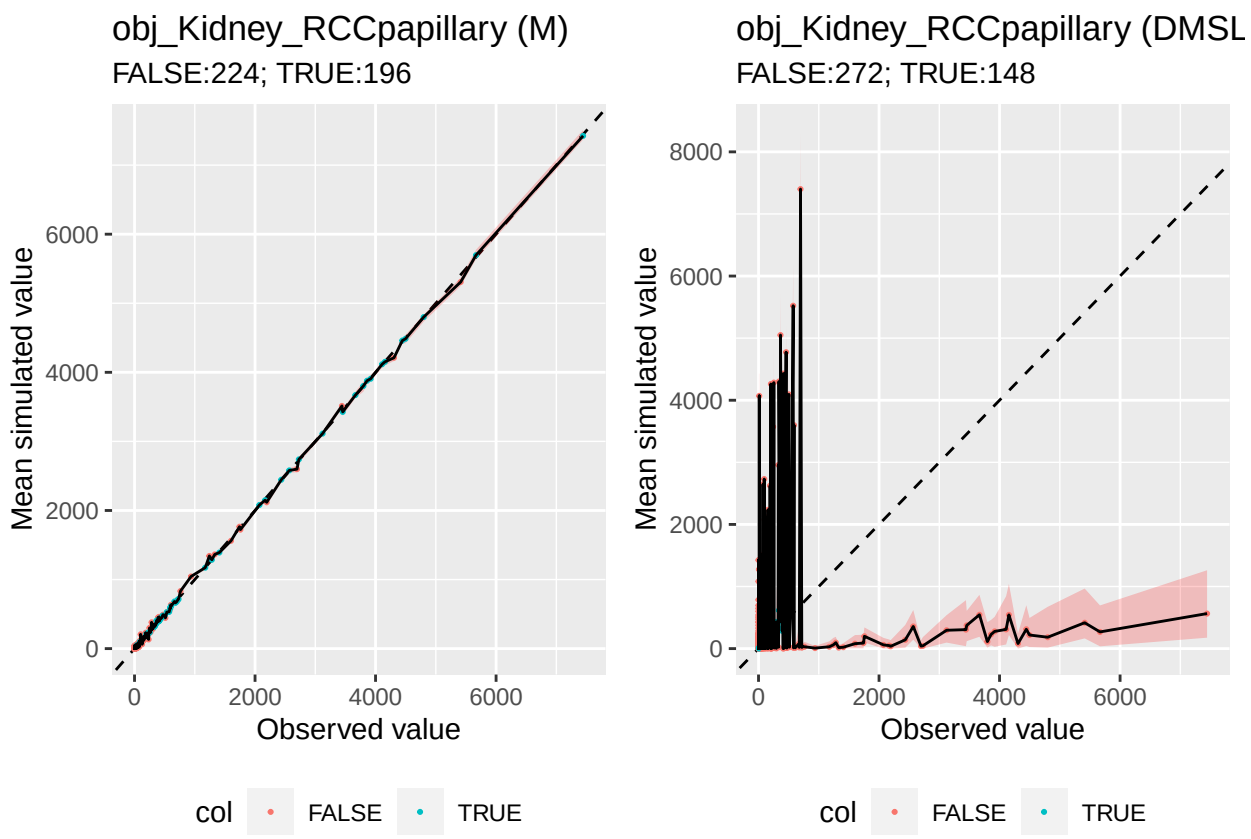
```
## [1] 30
```

```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```



Ranked plot for coverage

What has happened here?



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

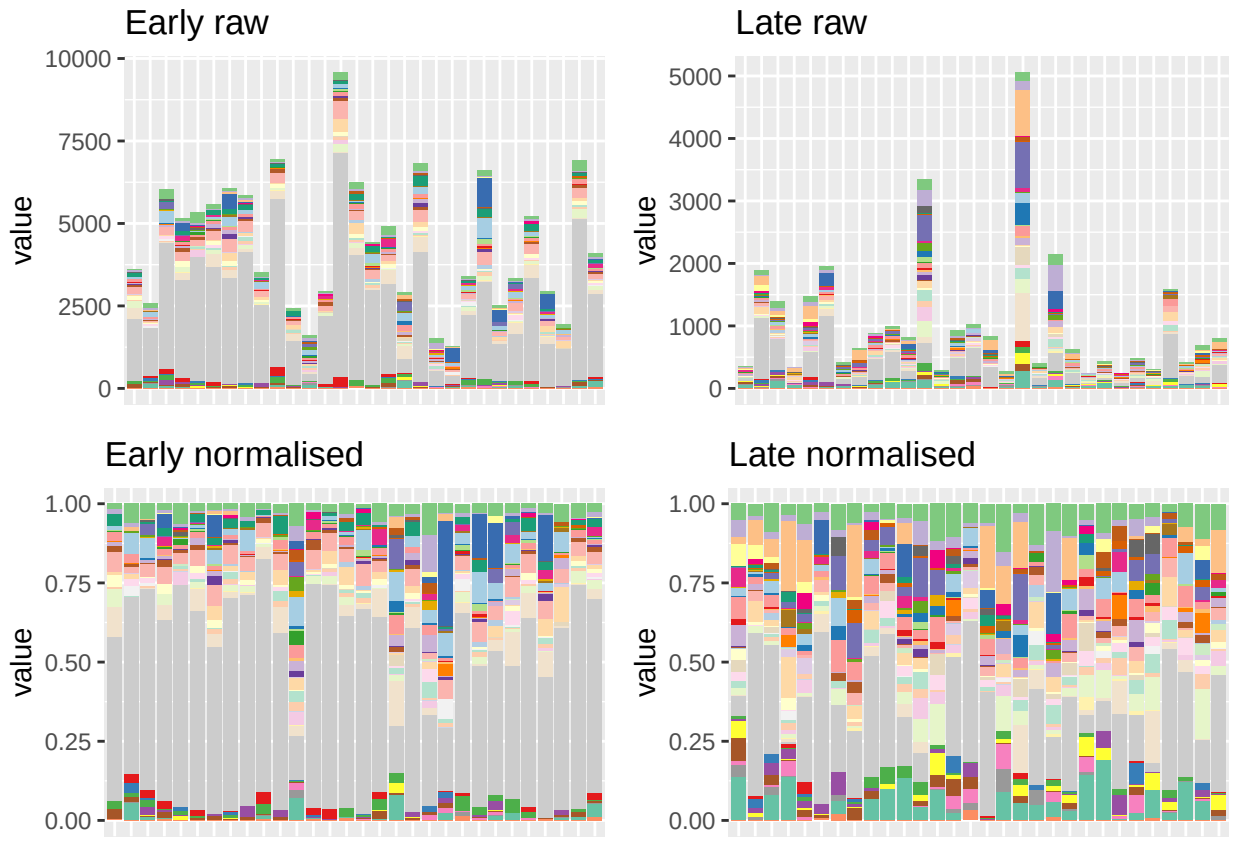
```
obj_Kidney_RCCpapillary_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

```
## [1] 30
```

```
give_barplot_from_obj(obj = obj_Kidney_RCCpapillary_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
```

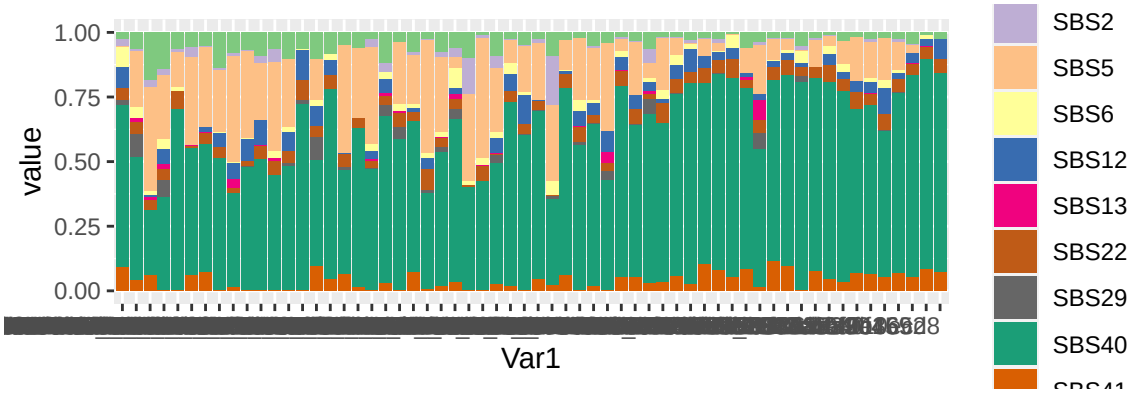
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Kidney_RCCpapillary$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Kidney_RCCpapillary$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 60
```

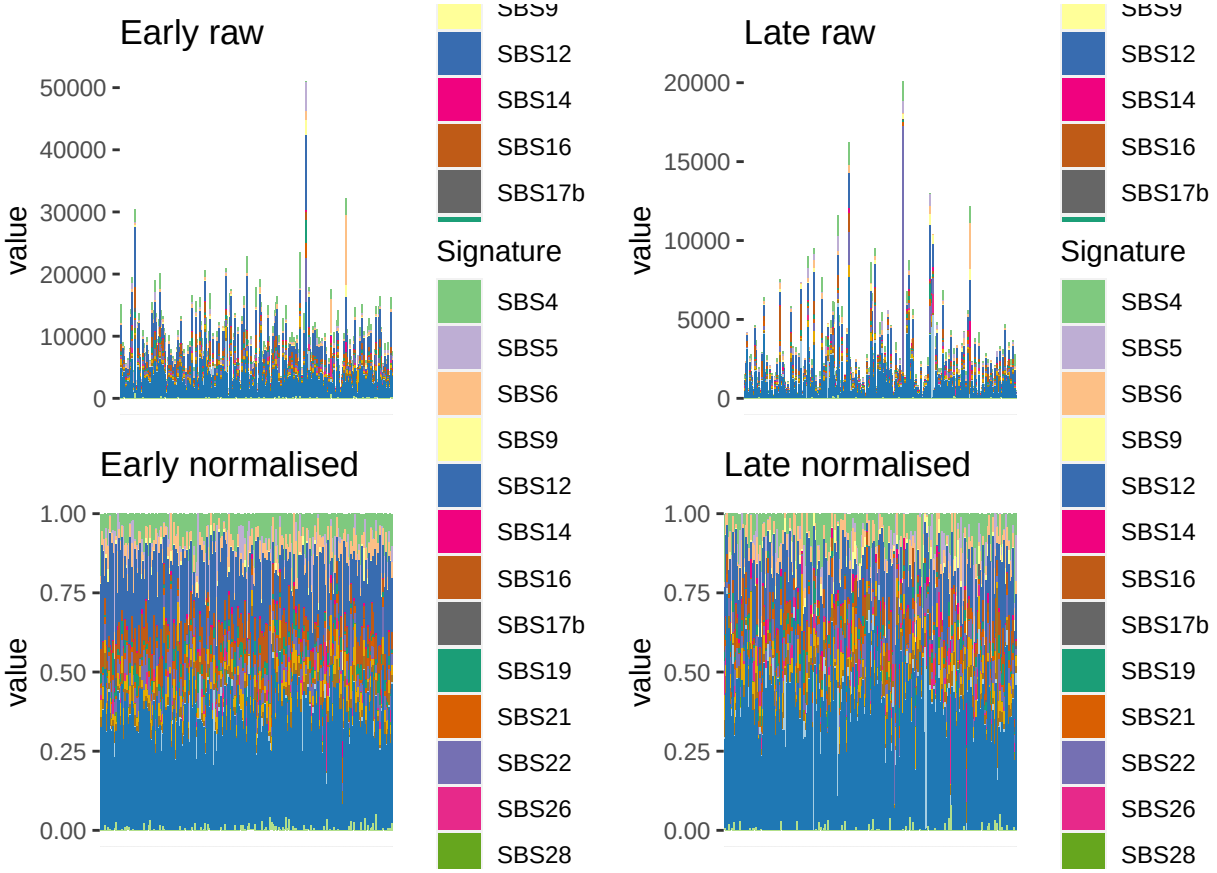


Liver-HCC

Barplot and general statistics

```
## [1] 207
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 207
## Creating plot... it might take some time if the data are large. Number of samples: 207
## Creating plot... it might take some time if the data are large. Number of samples: 207
## Creating plot... it might take some time if the data are large. Number of samples: 207
```



The number of samples and signatures is:

```
## [1] 414  18
```

The signatures are:

```
##  [1] "SBS4"   "SBS5"   "SBS6"   "SBS9"   "SBS12"  "SBS14"  "SBS16"  "SBS17b"
##  [9] "SBS19"  "SBS21"  "SBS22"  "SBS26"  "SBS28"  "SBS29"  "SBS30"  "SBS35"
## [17] "SBS40"  "SBS54"
```

Convergence table

The fullRE versions with all signatures have not converged. Neither has `fullRE_M_nonexo`, but `fullRE_DMSL_nonexo` has.

```
##        value                                L2                    L1
## 1  Liver-HCC    hessian_positivedefinite_bool                diagRE_M
```

```
## 2  Liver-HCC hessian_nonpositivedefinite_bool                fullRE_M
## 3  Liver-HCC hessian_nonpositivedefinite_bool              diagRE_DMDL
## 4  Liver-HCC                          Timeout            fullRE_halfDM
## 5  Liver-HCC hessian_nonpositivedefinite_bool              fullRE_DMDL
## 6  Liver-HCC    hessian_positivedefinite_bool              diagRE_DMSL
## 7  Liver-HCC    hessian_positivedefinite_bool            sparseRE_DMSL
## 8  Liver-HCC hessian_nonpositivedefinite_bool              fullRE_DMSL
## 9  Liver-HCC    hessian_positivedefinite_bool         fullRE_DMSL_SBS1
## 10 Liver-HCC hessian_nonpositivedefinite_bool          fullRE_M_nonexo
## 11 Liver-HCC    hessian_positivedefinite_bool       diagRE_DMSL_nonexo
## 12 Liver-HCC    hessian_positivedefinite_bool     sparseRE_DMSL_nonexo
## 13 Liver-HCC    hessian_positivedefinite_bool       fullRE_DMSL_nonexo
## 14 Liver-HCC hessian_nonpositivedefinite_bool       fullRE_DMDL_nonexo
## 15 Liver-HCC                          Timeout fullRE_DMDL_sortednonexo
```

Potentially problematic signatures

We explore whether there are problematic signatures:

```
colSums(obj_Liver_HCC$Y == 0)/nrow(obj_Liver_HCC$Y)
```

```
##        SBS4        SBS5        SBS6        SBS9       SBS12       SBS14
## 0.084541063 0.548309179 0.007246377 0.642512077 0.026570048 0.434782609
##       SBS16      SBS17b       SBS19       SBS21       SBS22       SBS26
## 0.048309179 0.649758454 0.120772947 0.176328502 0.012077295 0.613526570
##       SBS28       SBS29       SBS30       SBS35       SBS40       SBS54
## 0.934782609 0.096618357 0.113526570 0.628019324 0.007246377 0.649758454
```

```
colSums(obj_Liver_HCC$Y)/sum(obj_Liver_HCC$Y)
```

```
##        SBS4        SBS5        SBS6        SBS9       SBS12       SBS14
## 0.081740962 0.026465897 0.047036092 0.007670584 0.206143096 0.005884273
##       SBS16      SBS17b       SBS19       SBS21       SBS22       SBS26
## 0.068804779 0.001835835 0.028215636 0.016888238 0.058186725 0.011387208
##       SBS28       SBS29       SBS30       SBS35       SBS40       SBS54
## 0.000603818 0.036248511 0.025723410 0.015247453 0.357387133 0.004530350
```

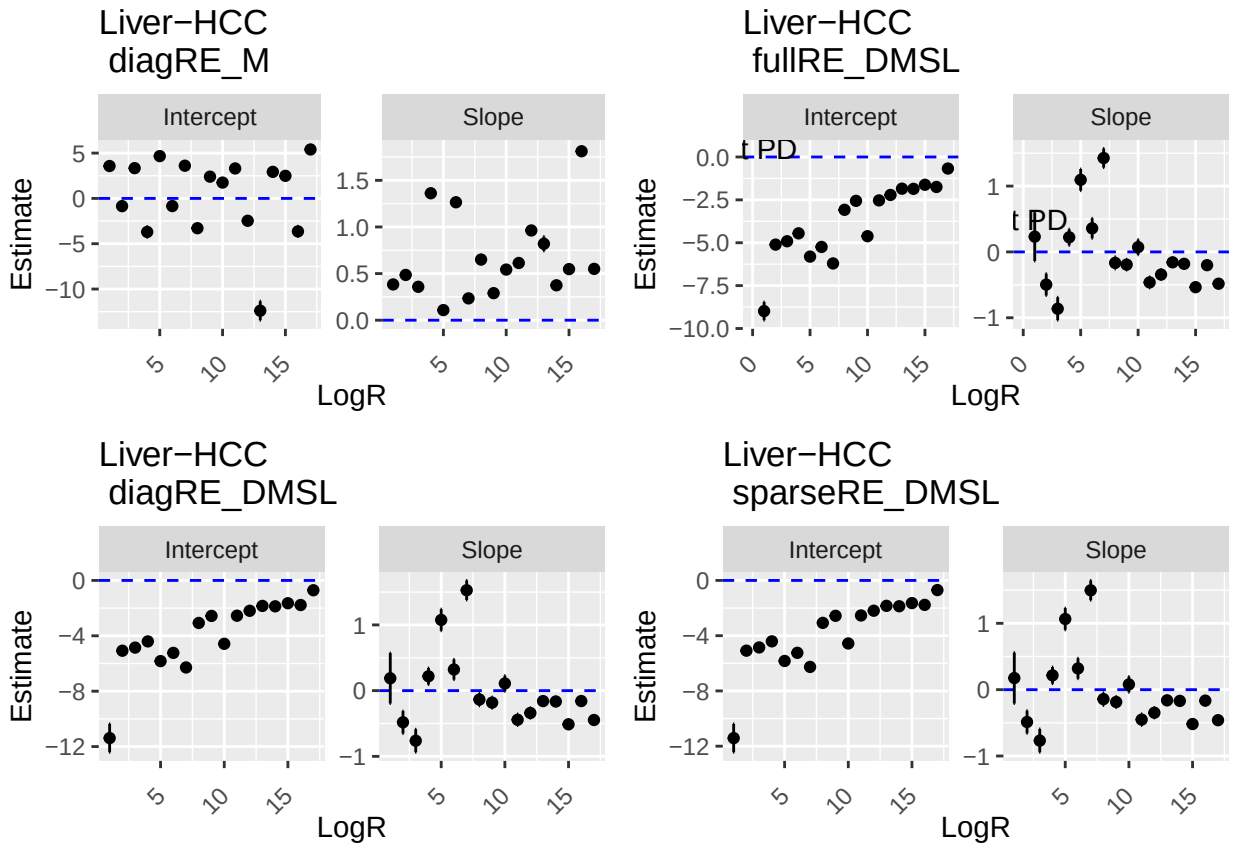
SBS28 is only present in 7% of samples and has extremely low exposure - we could consider removing it.

Betas

```
ct <- "Liver-HCC"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```

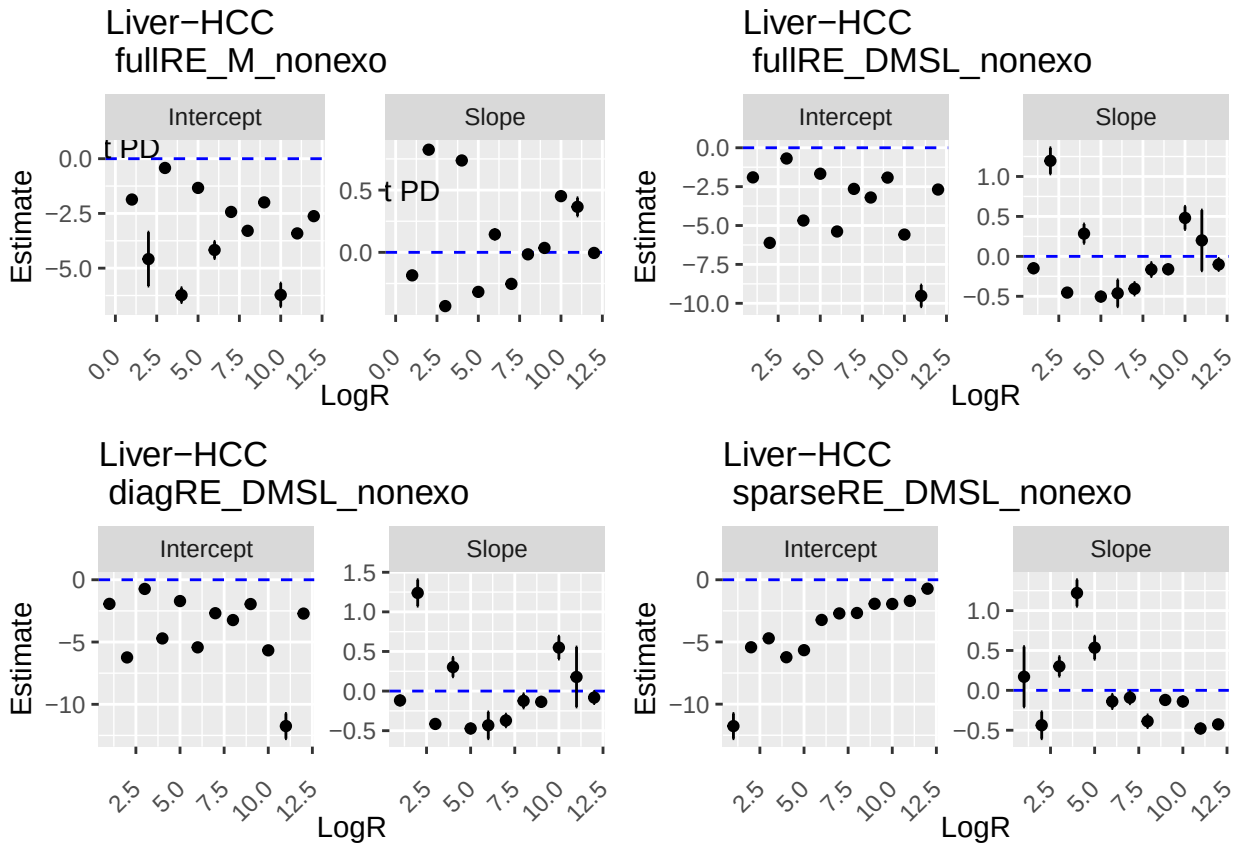
```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

```
## Warning in sqrt(as.numeric(object$diag.cov.random)): NaNs produced
```




```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(fullRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```

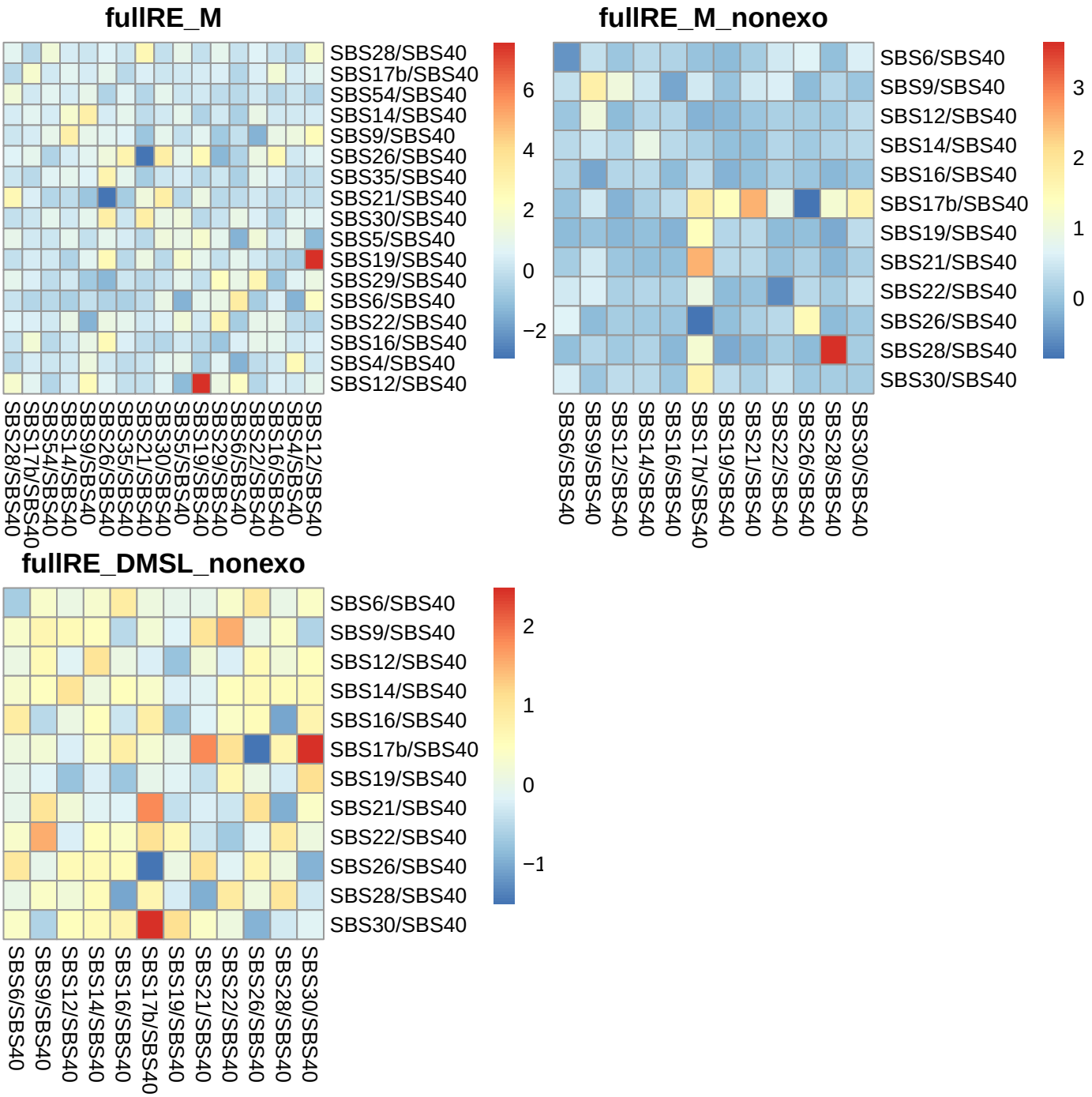
```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced

## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct

## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used

## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of $1.0407591 \times 10^{-55}$.

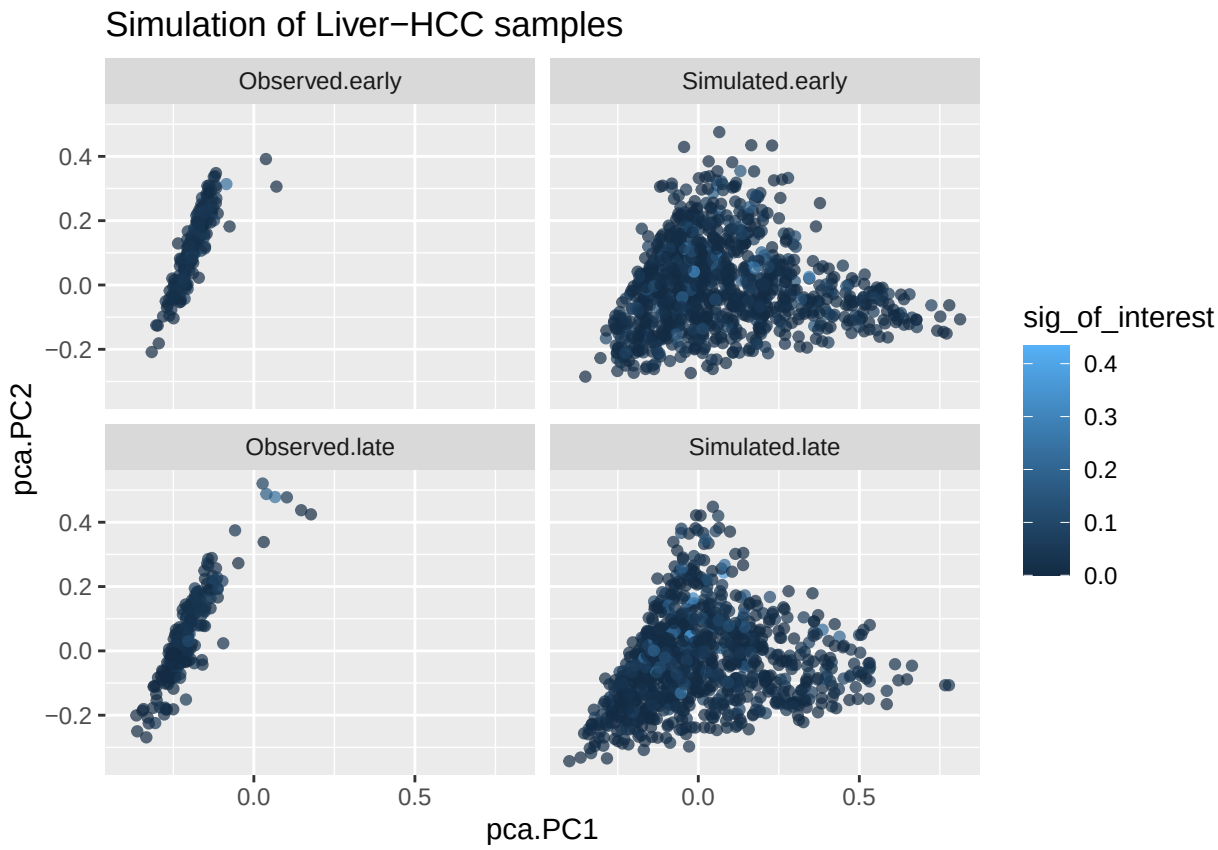
Covariance matrices



Simulation under inferred data

```
## [1] 207
```

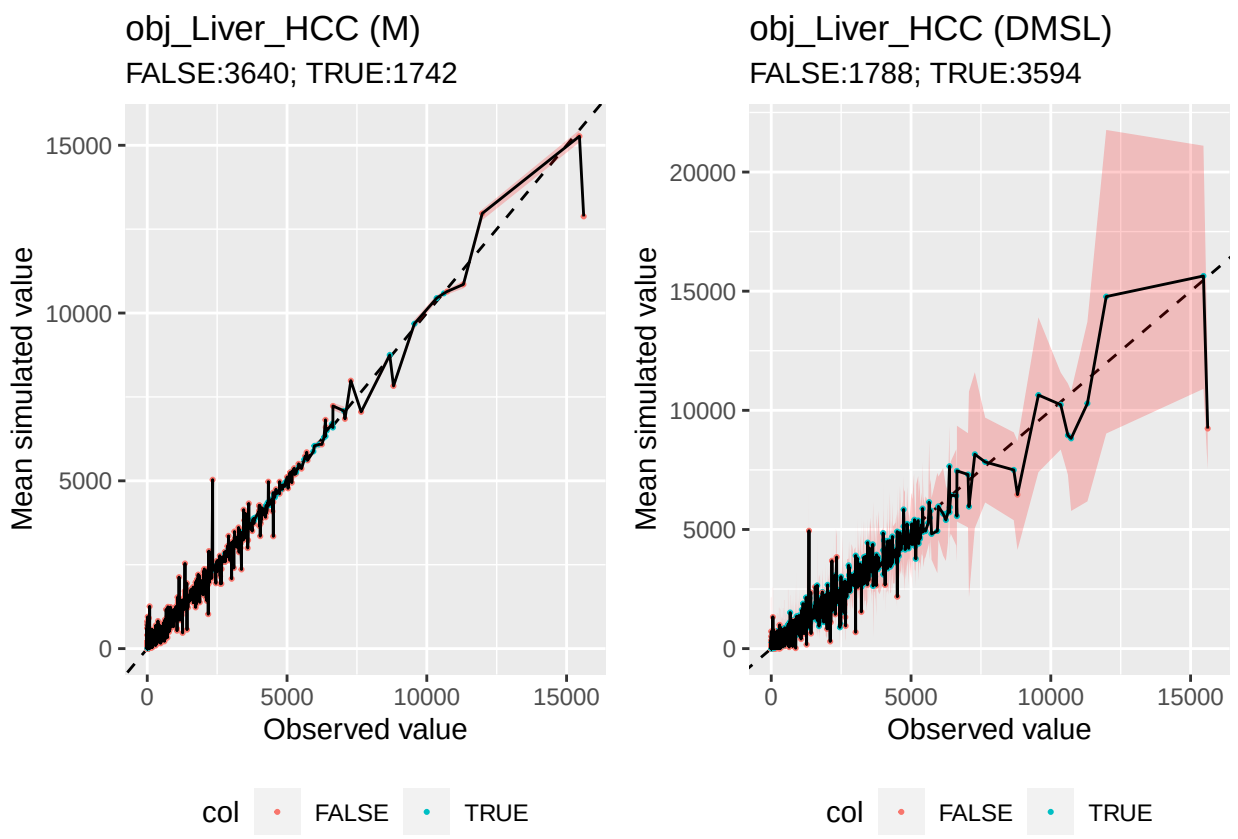
```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```



Ranked plot for coverage

Remember that fullRE M has not converged, and it should be re-run:

```
ct <- "Liver-HCC"
integer_overdispersion_param_DMSL <- 1
obj_Liver_HCC_nonexo <- give_subset_sigs_TMBobj(obj_Liver_HCC, sigs_to_remove = nonexogenous$V1)
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                  data_object = obj_Liver_HCC_nonexo,
                  print_plot = F, nreps = 20, model = "M")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Liver_HCC_nonexo,
                  loglog = F, title = 'obj_Liver_HCC (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = fullRE_DMSL_nor
                  data_object = obj_Liver_HCC_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Liver_HCC_nonexo,
            loglog = F, title = 'obj_Liver_HCC (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

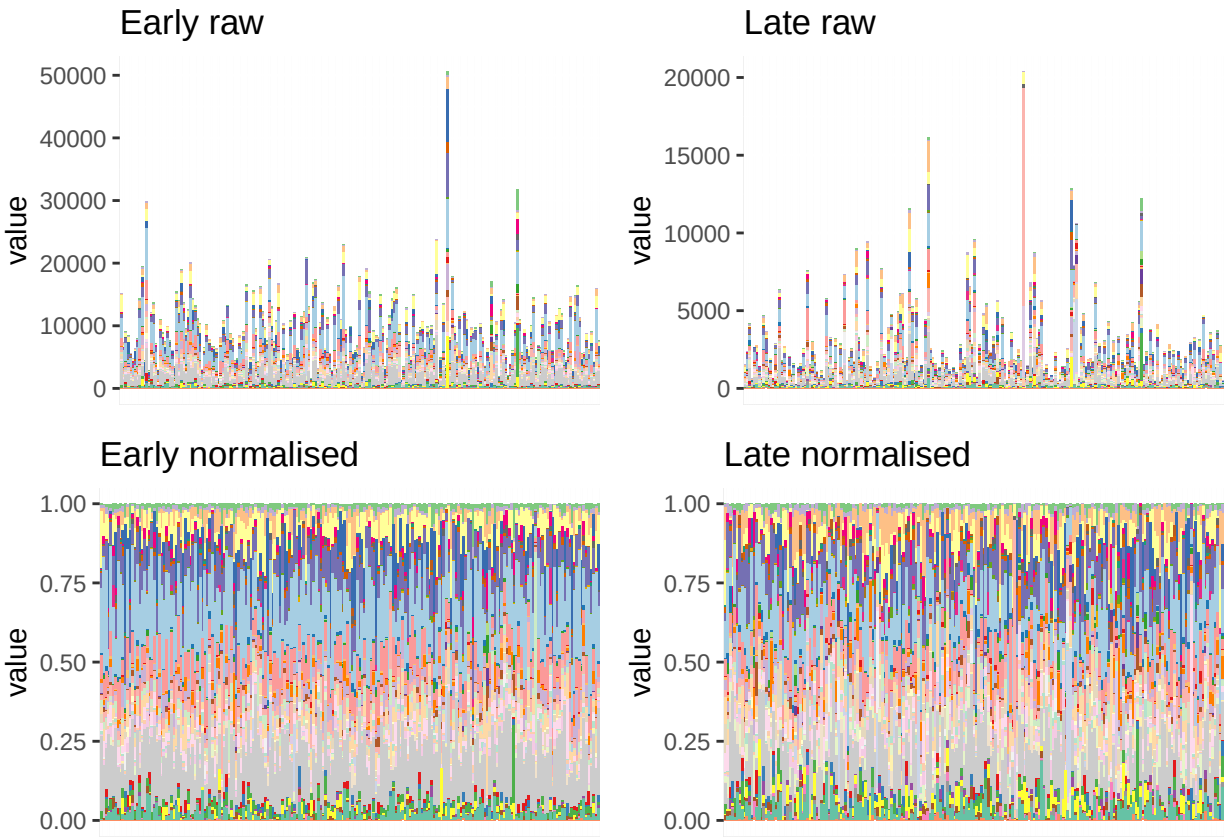
```
obj_Liver_HCC_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

```
## [1] 207
```

```
give_barplot_from_obj(obj = obj_Liver_HCC_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 207
## Creating plot... it might take some time if the data are large. Number of samples: 207
## Creating plot... it might take some time if the data are large. Number of samples: 207
## Creating plot... it might take some time if the data are large. Number of samples: 207
```

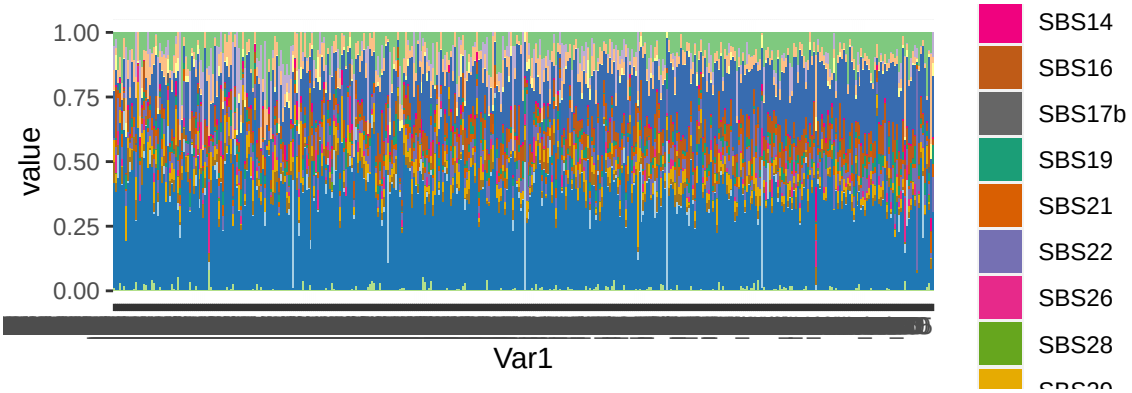
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Liver_HCC$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Liver_HCC$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 414
```



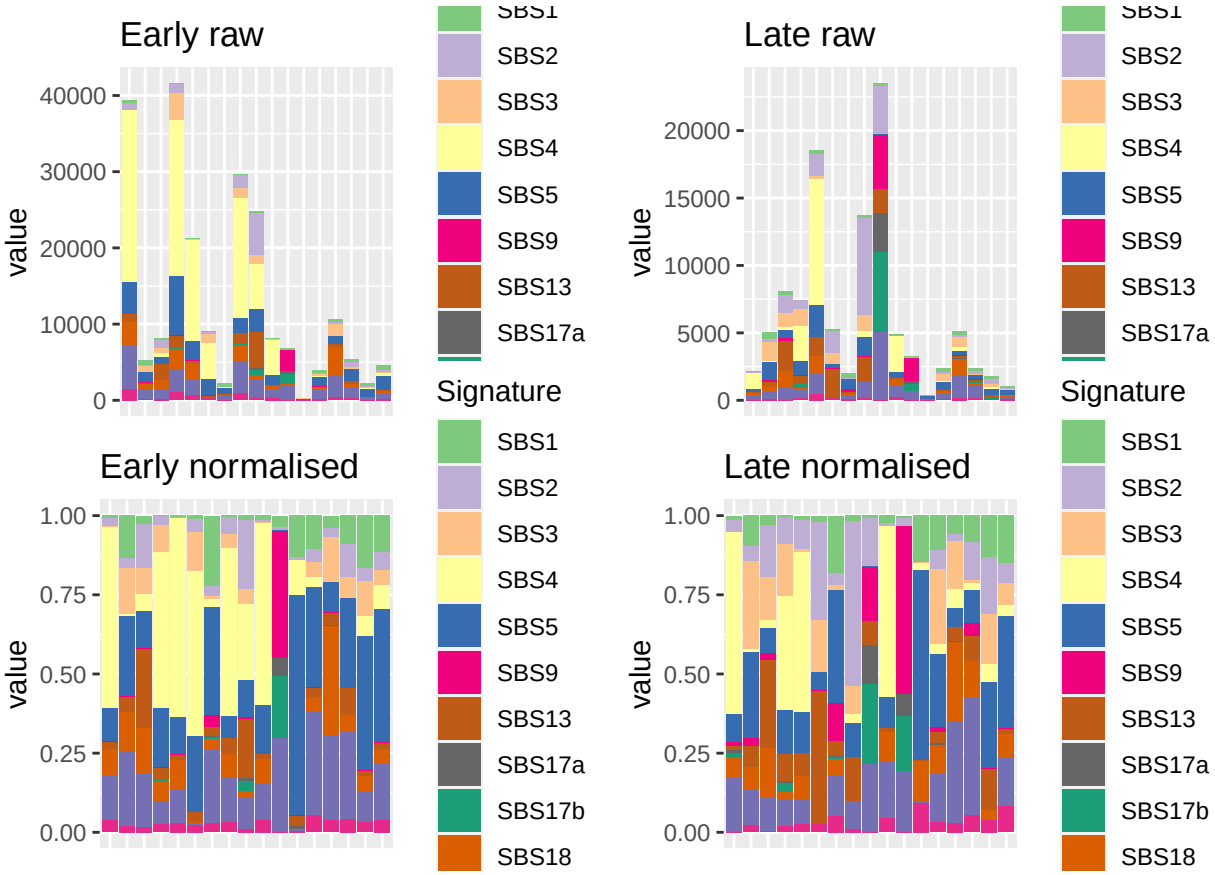
Lung-AdenoCA

How can we have such few samples?

Barplot and general statistics

```
## [1] 17
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 17
## Creating plot... it might take some time if the data are large. Number of samples: 17
## Creating plot... it might take some time if the data are large. Number of samples: 17
## Creating plot... it might take some time if the data are large. Number of samples: 17
```



The number of samples and signatures is:

```
## [1] 34 12
```

The signatures are:

```
##  [1] "SBS1"   "SBS2"   "SBS3"   "SBS4"   "SBS5"   "SBS9"   "SBS13"  "SBS17a"
##  [9] "SBS17b" "SBS18"  "SBS40"  "SBS50"
```

Convergence table

No fullRE DMSL have converged.

```
##           value                                L2                  L1
## 1  Lung-AdenoCA    hessian_positivedefinite_bool          diagRE_M
## 2  Lung-AdenoCA hessian_nonpositivedefinite_bool          fullRE_M
## 3  Lung-AdenoCA    hessian_positivedefinite_bool       diagRE_DMDL
## 4  Lung-AdenoCA hessian_nonpositivedefinite_bool      fullRE_halfDM
```

```
## 5  Lung-AdenoCA hessian_nonpositivedefinite_bool              fullRE_DMDL
## 6  Lung-AdenoCA    hessian_positivedefinite_bool              diagRE_DMSL
## 7  Lung-AdenoCA    hessian_positivedefinite_bool            sparseRE_DMSL
## 8  Lung-AdenoCA hessian_nonpositivedefinite_bool              fullRE_DMSL
## 9  Lung-AdenoCA hessian_nonpositivedefinite_bool         fullRE_DMSL_SBS1
## 10 Lung-AdenoCA    hessian_positivedefinite_bool          fullRE_M_nonexo
## 11 Lung-AdenoCA    hessian_positivedefinite_bool       diagRE_DMSL_nonexo
## 12 Lung-AdenoCA    hessian_positivedefinite_bool     sparseRE_DMSL_nonexo
## 13 Lung-AdenoCA hessian_nonpositivedefinite_bool       fullRE_DMSL_nonexo
## 14 Lung-AdenoCA hessian_nonpositivedefinite_bool       fullRE_DMDL_nonexo
## 15 Lung-AdenoCA hessian_nonpositivedefinite_bool fullRE_DMDL_sortednonexo
```

Re-running of fitting

Using fullRE_M_nonexo to fit fullRE_DMSL_nonexo. We re-run fullRE_M_nonexo and it has converged:

But fullRE DMSL hasn't:

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

If we use the values of the fullRE M exo as initial values for the fullRE DMSL exo does not converge:

```
## [1] FALSE
```

Potentially problematic signatures

We explore whether there are problematic signatures:

```
colSums(obj_Lung_AdenoCA$Y == 0)/nrow(obj_Lung_AdenoCA$Y)
```

```
##       SBS1       SBS2       SBS3       SBS4       SBS5       SBS9      SBS13
## 0.02941176 0.02941176 0.26470588 0.17647059 0.08823529 0.58823529 0.08823529
##     SBS17a     SBS17b      SBS18      SBS40      SBS50
## 0.64705882 0.64705882 0.14705882 0.14705882 0.11764706
```

```
colSums(obj_Lung_AdenoCA$Y)/sum(obj_Lung_AdenoCA$Y)
```

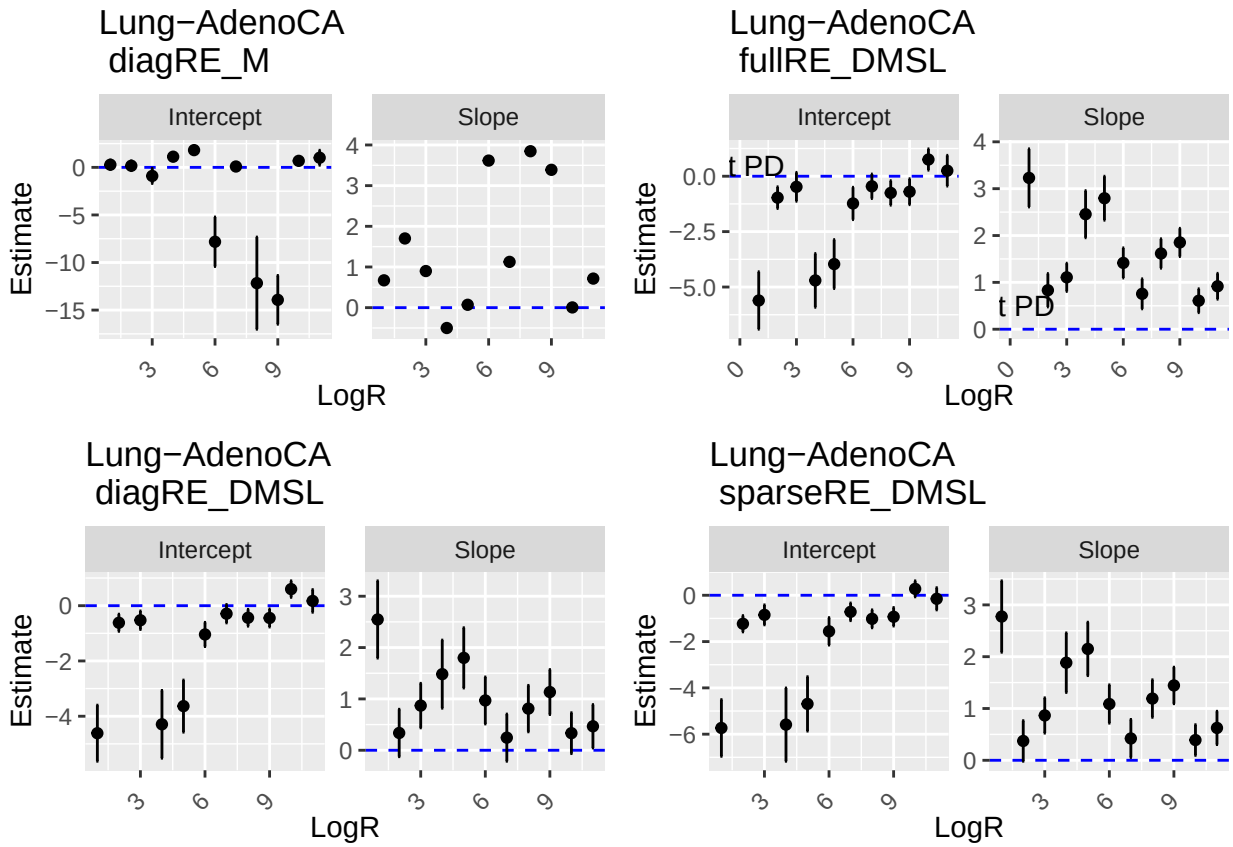
```
##       SBS1       SBS2       SBS3       SBS4       SBS5       SBS9      SBS13
## 0.02550030 0.09137609 0.05699124 0.32022800 0.13218445 0.02860308 0.07430021
##     SBS17a     SBS17b      SBS18      SBS40      SBS50
## 0.01139098 0.02722878 0.07136089 0.13654347 0.02429249
```

None seem to be problematic.

Betas

```
ct <- "Lung-AdenoCA"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```

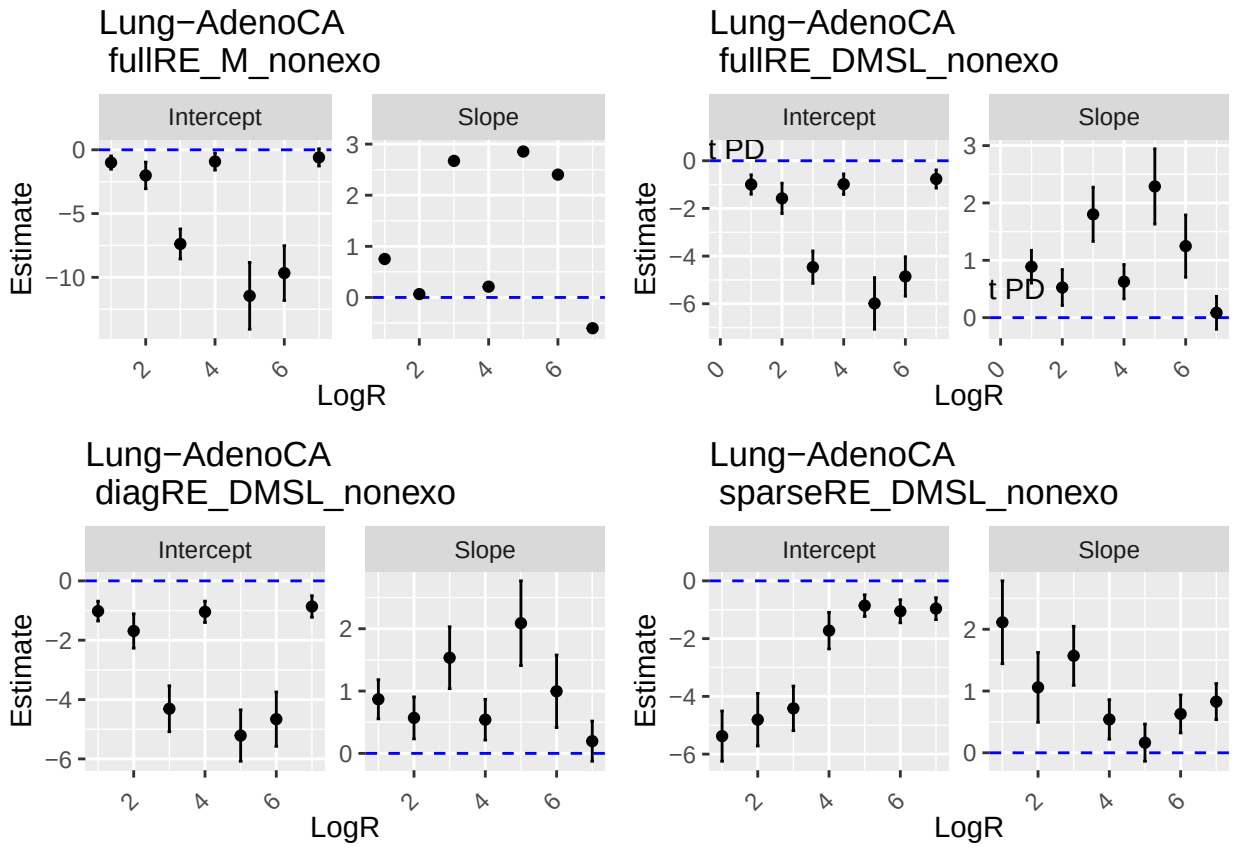
```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```




```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(fullRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

```
## Warning in sqrt(as.numeric(object$diag.cov.random)): NaNs produced
```



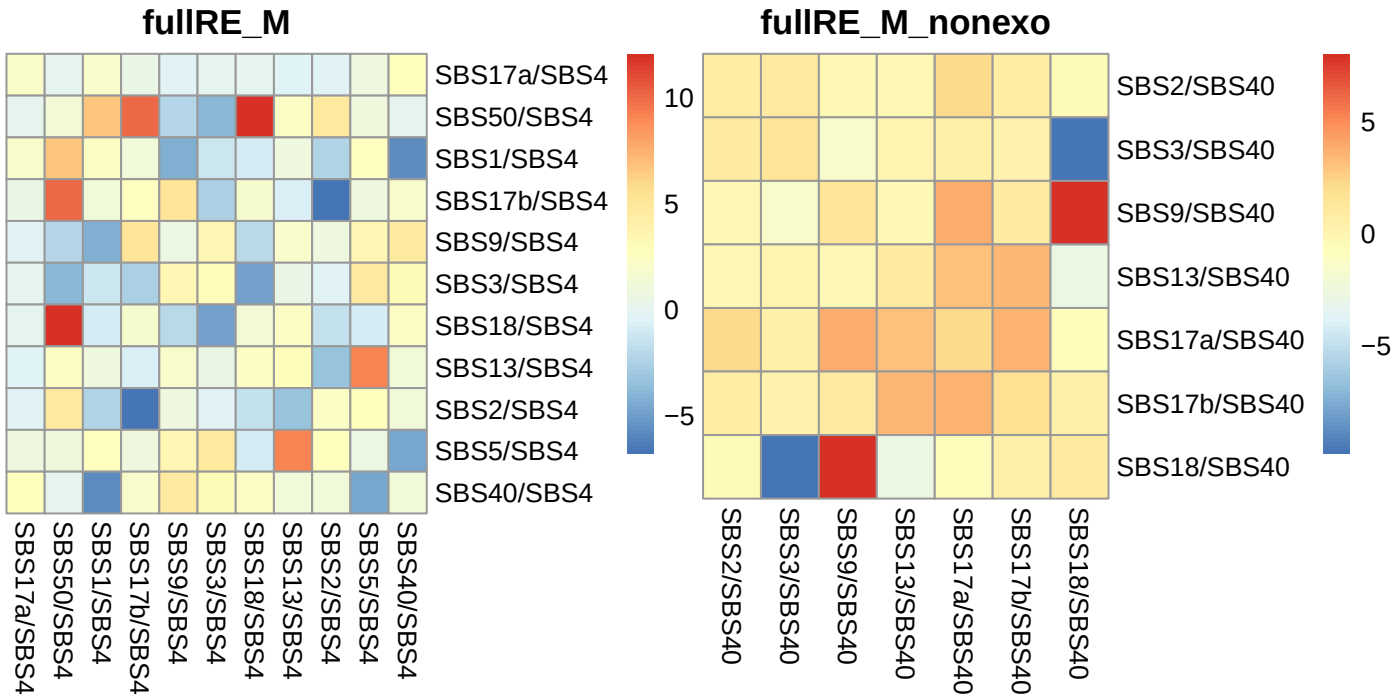

```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct
```

```
## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used
```

```
## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of 0.0034356.

Covariance matrices



Simulation under inferred data

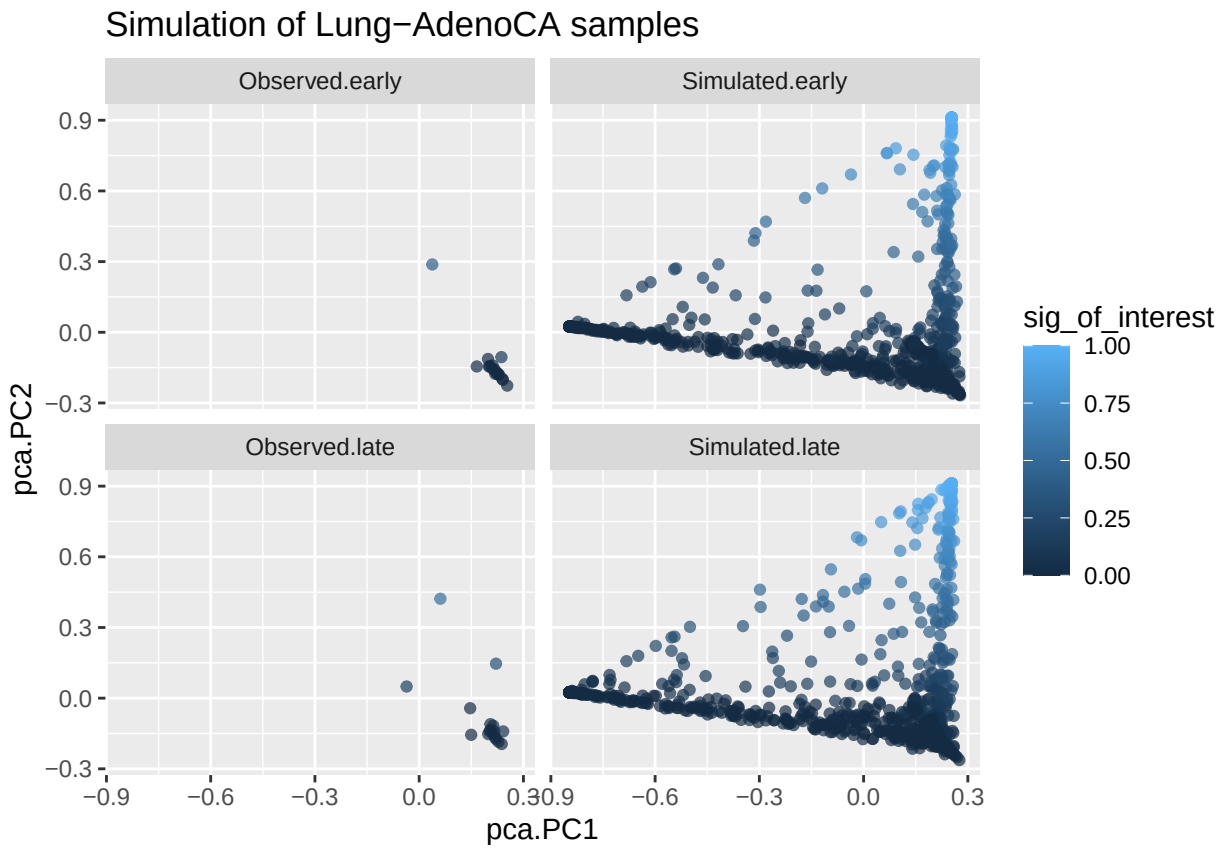
```
## [1] 17
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

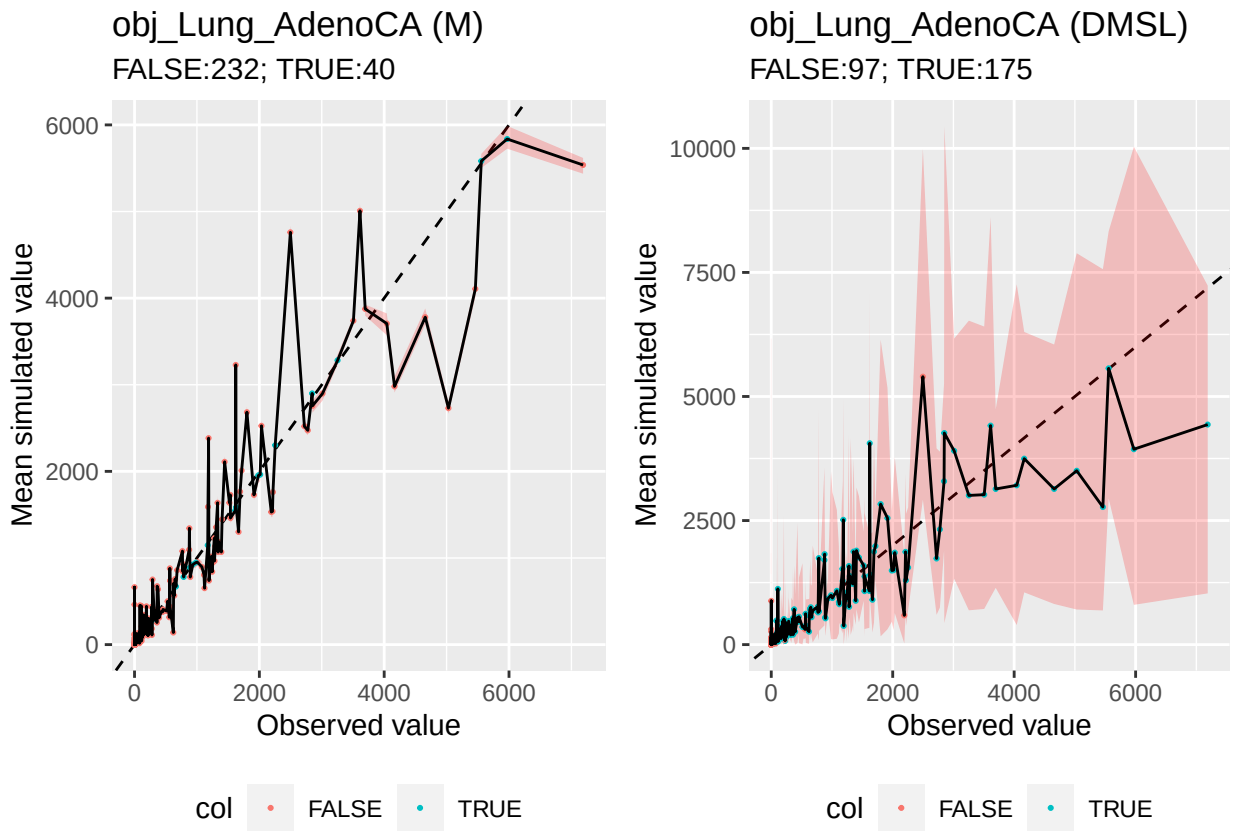
```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```



Ranked plot for coverage

THIS IS PROBABLY INCORRECT! THE OBJECT SHOULD BE SORTED

```
ct <- "Lung-AdenoCA"
integer_overdispersion_param_DMSL <- 1
obj_Lung_AdenoCA_nonexo <- give_subset_sigs_TMBobj(obj_Lung_AdenoCA, sigs_to_remove = nonexogenous$V1)
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                  data_object = obj_Lung_AdenoCA_nonexo,
                  print_plot = F, nreps = 20, model = "M")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Lung_AdenoCA_nonexo,
                  loglog = F, title = 'obj_Lung_AdenoCA (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = diagRE_DMSL_nor
                  data_object = obj_Lung_AdenoCA_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Lung_AdenoCA_nonexo,
            loglog = F, title = 'obj_Lung_AdenoCA (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

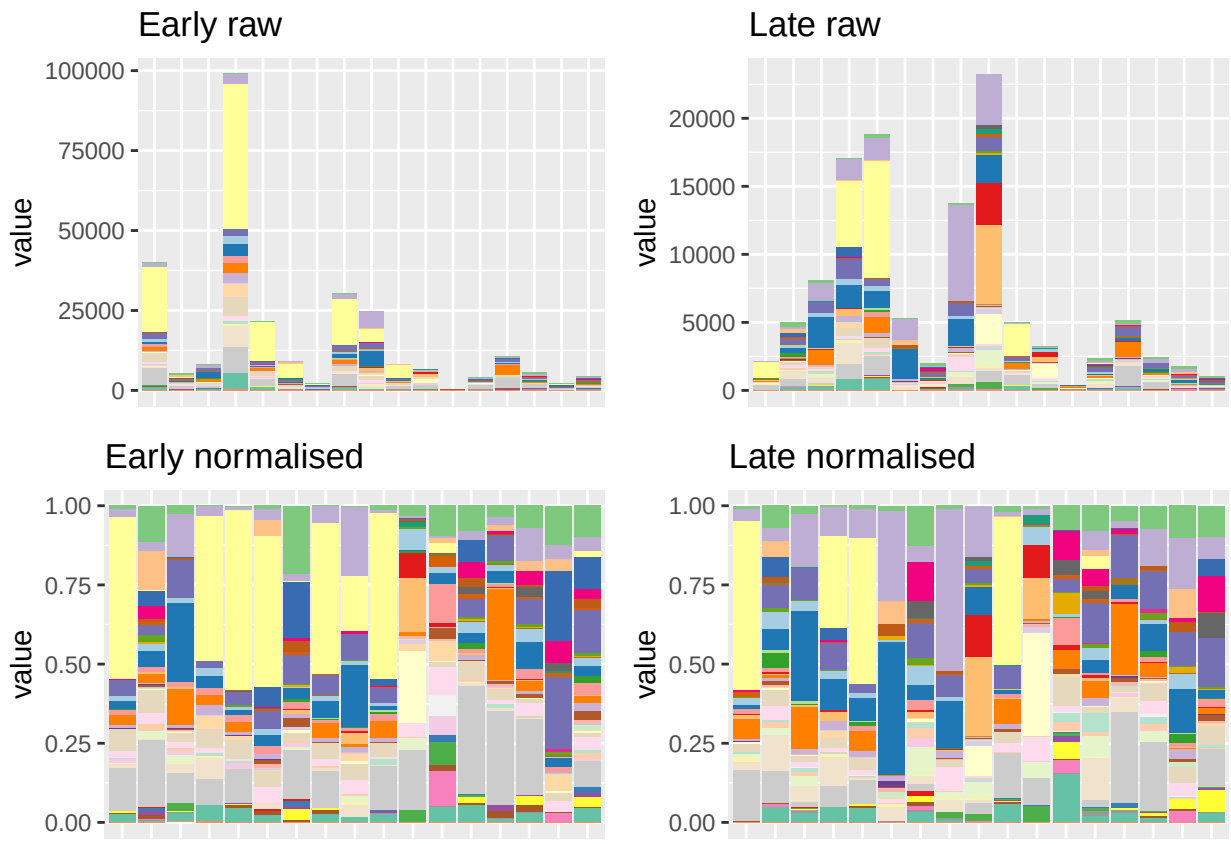
```
obj_Lung_AdenoCA_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

```
## [1] 17
```

```
give_barplot_from_obj(obj = obj_Lung_AdenoCA_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 17
## Creating plot... it might take some time if the data are large. Number of samples: 17
## Creating plot... it might take some time if the data are large. Number of samples: 17
## Creating plot... it might take some time if the data are large. Number of samples: 17
```

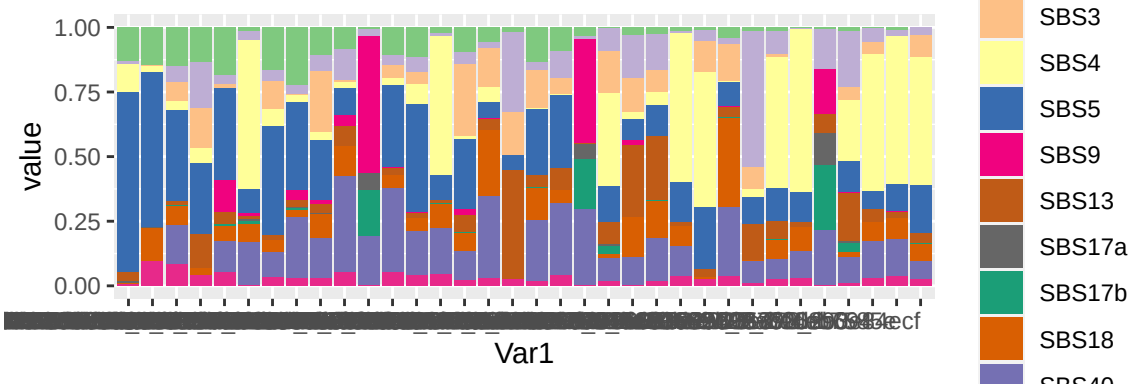
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: there is a trend in which SBS5 decreases and SBS4 increases with the number of mutations.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Lung_AdenoCA$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Lung_AdenoCA$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 34
```

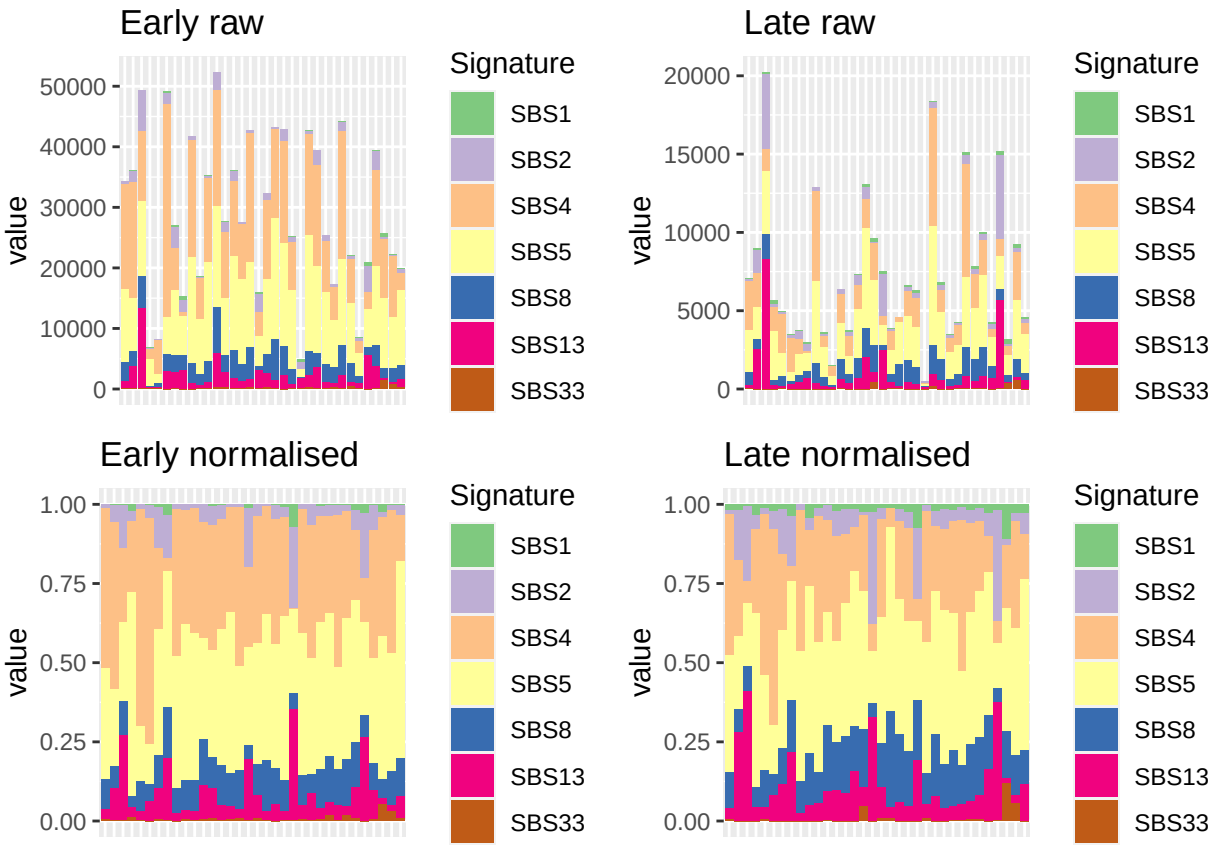


Lung-SCC

Barplot and general statistics

```
## [1] 34
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 34
## Creating plot... it might take some time if the data are large. Number of samples: 34
## Creating plot... it might take some time if the data are large. Number of samples: 34
## Creating plot... it might take some time if the data are large. Number of samples: 34
```



The number of samples and signatures is:

```
## [1] 68  7
```

The signatures are:

```
## [1] "SBS1"  "SBS2"  "SBS4"  "SBS5"  "SBS8"  "SBS13" "SBS33"
```

Convergence table

We have converged results in most cases, and all in nonexo.

```
##       value                                L2                 L1
## 1  Lung-SCC    hessian_positivedefinite_bool          diagRE_M
## 2  Lung-SCC    hessian_positivedefinite_bool          fullRE_M
## 3  Lung-SCC hessian_nonpositivedefinite_bool       diagRE_DMDL
## 4  Lung-SCC                         Timeout     fullRE_halfDM
## 5  Lung-SCC hessian_nonpositivedefinite_bool       fullRE_DMDL
```

```
## 6  Lung-SCC    hessian_positivedefinite_bool             diagRE_DMSL
## 7  Lung-SCC    hessian_positivedefinite_bool           sparseRE_DMSL
## 8  Lung-SCC    hessian_positivedefinite_bool             fullRE_DMSL
## 9  Lung-SCC hessian_nonpositivedefinite_bool        fullRE_DMSL_SBS1
## 10 Lung-SCC    hessian_positivedefinite_bool         fullRE_M_nonexo
## 11 Lung-SCC hessian_nonpositivedefinite_bool      diagRE_DMSL_nonexo
## 12 Lung-SCC    hessian_positivedefinite_bool    sparseRE_DMSL_nonexo
## 13 Lung-SCC    hessian_positivedefinite_bool      fullRE_DMSL_nonexo
## 14 Lung-SCC    hessian_positivedefinite_bool      fullRE_DMDL_nonexo
## 15 Lung-SCC                          Timeout fullRE_DMDL_sortednonexo
```

Potentially problematic signatures

We explore whether there are problematic signatures; none are.

```
colSums(obj_Lung_SCC$Y == 0)/nrow(obj_Lung_SCC$Y)
```

```
##       SBS1       SBS2       SBS4       SBS5       SBS8      SBS13      SBS33
## 0.11764706 0.01470588 0.01470588 0.00000000 0.00000000 0.00000000 0.35294118
```

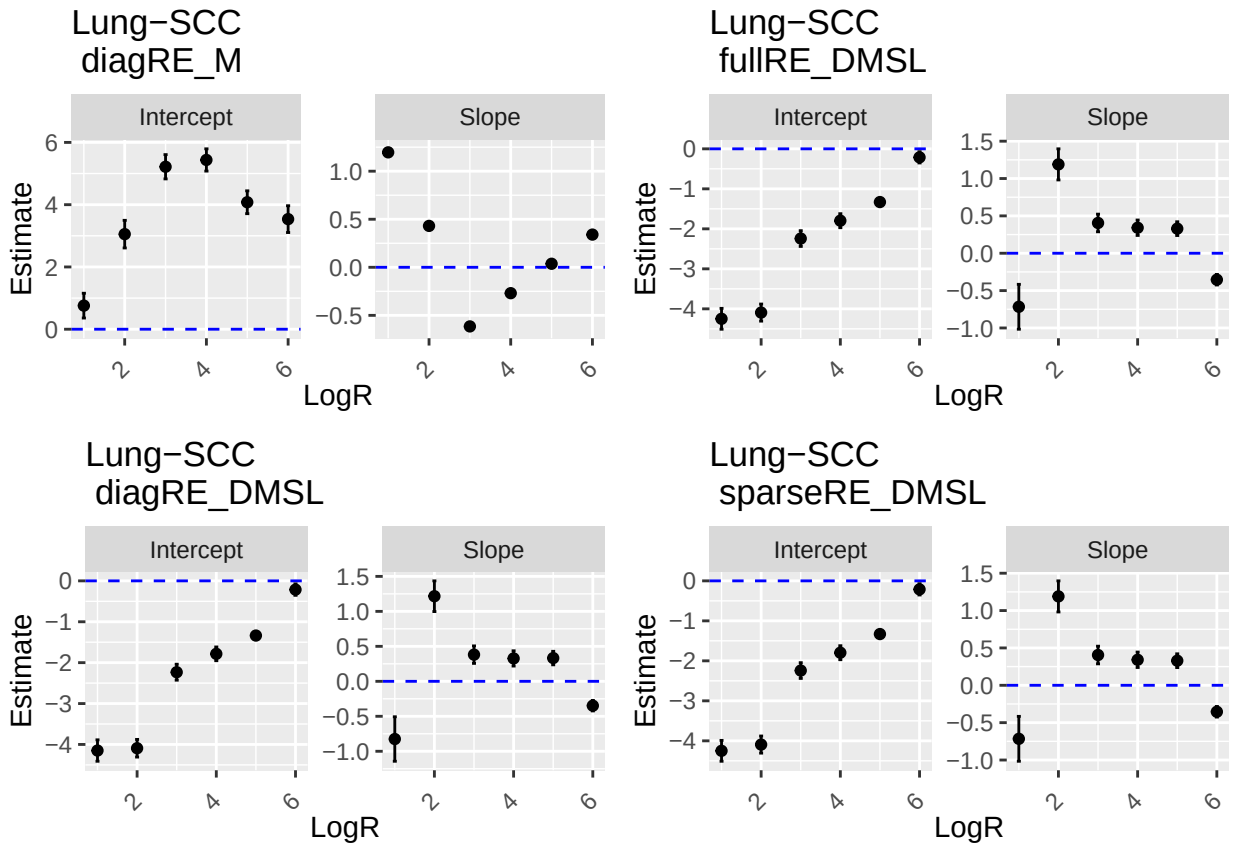
```
colSums(obj_Lung_SCC$Y)/sum(obj_Lung_SCC$Y)
```

```
##        SBS1        SBS2        SBS4        SBS5        SBS8       SBS13
## 0.007157222 0.057307486 0.361344268 0.373780803 0.107939657 0.086773493
##       SBS33
## 0.005697071
```

Betas

Very clear example of only one signature changing:

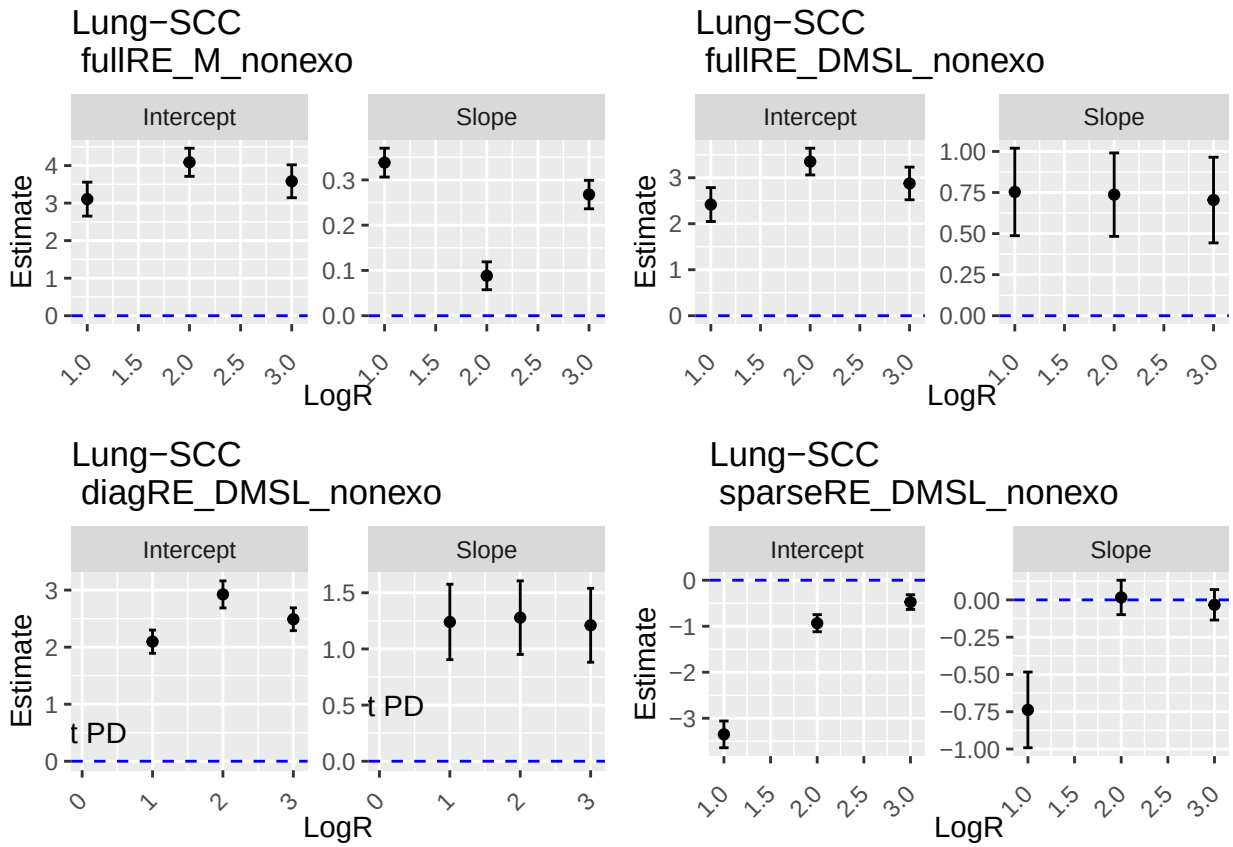
```
ct <- "Lung-SCC"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```




```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(fullRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

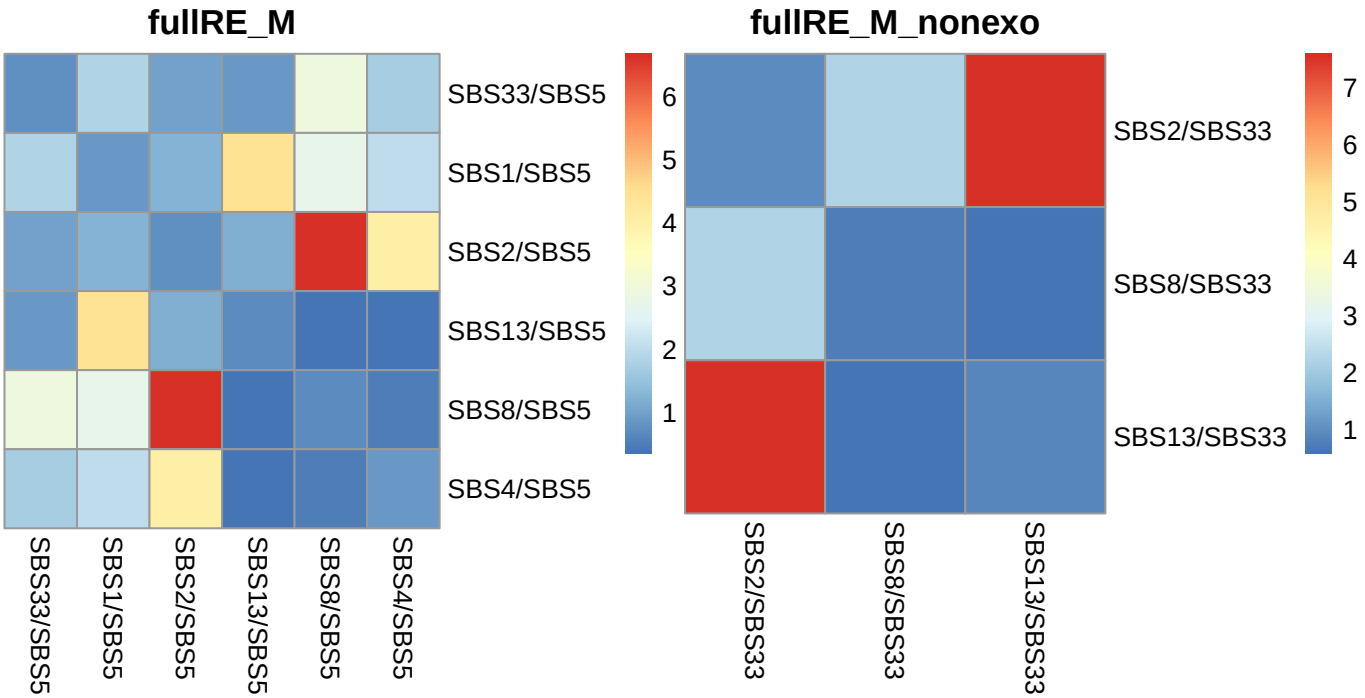
```
## Warning in sqrt(as.numeric(object$diag.cov.random)): NaNs produced
```

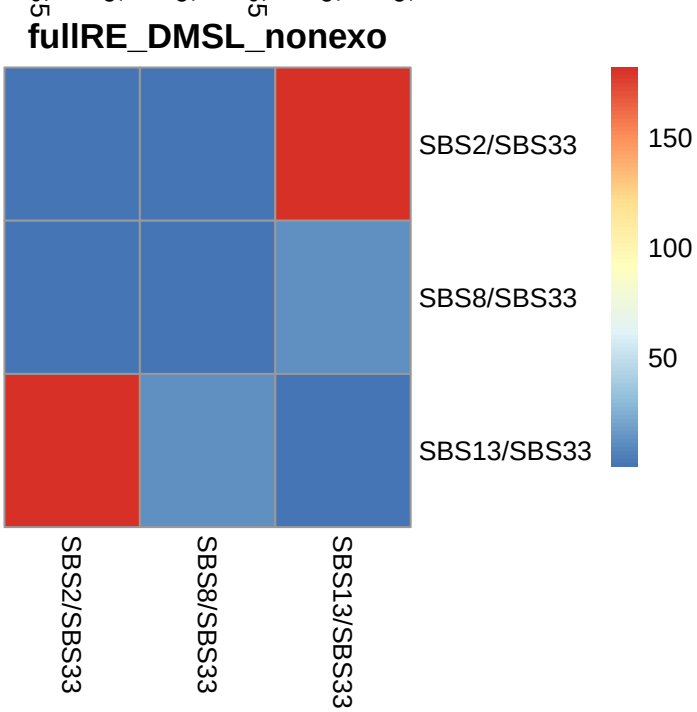



```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct

## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used

## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

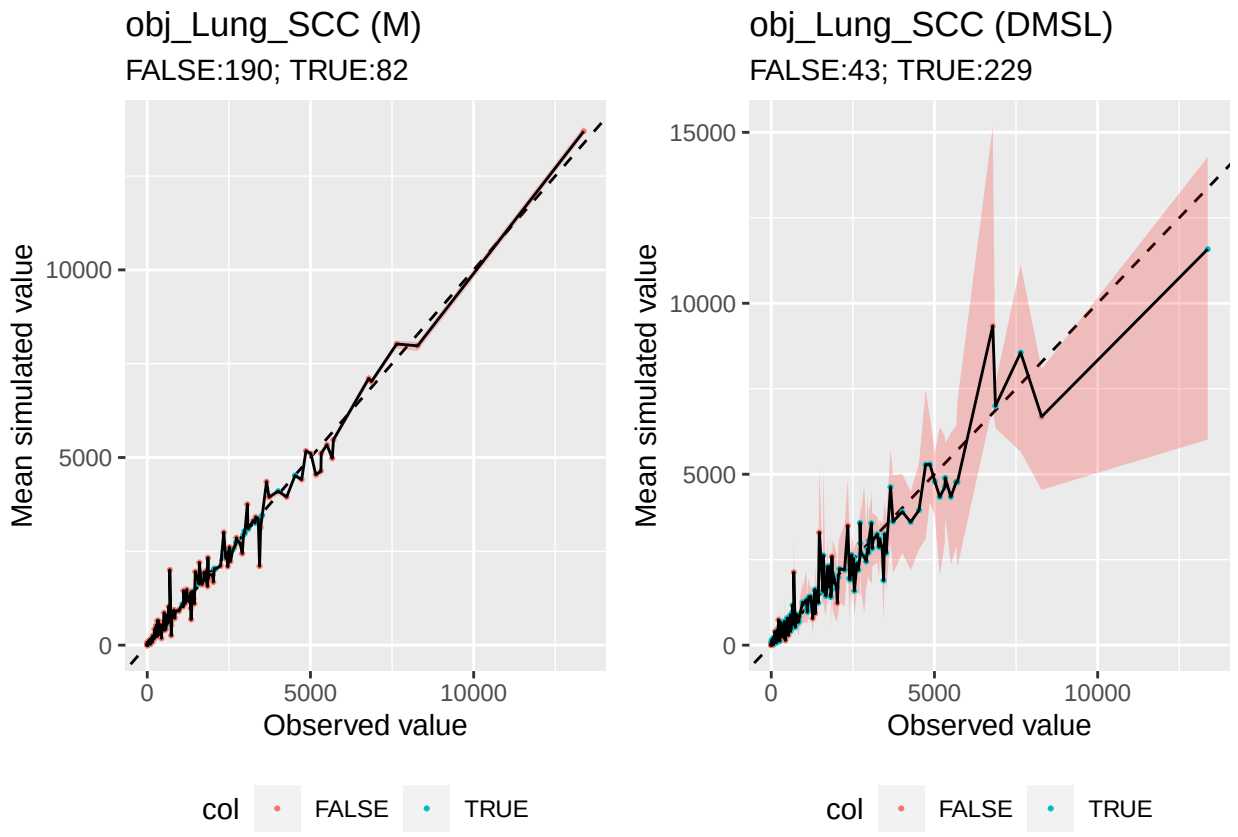
We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 0.0338506.

Covariance matrices





Ranked plot for coverage



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

```
obj_Lung_SCC_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

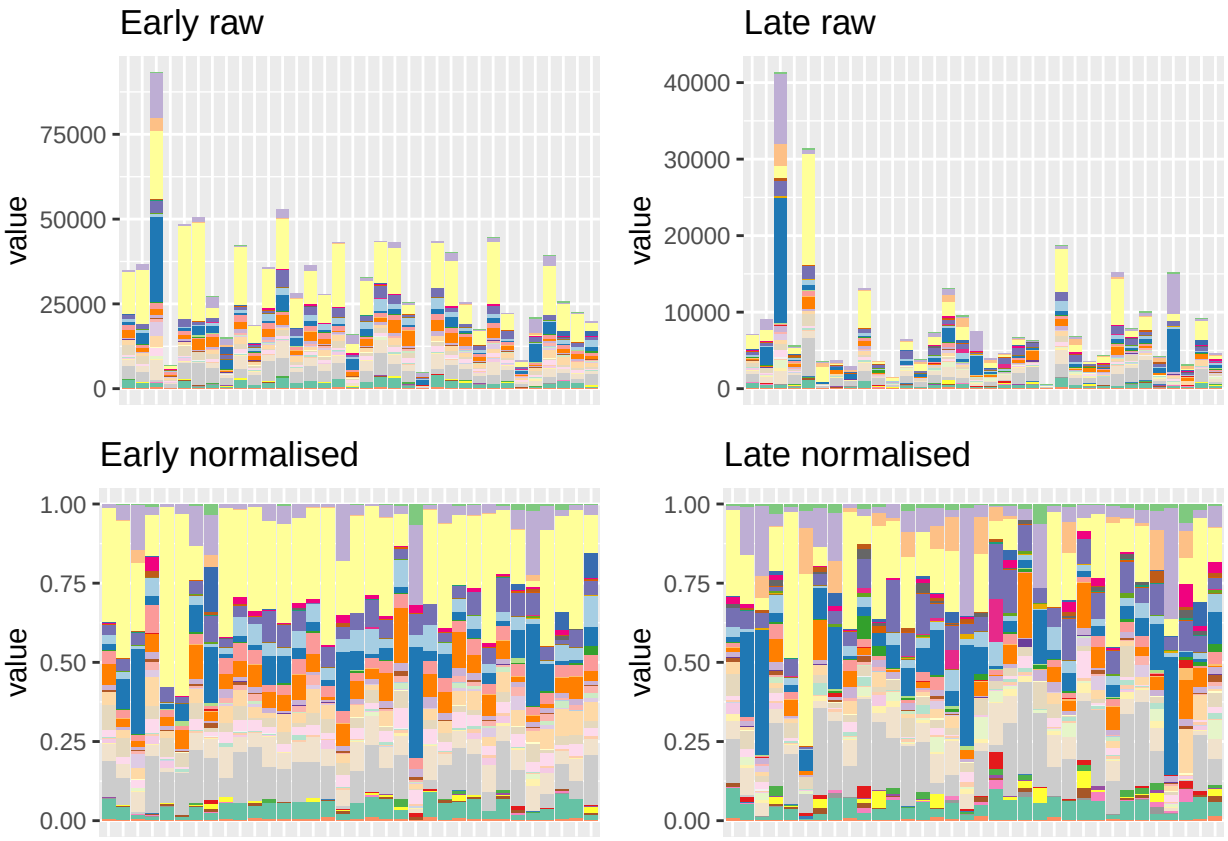
```
## [1] 34
```

```
give_barplot_from_obj(obj = obj_Lung_SCC_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 34
## Creating plot... it might take some time if the data are large. Number of samples: 34
## Creating plot... it might take some time if the data are large. Number of samples: 34
## Creating plot... it might take some time if the data are large. Number of samples: 34
```

```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```

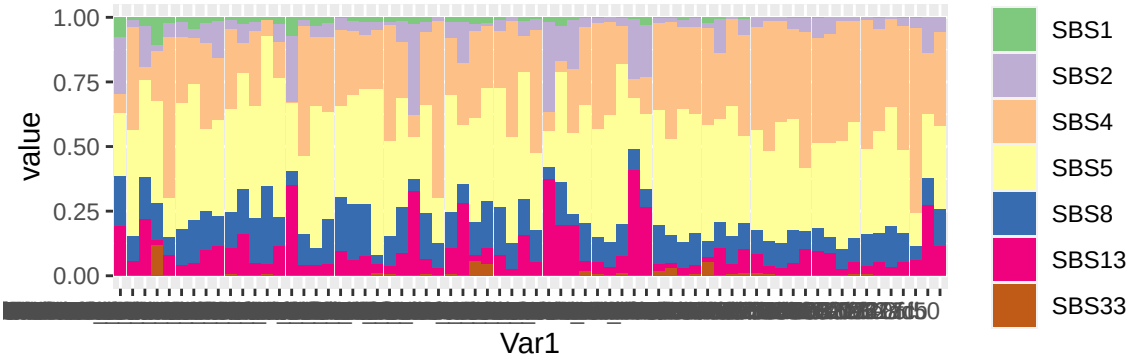
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Lung_SCC$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Lung_SCC$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 68
```

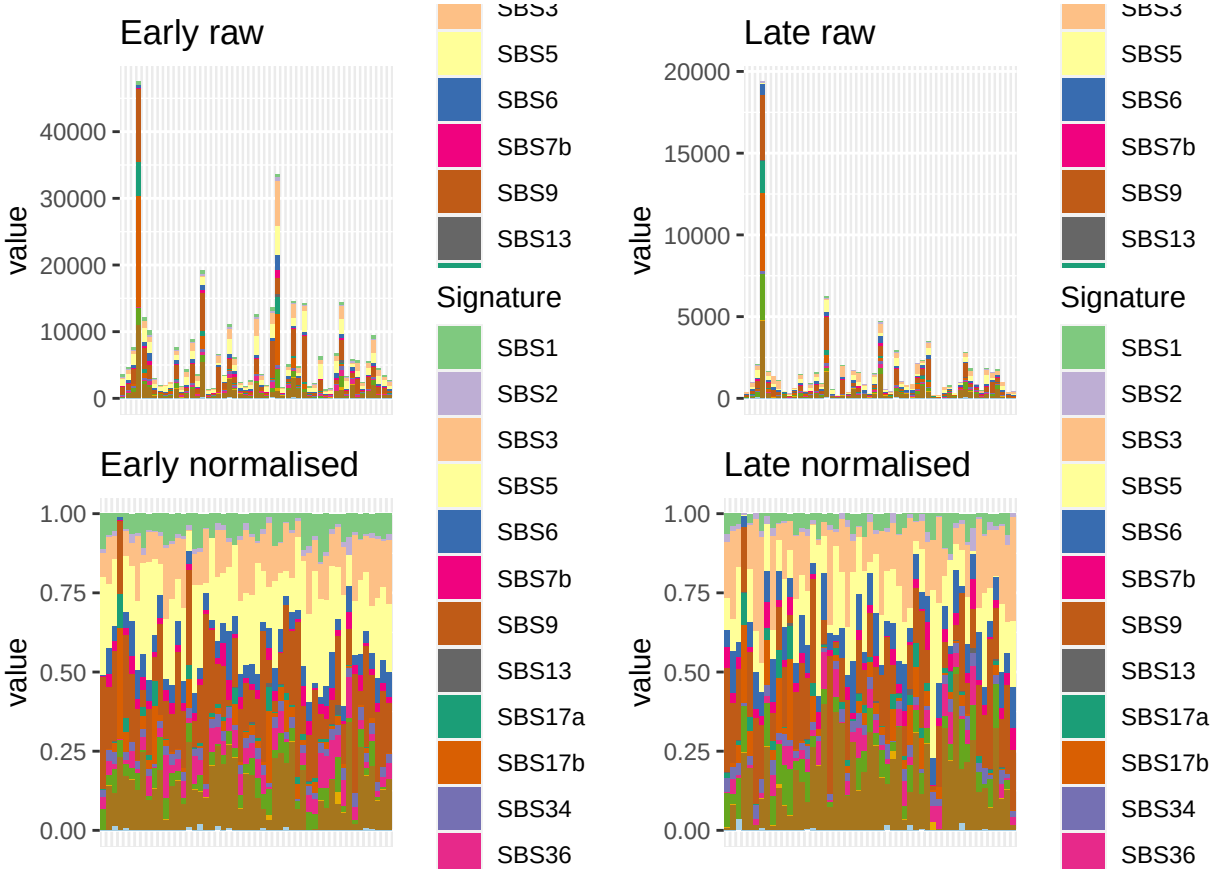


Lymph-BNHL

Barplot and general statistics

```
## [1] 51
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 51
## Creating plot... it might take some time if the data are large. Number of samples: 51
## Creating plot... it might take some time if the data are large. Number of samples: 51
## Creating plot... it might take some time if the data are large. Number of samples: 51
```



The number of samples and signatures is:

```
## [1] 102  16
```

The signatures are:

```
##  [1] "SBS1"   "SBS2"   "SBS3"   "SBS5"   "SBS6"   "SBS7b"  "SBS9"   "SBS13"
##  [9] "SBS17a" "SBS17b" "SBS34"  "SBS36"  "SBS37"  "SBS39"  "SBS40"  "SBS56"
```

Convergence table

fullRE_DMSL_nonexo had not run, and fullRE_M_nonexo didn't converge.

```
##         value                                L2                  L1
## 1  Lymph-BNHL    hessian_positivedefinite_bool            diagRE_M
## 2  Lymph-BNHL hessian_nonpositivedefinite_bool            fullRE_M
## 3  Lymph-BNHL    hessian_positivedefinite_bool          diagRE_DMDL
```

```
## 4  Lymph-BNHL                          Timeout            fullRE_halfDM
## 5  Lymph-BNHL                          Timeout              fullRE_DMDL
## 6  Lymph-BNHL    hessian_positivedefinite_bool              diagRE_DMSL
## 7  Lymph-BNHL    hessian_positivedefinite_bool            sparseRE_DMSL
## 8  Lymph-BNHL hessian_nonpositivedefinite_bool              fullRE_DMSL
## 9  Lymph-BNHL hessian_nonpositivedefinite_bool         fullRE_DMSL_SBS1
## 10 Lymph-BNHL hessian_nonpositivedefinite_bool          fullRE_M_nonexo
## 11 Lymph-BNHL    hessian_positivedefinite_bool       diagRE_DMSL_nonexo
## 12 Lymph-BNHL    hessian_positivedefinite_bool     sparseRE_DMSL_nonexo
## 13 Lymph-BNHL                          Timeout       fullRE_DMSL_nonexo
## 14 Lymph-BNHL hessian_nonpositivedefinite_bool       fullRE_DMDL_nonexo
## 15 Lymph-BNHL    hessian_positivedefinite_bool fullRE_DMDL_sortednonexo
```

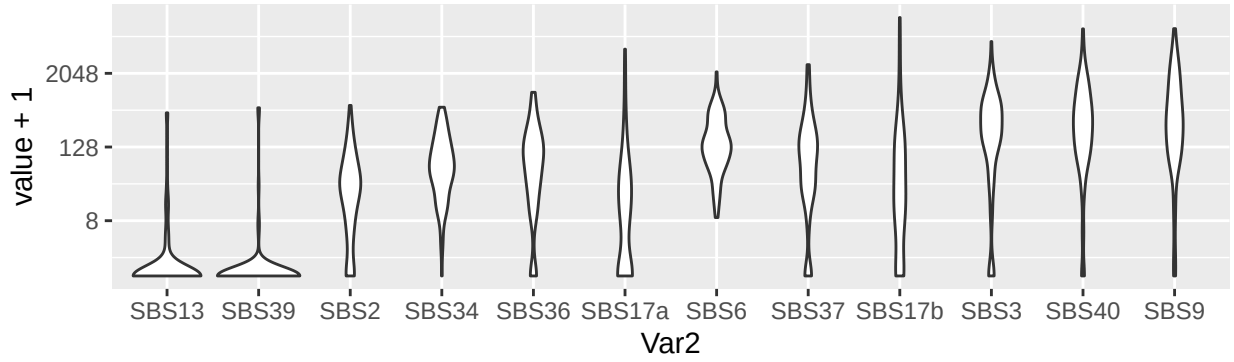
Re-running of fitting

Using fullRE_M_nonexo to fit fullRE_DMSL_nonexo. Very clearly there are too many signatures.

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

Which signatures should be omitted from the analysis?

```
ggplot(melt(obj_LymphBNHL$Y), aes(x=Var2, y=value+1))+geom_violin()+scale_y_continuous(trans = "log2")
```



SBS13 and SBS39 should definitely be removed.

Has fullRE M now converged? converge:

```
## [1] TRUE
```

it has. I now run DM with this subset

Its convergence is as follows:

```
## [1] TRUE
```

it has also converged

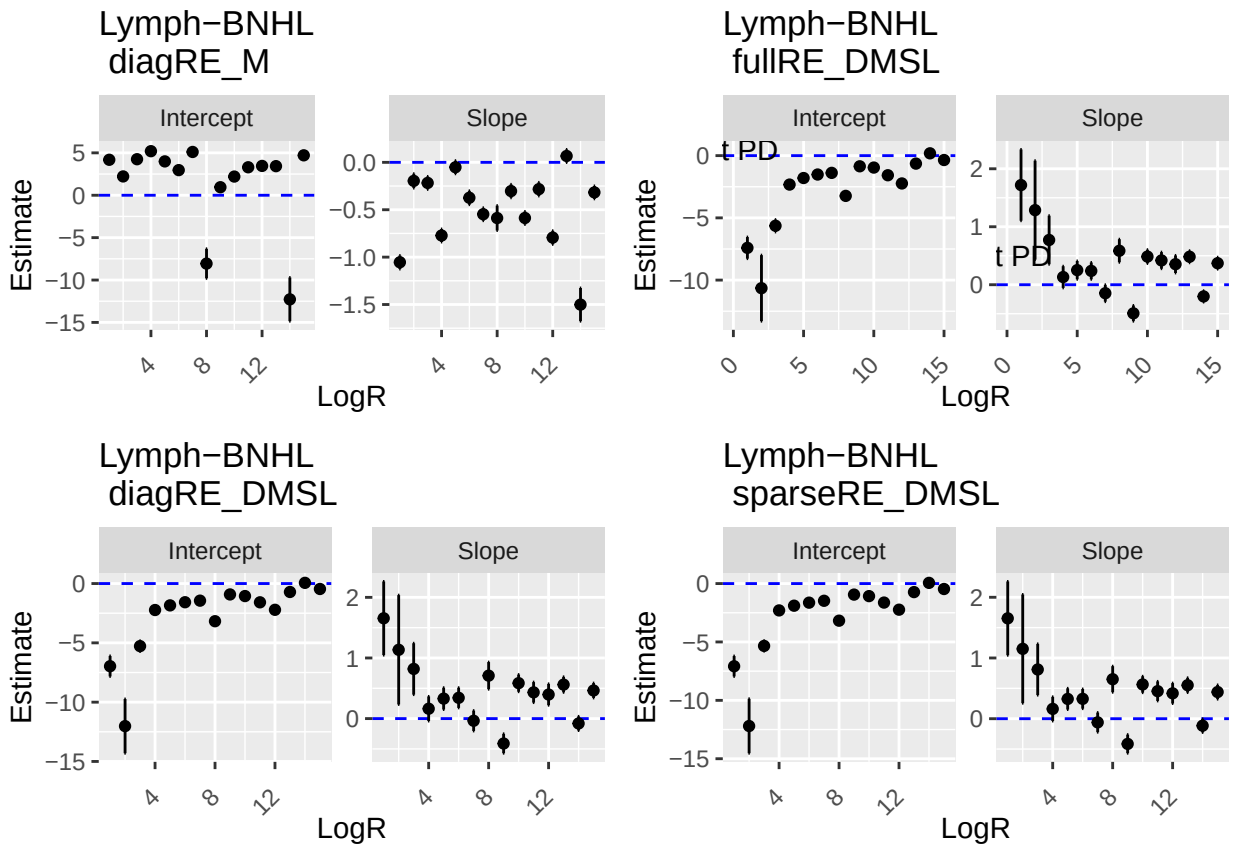
```
additional_sortedMnonexo[["Lymph-BNHL"]] <- sortedM_LymphBNHL
additional_sortedDMSLnonexo[["Lymph-BNHL"]] <- sortedDM_LymphBNHL
```

Betas

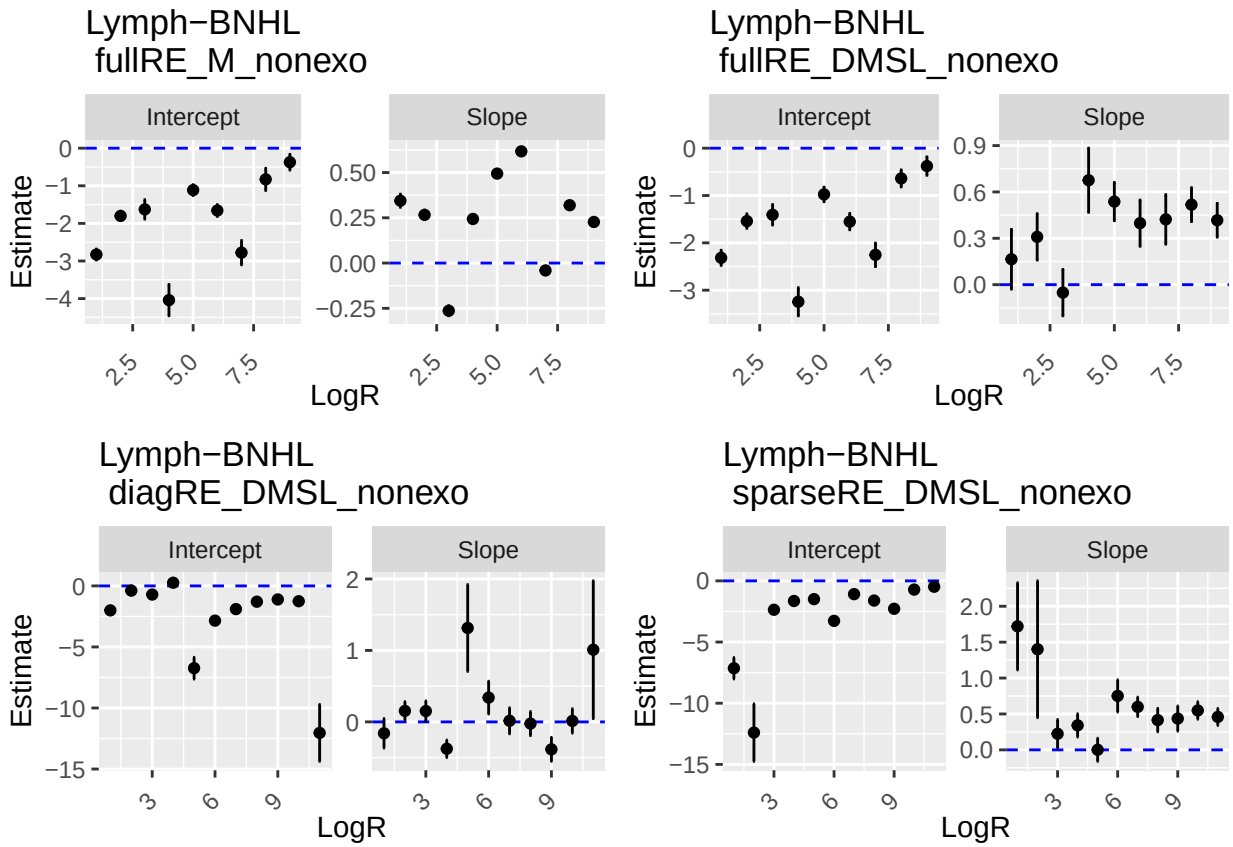
```
ct <- "Lymph-BNHL"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
```

```
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```




```
grid.arrange(
  plot_betas(additional_sortedMnonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(additional_sortedDMSLnonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```



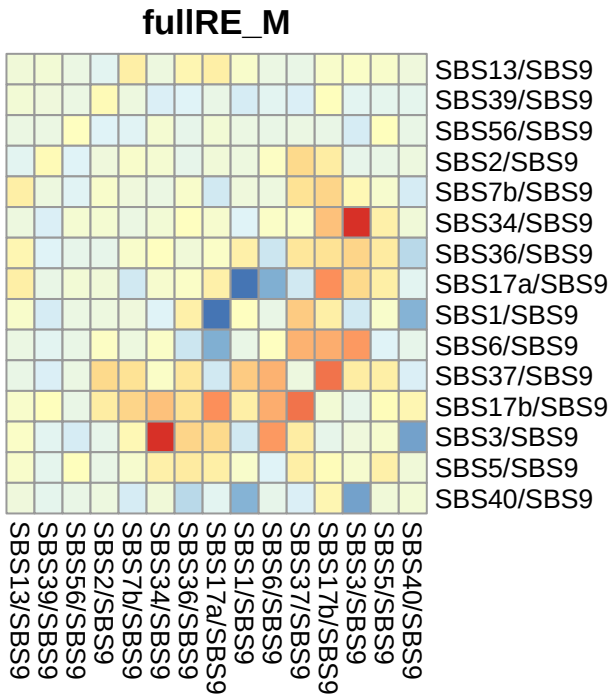

```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct
```

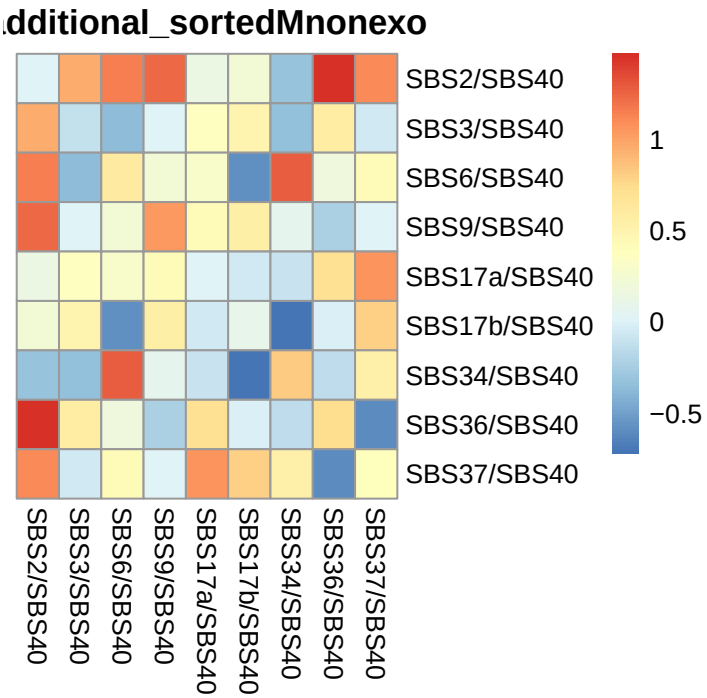
```
## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used
```

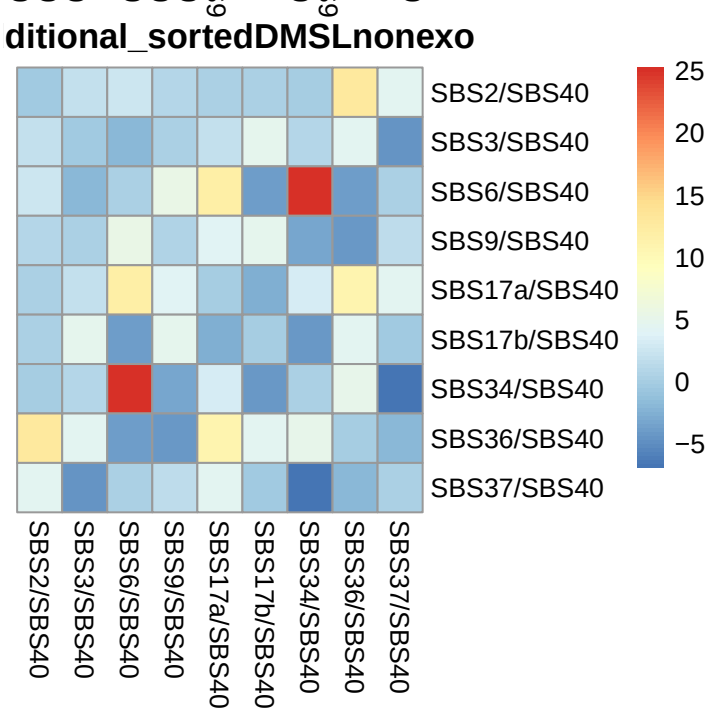
```
## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the full RE single lambda DM with the subset of signatures (removing thw two problematic ones) to test for differential abundance, giving a p-value of 9.5835037×10^{-7}.

Covariance matrices



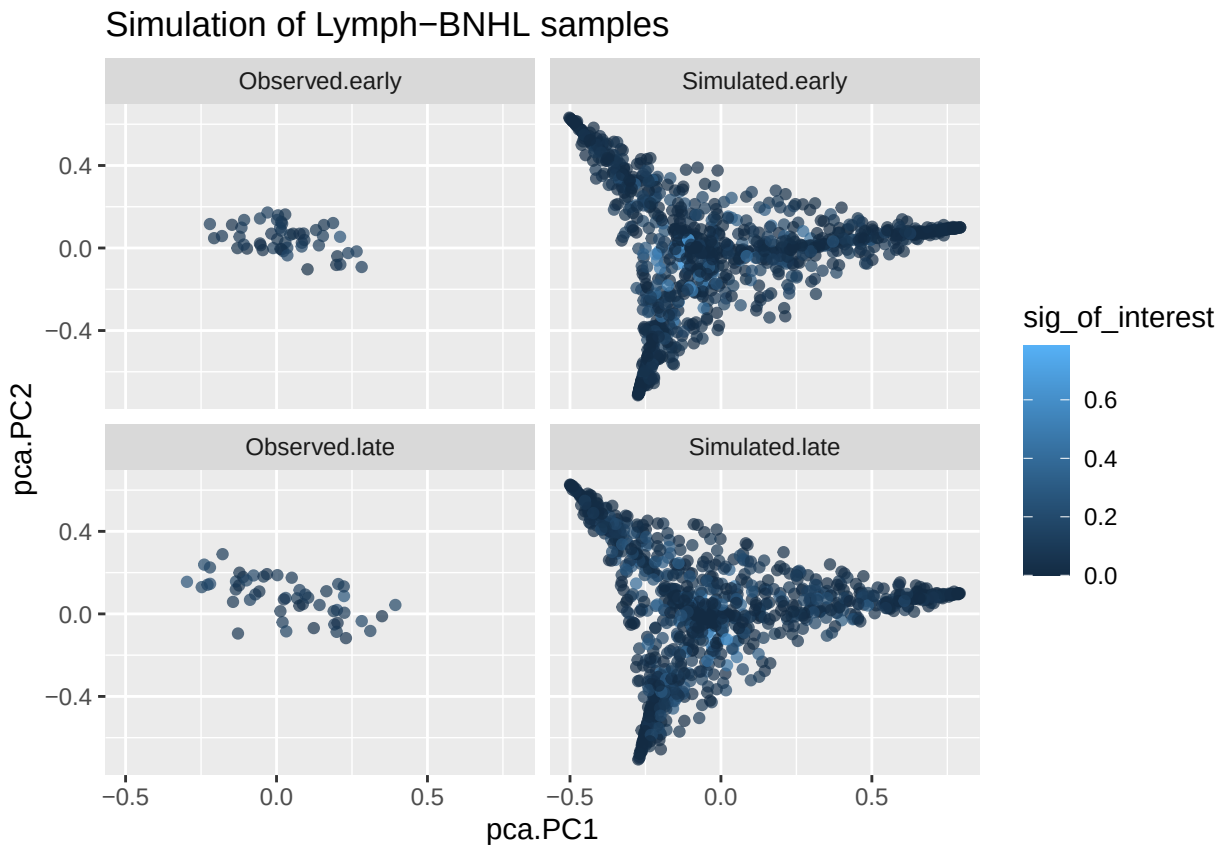




Simulation under inferred data

```
## [1] 51
```

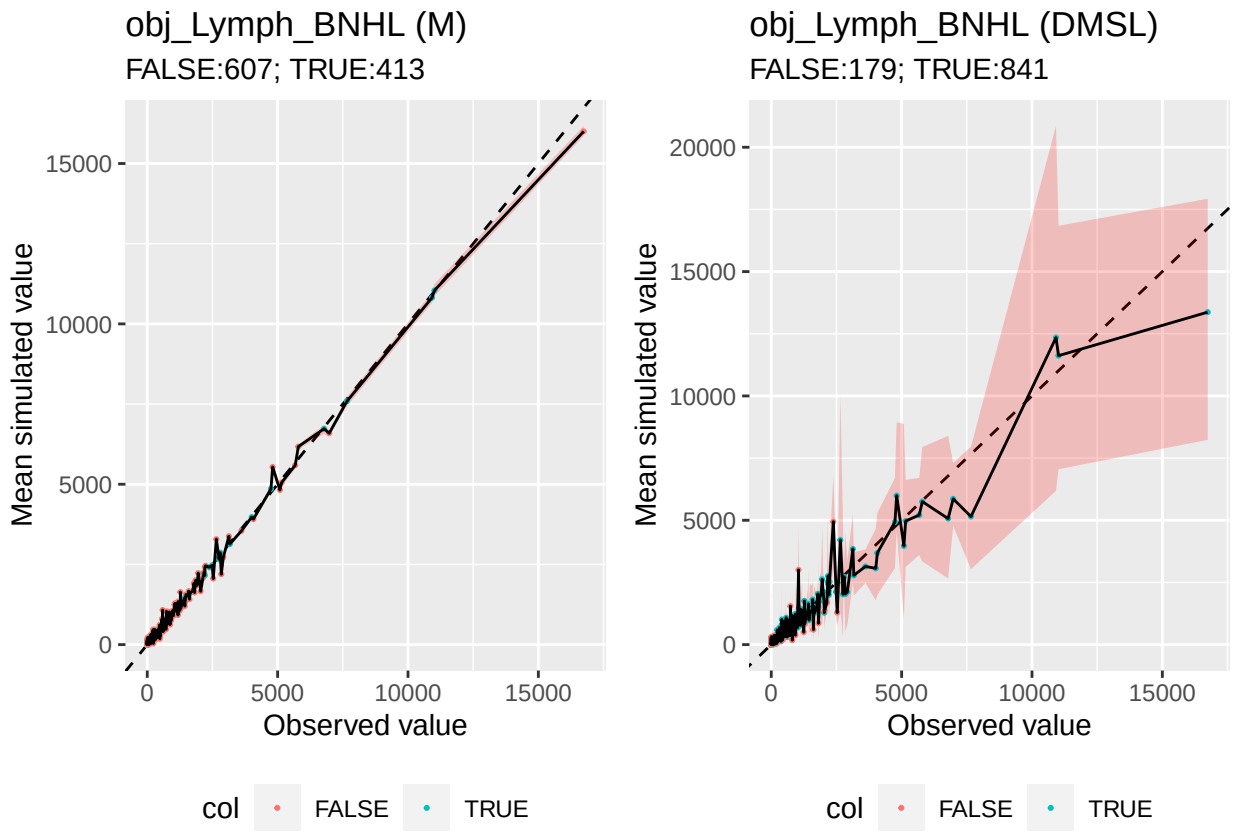
```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```



Ranked plot for coverage

Should it be simply give_subset_sigs_TMBobj or additionally also sort_columns_TMB? If I only use give_subset_sigs_TMBobj I get very strange results. This should perhaps be changed to all chunks above!!

```
ct <- "Lymph-BNHL"
integer_overdispersion_param_DMSL <- 1
obj_Lymph_BNHL_nonexo <- sort_columns_TMB(give_subset_sigs_TMBobj(obj_Lymph_BNHL,
                                                  sigs_to_remove = c(nonexogenous$V1, 'SBS13', 'SBS39')))
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = sor
                  data_object = obj_Lymph_BNHL_nonexo,
                  print_plot = F, nreps = 20, model = "M")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Lymph_BNHL_nonexo,
                  loglog = F, title = 'obj_Lymph_BNHL (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = sortedDM_LymphB
                  data_object = obj_Lymph_BNHL_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Lymph_BNHL_nonexo,
           loglog = F, title = 'obj_Lymph_BNHL (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

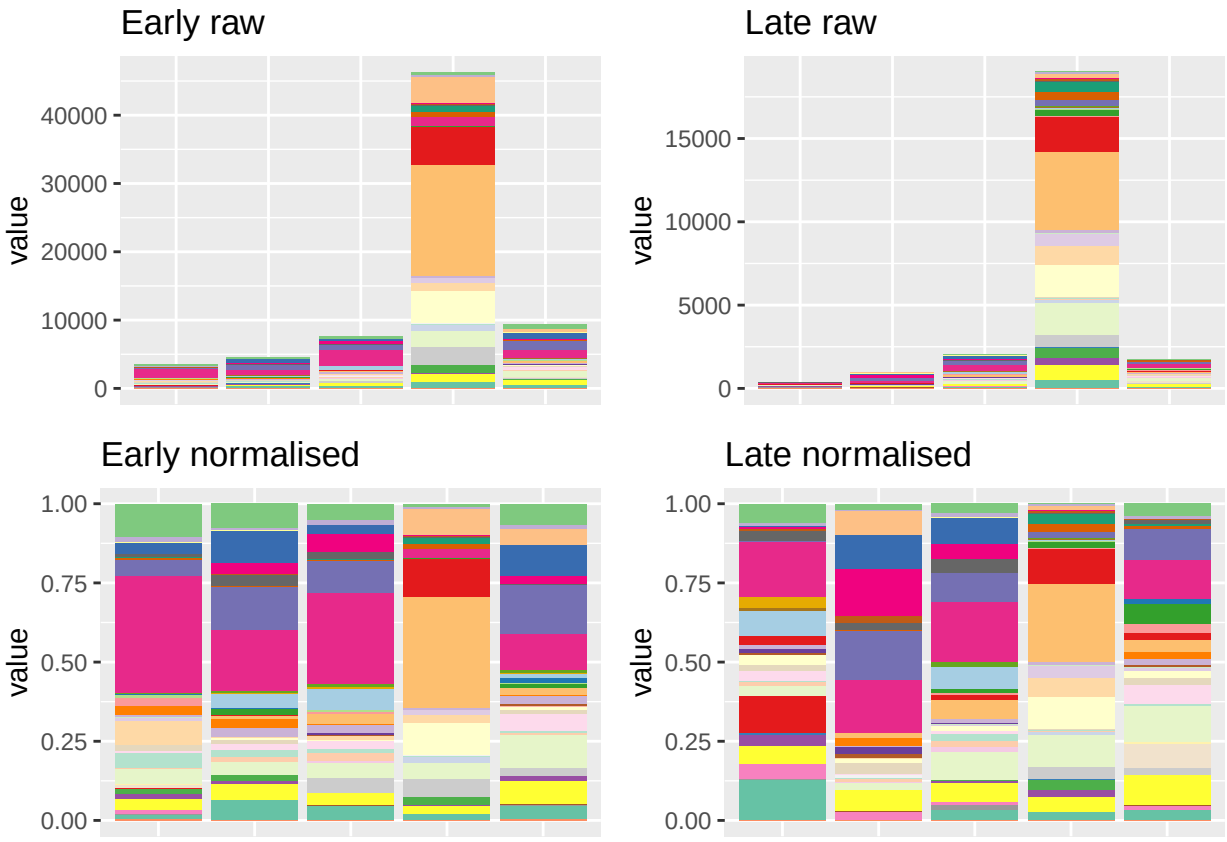
```
obj_Lymph_BNHL_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                  path_to_data = "../../data/")
```

```
## [1] 5
```

```
give_barplot_from_obj(obj = obj_Lymph_BNHL_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 5
## Creating plot... it might take some time if the data are large. Number of samples: 5
## Creating plot... it might take some time if the data are large. Number of samples: 5
## Creating plot... it might take some time if the data are large. Number of samples: 5
```

```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```

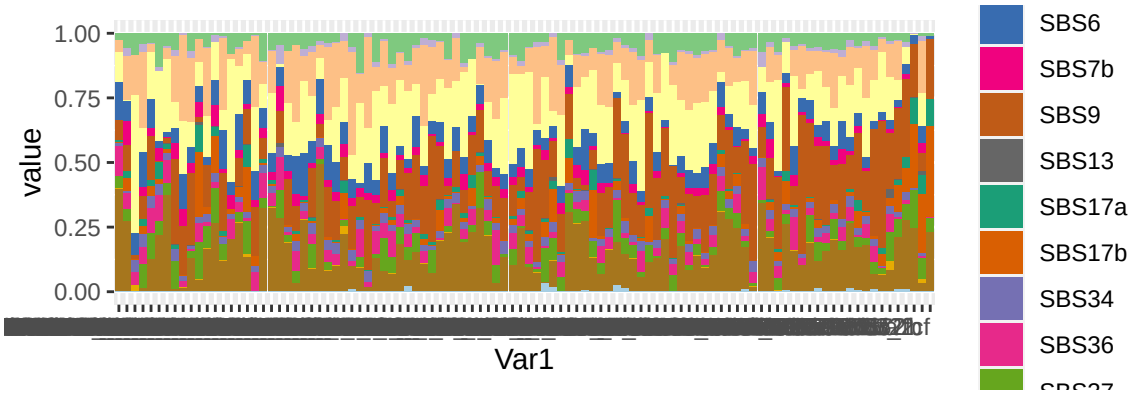


something must have gone wrong here.

Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Lymph_BNHL$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Lymph_BNHL$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 102
```

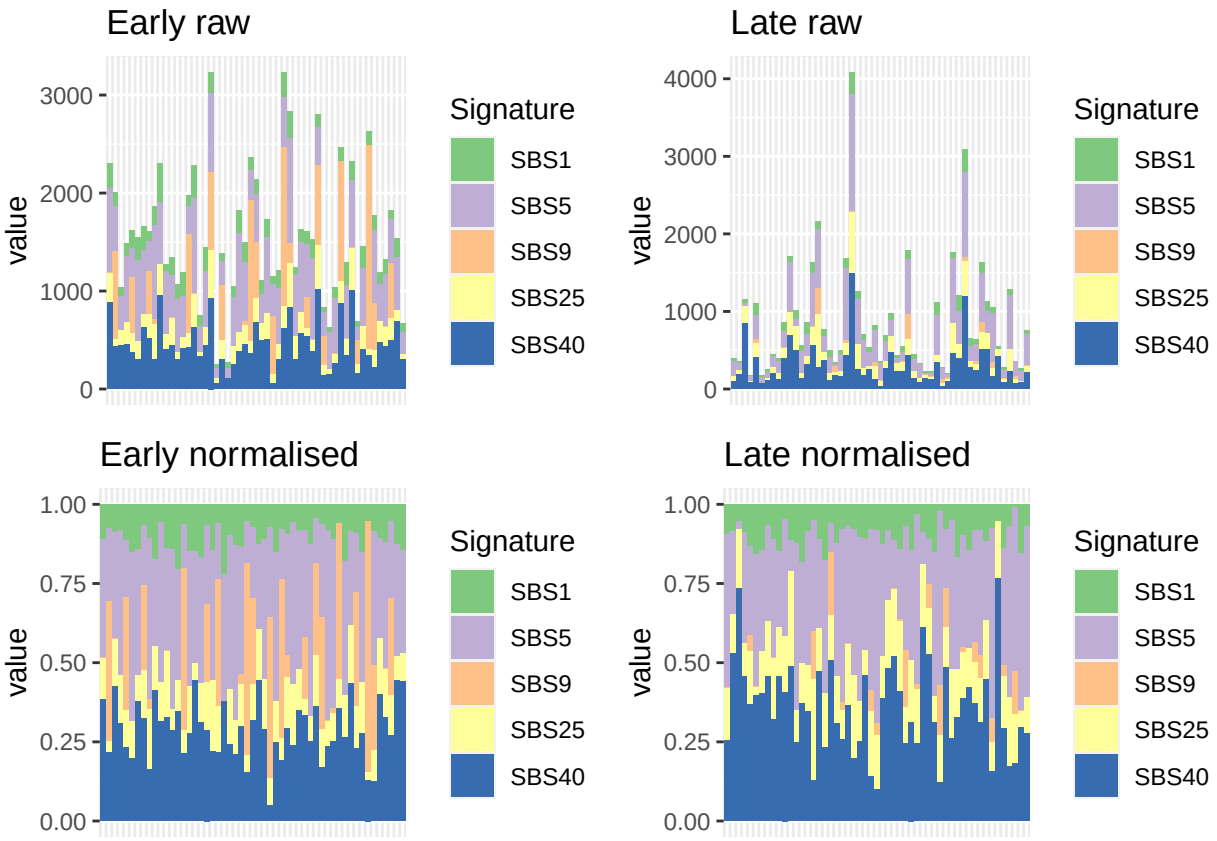


Lymph-CLL

Barplot and general statistics

```
## [1] 53
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 53
## Creating plot... it might take some time if the data are large. Number of samples: 53
## Creating plot... it might take some time if the data are large. Number of samples: 53
## Creating plot... it might take some time if the data are large. Number of samples: 53
```



The number of samples and signatures is:

```
## [1] 106   5
```

The signatures are:

```
## [1] "SBS1"  "SBS5"  "SBS9"  "SBS25" "SBS40"
```

Convergence table

We have converged results in most cases

```
##        value                                L2                  L1
## 1  Lymph-CLL    hessian_positivedefinite_bool             diagRE_M
## 2  Lymph-CLL    hessian_positivedefinite_bool              fullRE_M
## 3  Lymph-CLL    hessian_positivedefinite_bool           diagRE_DMDL
## 4  Lymph-CLL                           Timeout          fullRE_halfDM
## 5  Lymph-CLL hessian_nonpositivedefinite_bool           fullRE_DMDL
```

```
## 6  Lymph-CLL    hessian_positivedefinite_bool             diagRE_DMSL
## 7  Lymph-CLL    hessian_positivedefinite_bool           sparseRE_DMSL
## 8  Lymph-CLL hessian_nonpositivedefinite_bool             fullRE_DMSL
## 9  Lymph-CLL hessian_nonpositivedefinite_bool        fullRE_DMSL_SBS1
## 10 Lymph-CLL    hessian_positivedefinite_bool         fullRE_M_nonexo
## 11 Lymph-CLL    hessian_positivedefinite_bool      diagRE_DMSL_nonexo
## 12 Lymph-CLL                         Timeout    sparseRE_DMSL_nonexo
## 13 Lymph-CLL    hessian_positivedefinite_bool      fullRE_DMSL_nonexo
## 14 Lymph-CLL    hessian_positivedefinite_bool      fullRE_DMDL_nonexo
## 15 Lymph-CLL                         Timeout fullRE_DMDL_sortednonexo
```

Potentially problematic signatures

SBS9 has quite a lot of zeros.

```
colSums(obj_Lymph_CLL$Y == 0)/nrow(obj_Lymph_CLL$Y)
```

```
##        SBS1        SBS5        SBS9       SBS25       SBS40
## 0.000000000 0.028301887 0.613207547 0.009433962 0.000000000
```

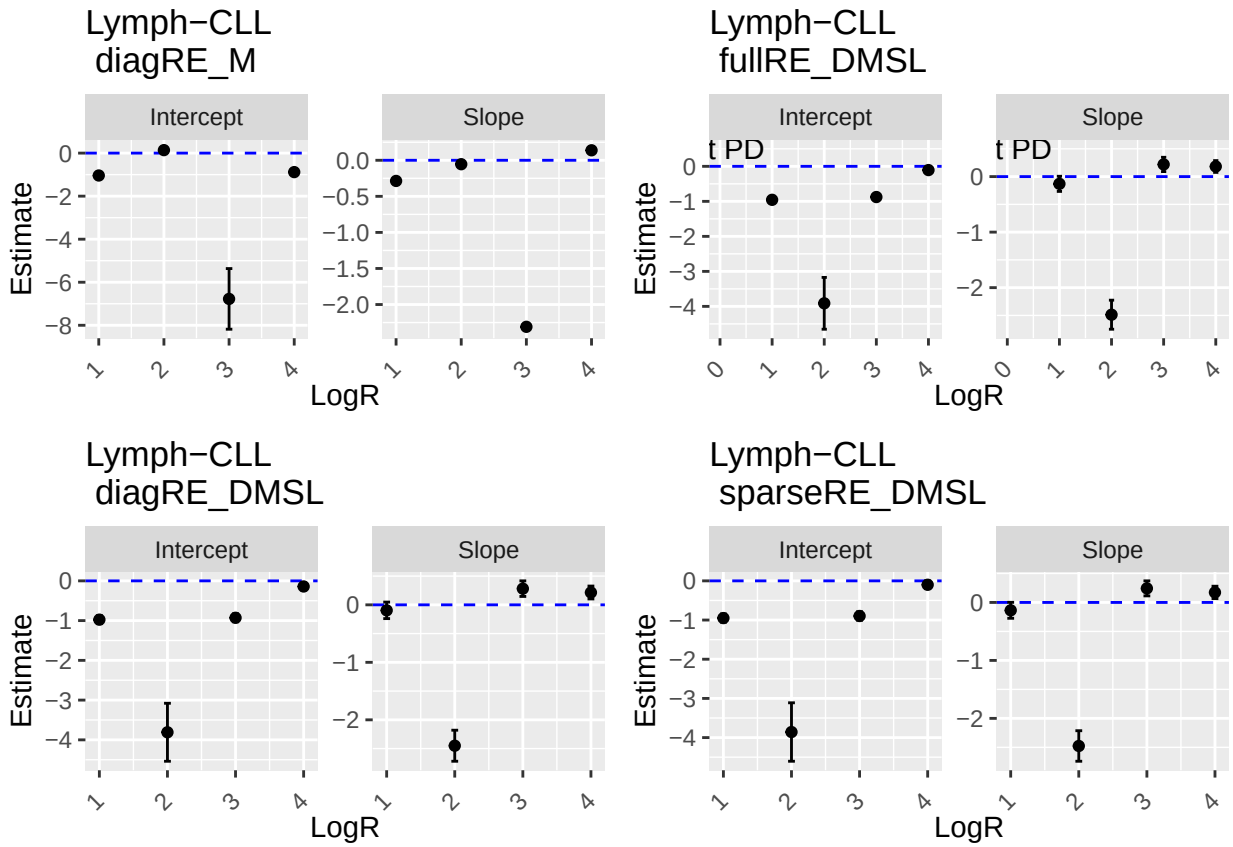
```
colSums(obj_Lymph_CLL$Y)/sum(obj_Lymph_CLL$Y)
```

```
##       SBS1       SBS5       SBS9      SBS25      SBS40
## 0.09712712 0.33726681 0.12275176 0.13805198 0.30480234
```

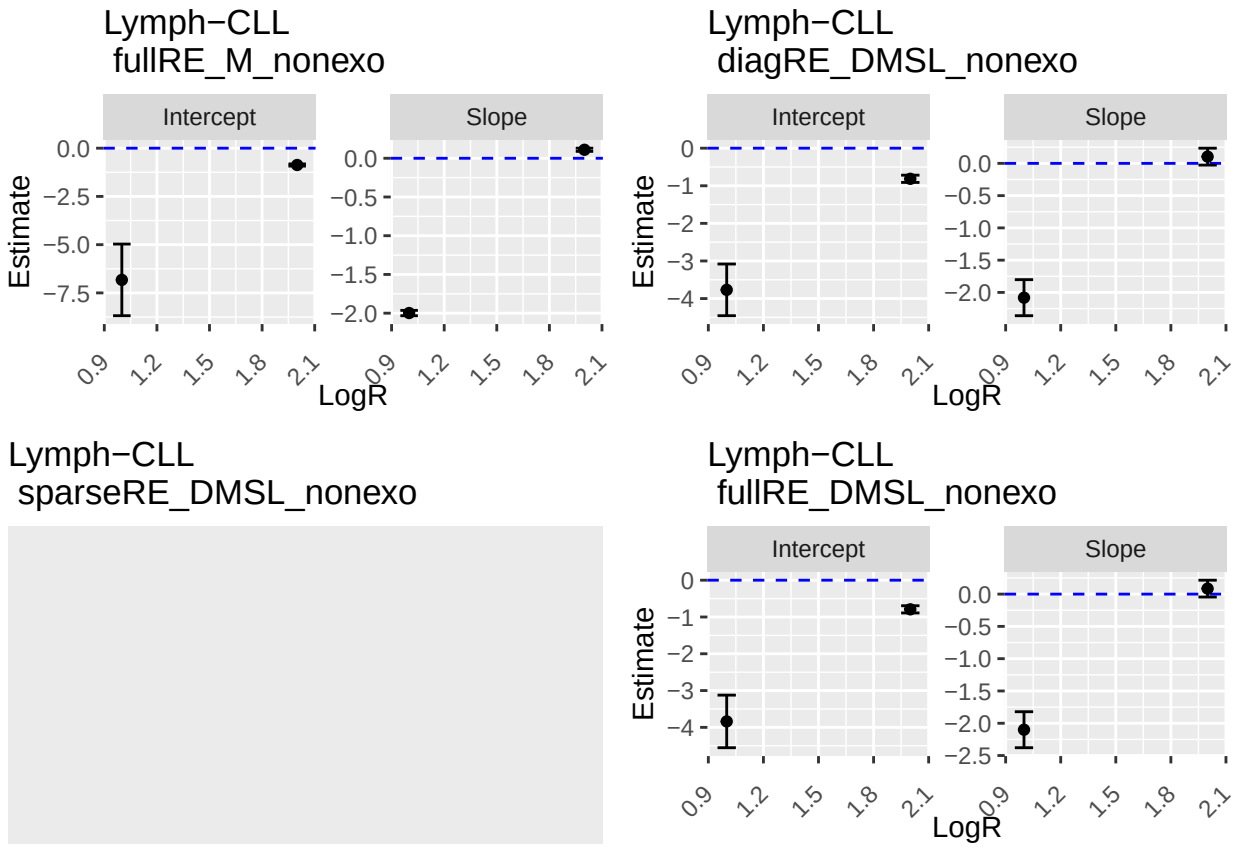
Betas

It's interesting the very high correlation between intercept and slope betas.

```
ct <- "Lymph-CLL"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```



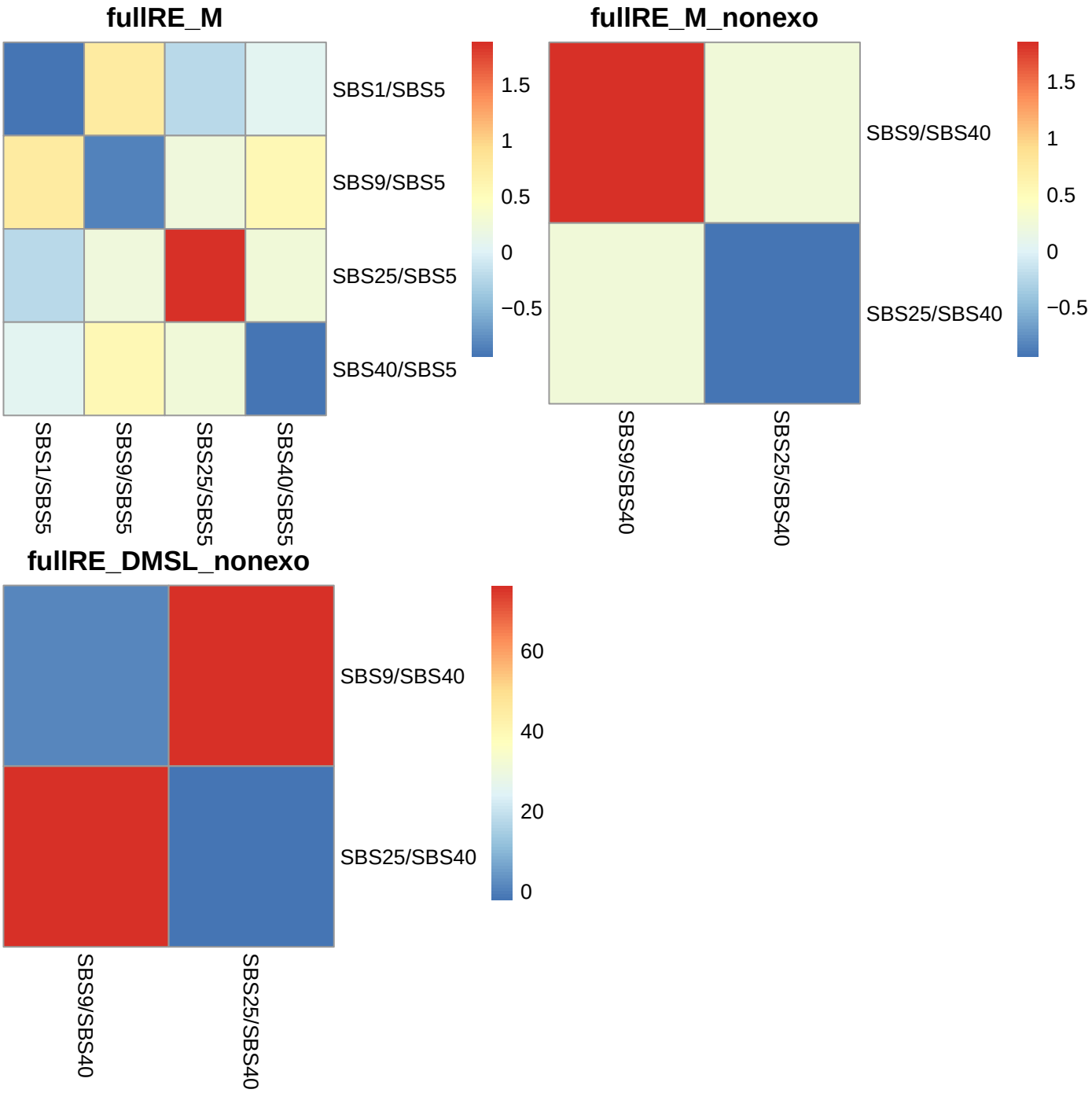

```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
  plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')),
  plot_betas(fullRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')), nrow=2)
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct

## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used

## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of $6.1779312 \times 10^{-14}$.

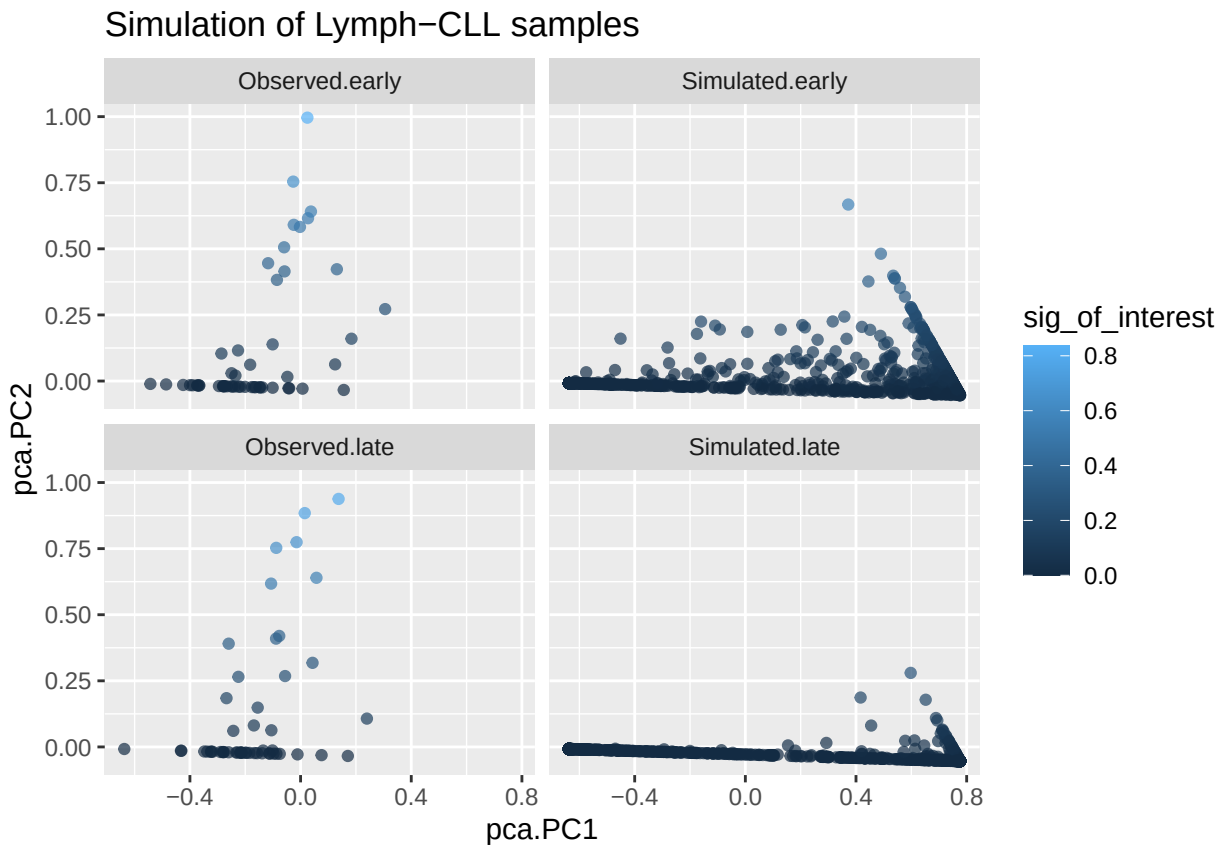
Covariance matrices



Simulation under inferred data

```
## [1] 53
```

```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```

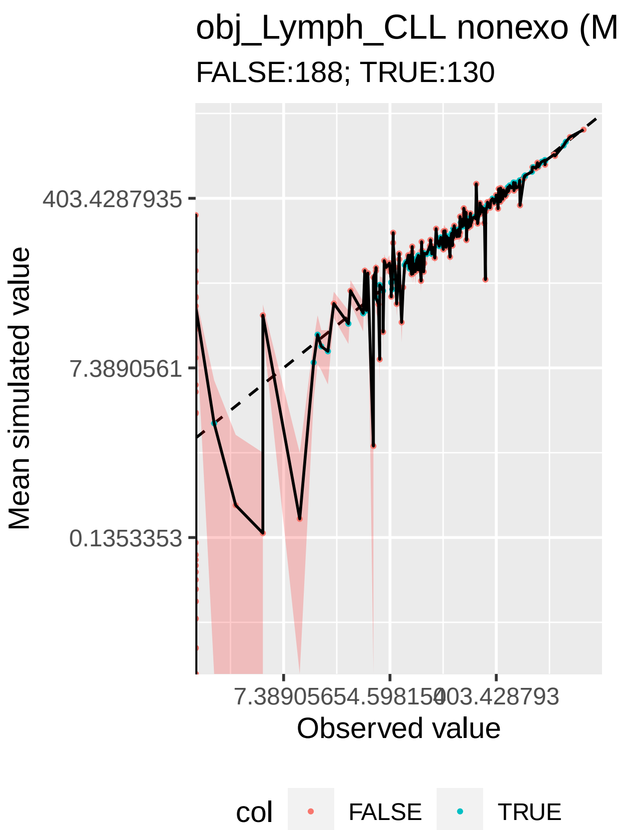


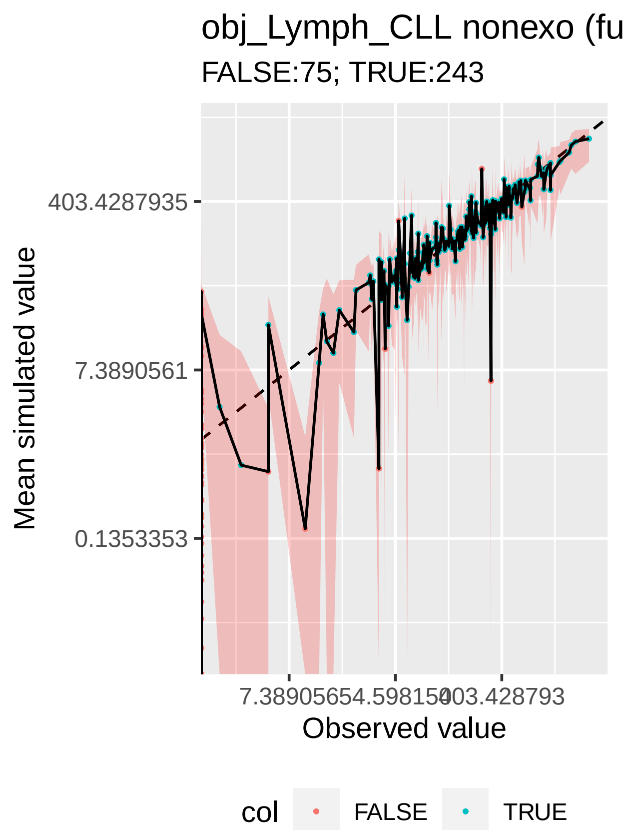
Ranked plot for coverage

```
ct <- "Lymph-CLL"
integer_overdispersion_param_DMSL <- 1
obj_Lymph_CLL_nonexo <- give_subset_sigs_TMBobj(obj_Lymph_CLL, sigs_to_remove = nonexogenous$V1)
for(loglog_bool_it in c(T,F)){
  .full_rankedplot <-    give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_
                   data_object = obj_Lymph_CLL_nonexo,
                   print_plot = F, nreps = 100, model = "DMSL", integer_overdispersion_param = integer_ov
                     lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                            rank_number=1:length(j)) )})[[1]],
                   data_object = obj_Lymph_CLL_nonexo,
              loglog = loglog_bool_it, title = 'obj_Lymph_CLL nonexo (fullRE DMSL)')
  grid.arrange(
    give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = fullRE_M_non
                   data_object = obj_Lymph_CLL_nonexo,
                   print_plot = F, nreps = 100, model = "M")), function(i){
                     lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                            rank_number=1:length(j)) )})[[1]],
                   data_object = obj_Lymph_CLL_nonexo,
                   loglog = loglog_bool_it, title = 'obj_Lymph_CLL nonexo (M)'),
    .full_rankedplot, ncol=2)

  grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = d
```

```
                    data_object = obj_Lymph_CLL_nonexo,
                    print_plot = F, nreps = 100, model = "DMSL",
                    integer_overdispersion_param = integer_overdispersion_param_DMSL)), function(i){
                      lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                             rank_number=1:length(j)) )})[[1]],
                    data_object = obj_Lymph_CLL_nonexo,
                    loglog = loglog_bool_it, title = 'obj_Lymph_CLL nonexo (diagRE DMSL)'),
                .full_rankedplot, ncol=2)

}
```

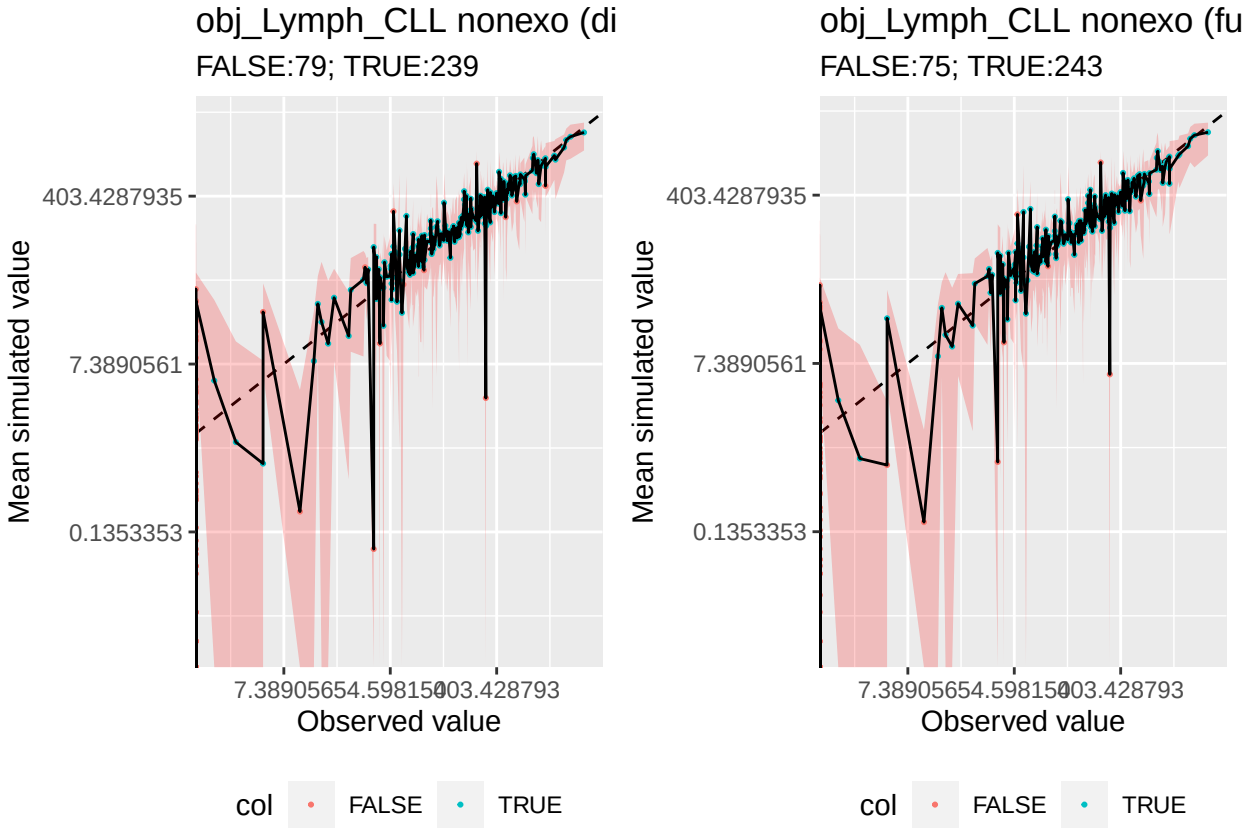
```
## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous x-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous x-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous x-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous x-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous x-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous x-axis
```

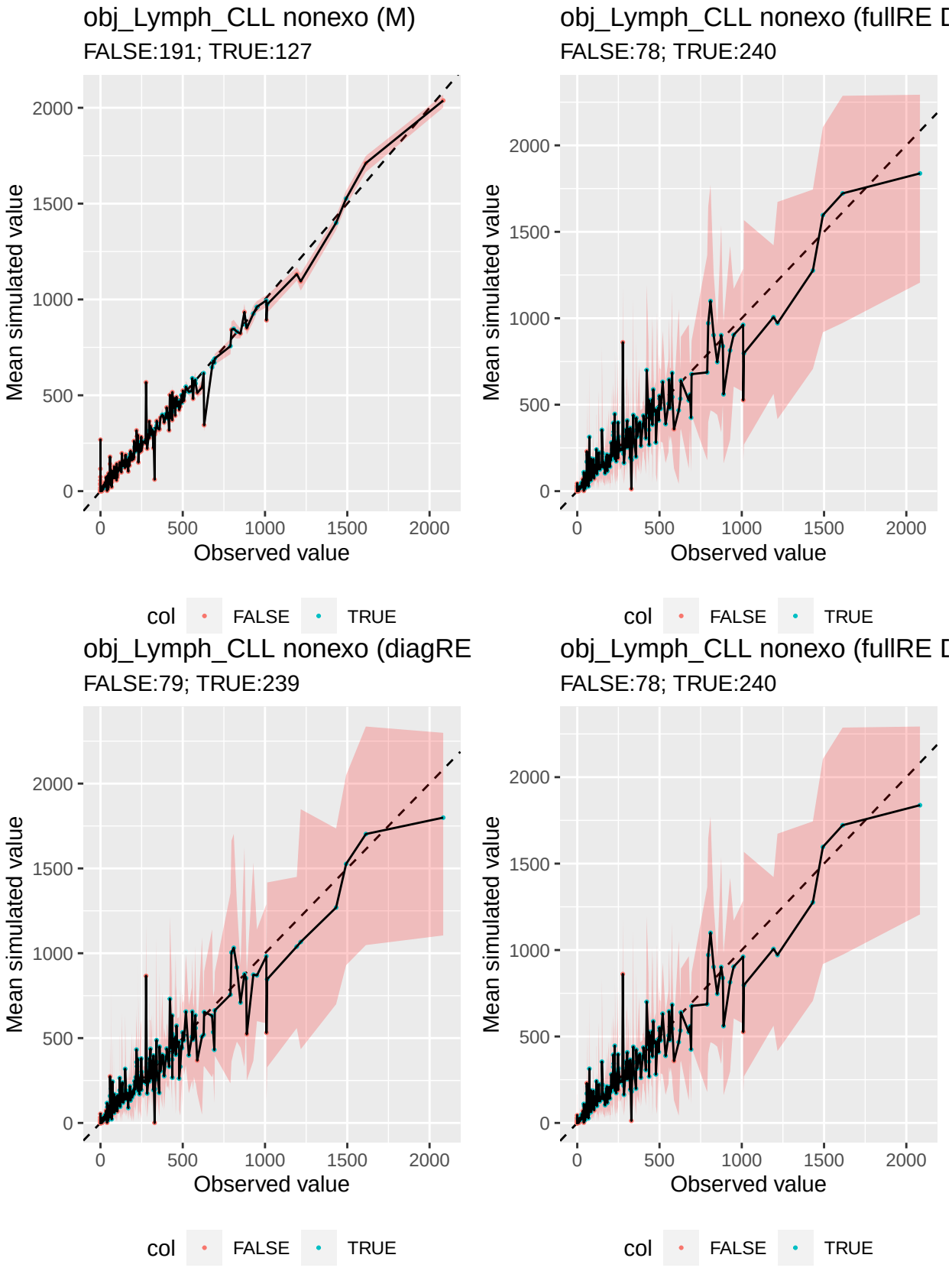





```
## Warning: Transformation introduced infinite values in continuous y-axis
## Warning: Transformation introduced infinite values in continuous y-axis
## Warning: Transformation introduced infinite values in continuous x-axis
## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis
## Warning: Transformation introduced infinite values in continuous x-axis
## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis
## Warning: Transformation introduced infinite values in continuous x-axis
## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis
## Warning: Transformation introduced infinite values in continuous x-axis
## Warning: Transformation introduced infinite values in continuous y-axis
```

```
## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous x-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous y-axis

## Warning: Transformation introduced infinite values in continuous x-axis
```




obj_Lymph_CLL nonexo (M)
FALSE:191; TRUE:127
obj_Lymph_CLL nonexo (fullRE D
FALSE:78; TRUE:240
obj_Lymph_CLL nonexo (diagRE
FALSE:79; TRUE:239
obj_Lymph_CLL nonexo (fullRE D
FALSE:78; TRUE:240
Mean simulated value
Observed value
0
500
1000
1500
2000
col
FALSE
TRUE

Signatures from mutSigExtractor

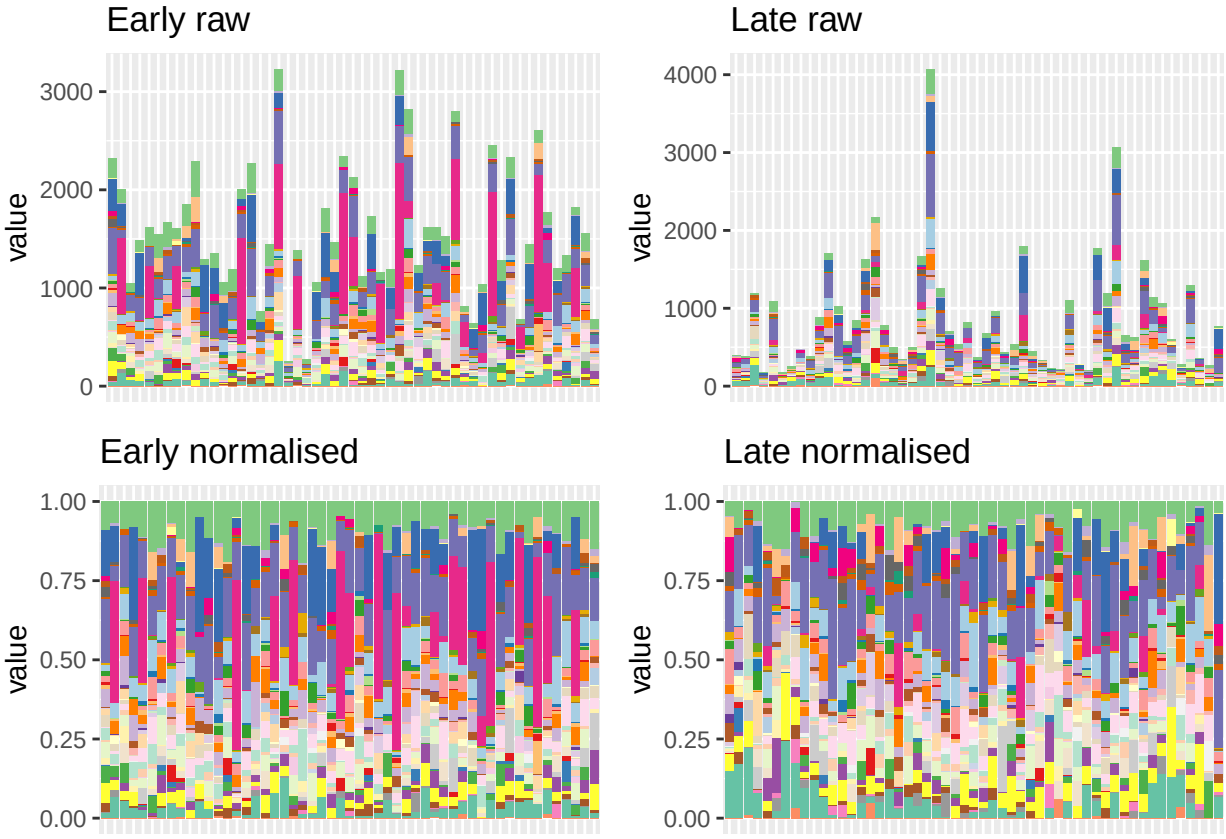
These are the signatures from mutSigExtractor:

```
obj_Lymph_CLL_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

```
## [1] 53
```

```
give_barplot_from_obj(obj = obj_Lymph_CLL_mutSigExtractor, legend_on = FALSE)
```

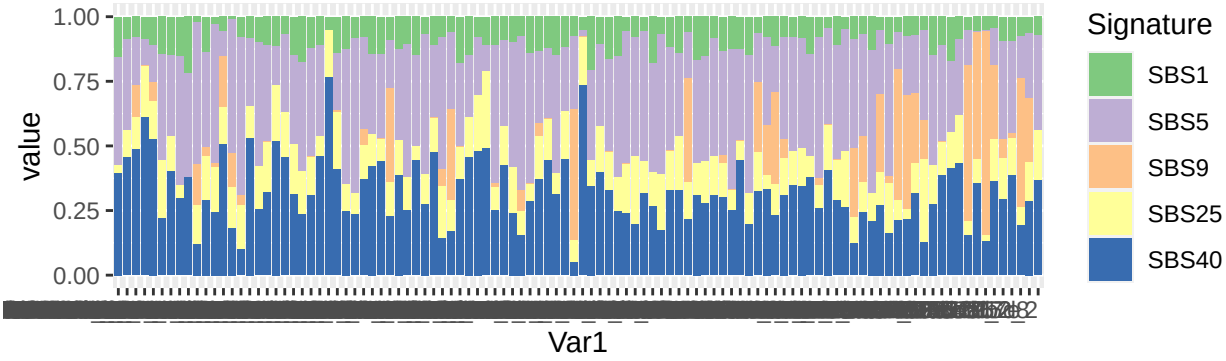
```
## Creating plot... it might take some time if the data are large. Number of samples: 53
## Creating plot... it might take some time if the data are large. Number of samples: 53
## Creating plot... it might take some time if the data are large. Number of samples: 53
## Creating plot... it might take some time if the data are large. Number of samples: 53
```



Exposures sorted by increasing number of mutations: SBS9 and SBS25 seem to be somewhat associated with samples with a high number of mutations.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Lymph_CLL$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Lymph_CLL$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 106
```

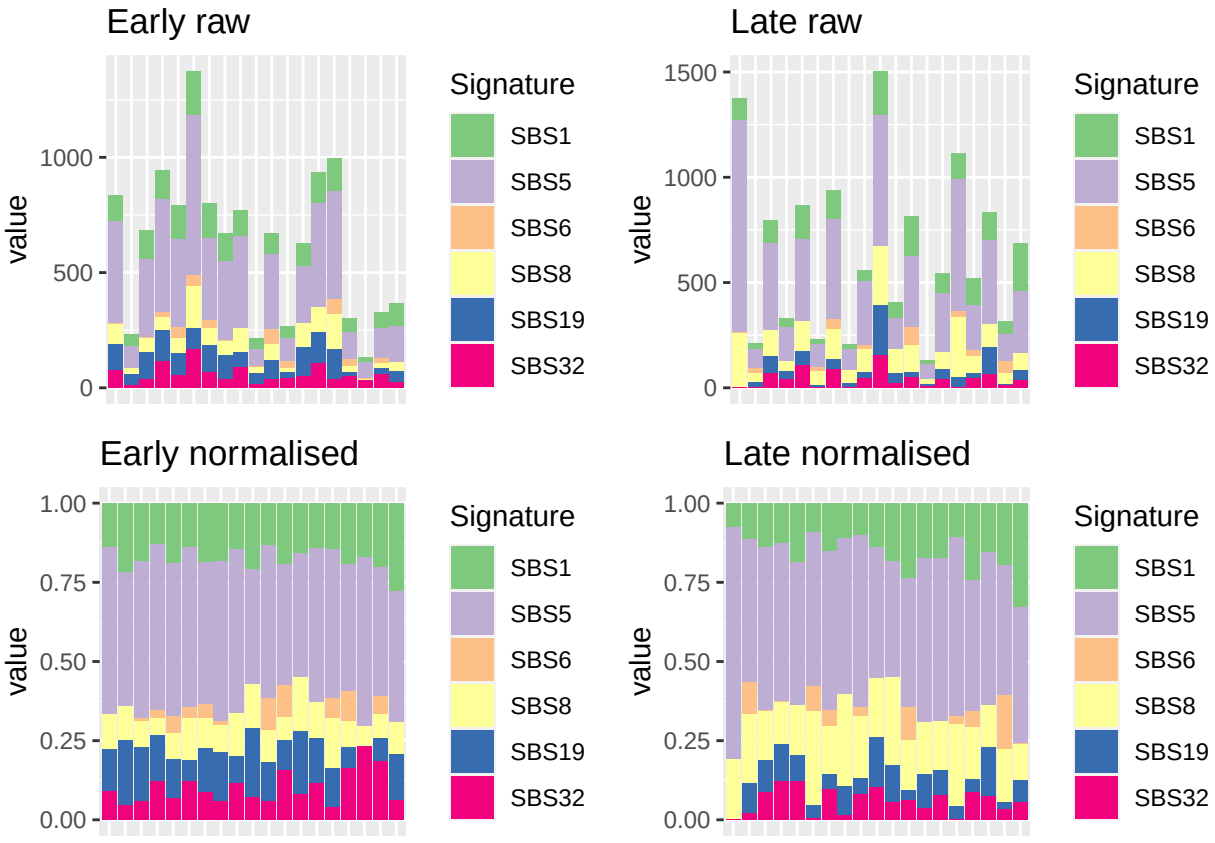


Myeloid-MPN

Barplot and general statistics

```
## [1] 19
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 19
## Creating plot... it might take some time if the data are large. Number of samples: 19
## Creating plot... it might take some time if the data are large. Number of samples: 19
## Creating plot... it might take some time if the data are large. Number of samples: 19
```



The number of samples and signatures is:

```
## [1] 38  6
```

The signatures are:

```
## [1] "SBS1"  "SBS5"  "SBS6"  "SBS8"  "SBS19" "SBS32"
```

Convergence table

These are the results for the convergence of models fits. The fullRE DMSL have not converged, or have not run.

```
##          value                                 L2                     L1
## 1  Myeloid-MPN    hessian_positivedefinite_bool                diagRE_M
## 2  Myeloid-MPN    hessian_positivedefinite_bool                fullRE_M
## 3  Myeloid-MPN    hessian_positivedefinite_bool             diagRE_DMDL
## 4  Myeloid-MPN                          Timeout            fullRE_halfDM
## 5  Myeloid-MPN hessian_nonpositivedefinite_bool              fullRE_DMDL
## 6  Myeloid-MPN    hessian_positivedefinite_bool              diagRE_DMSL
## 7  Myeloid-MPN    hessian_positivedefinite_bool            sparseRE_DMSL
## 8  Myeloid-MPN hessian_nonpositivedefinite_bool              fullRE_DMSL
## 9  Myeloid-MPN hessian_nonpositivedefinite_bool         fullRE_DMSL_SBS1
## 10 Myeloid-MPN    hessian_positivedefinite_bool          fullRE_M_nonexo
## 11 Myeloid-MPN    hessian_positivedefinite_bool       diagRE_DMSL_nonexo
## 12 Myeloid-MPN                          Timeout     sparseRE_DMSL_nonexo
## 13 Myeloid-MPN                          Timeout       fullRE_DMSL_nonexo
## 14 Myeloid-MPN    hessian_positivedefinite_bool       fullRE_DMDL_nonexo
## 15 Myeloid-MPN    hessian_positivedefinite_bool fullRE_DMDL_sortednonexo
```

Re-running of fitting

Using fullRE_M_nonexo to fit fullRE_DMSL_nonexo.

If we use the values of the fullRE M exo as initial values for the fullRE DMSL exo do converge:

```
## [1] TRUE
```

Potentially problematic signatures

We explore whether there are problematic signatures. There are none.

```
colSums(obj_Myeloid_MPN$Y == 0)/nrow(obj_Myeloid_MPN$Y)
```

```
##       SBS1       SBS5       SBS6       SBS8      SBS19      SBS32
## 0.00000000 0.00000000 0.50000000 0.00000000 0.05263158 0.05263158
```

```
colSums(obj_Myeloid_MPN$Y)/sum(obj_Myeloid_MPN$Y)
```

```
##       SBS1       SBS5       SBS6       SBS8      SBS19      SBS32
## 0.16009042 0.48849157 0.02737361 0.14488286 0.10098644 0.07817509
```

```
additional_sortedMnonexo[["Myeloid-MPN"]] <- sortedM_MyeloidMPN
additional_sortedDMSLnonexo[["Myeloid-MPN"]] <- sortedDM_MyeloidMPN
```

```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct
```

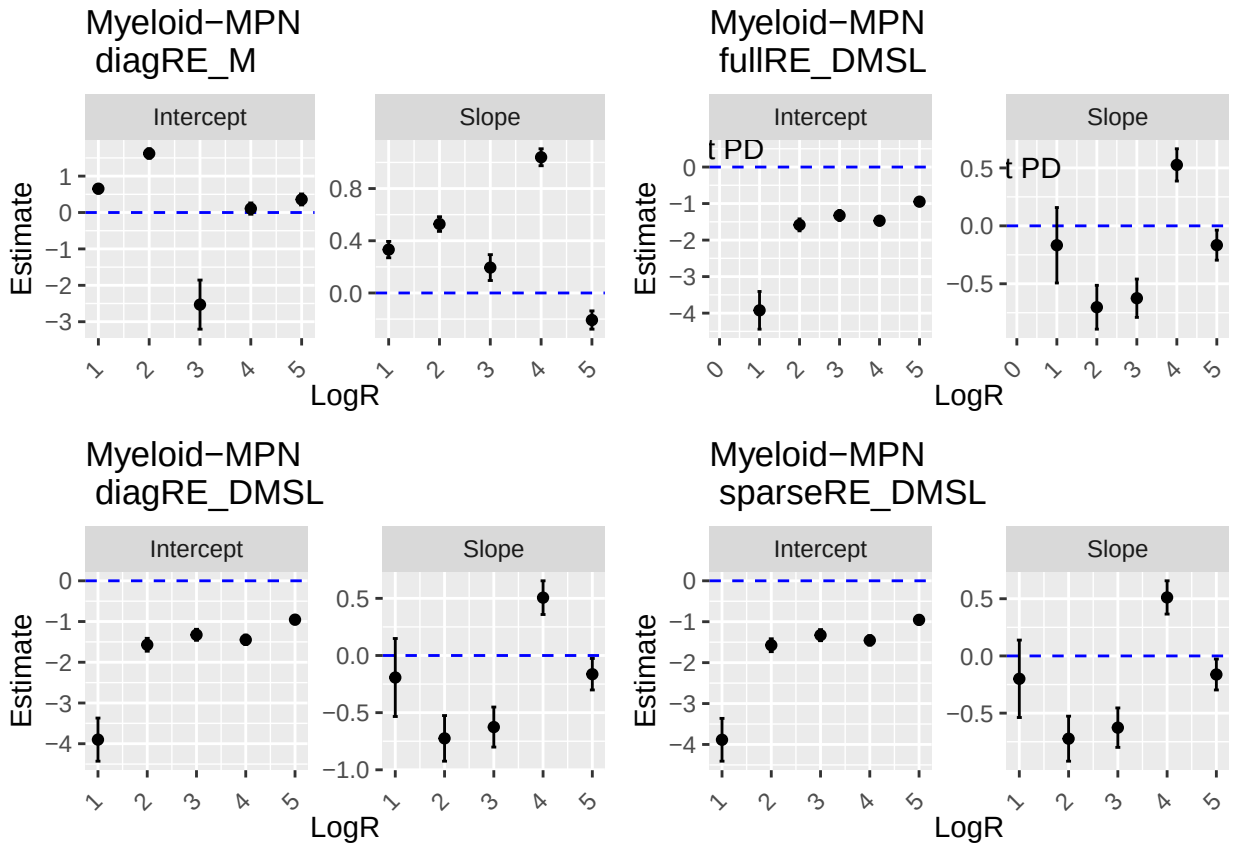
```
## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used
```

```
## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

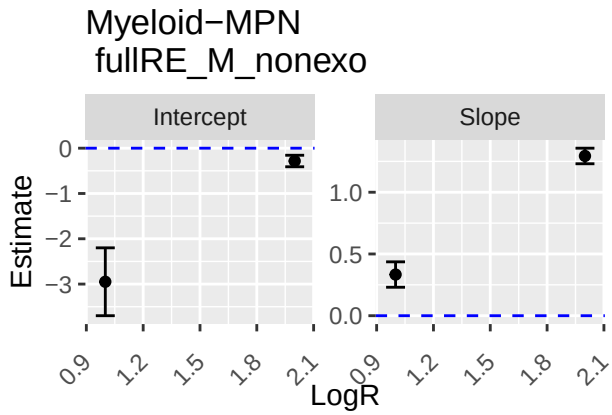
We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 1.367896×10^{-5}.

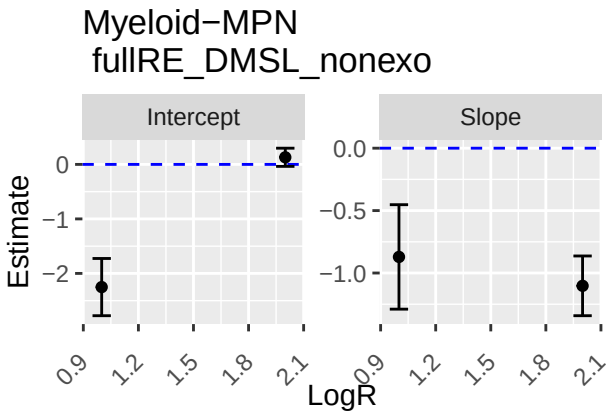
Betas

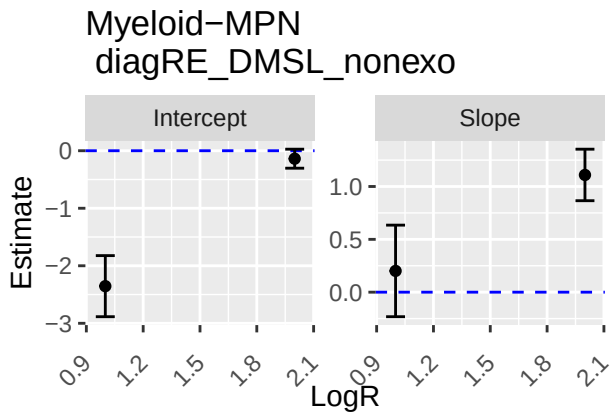
```
ct <- "Myeloid-MPN"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```



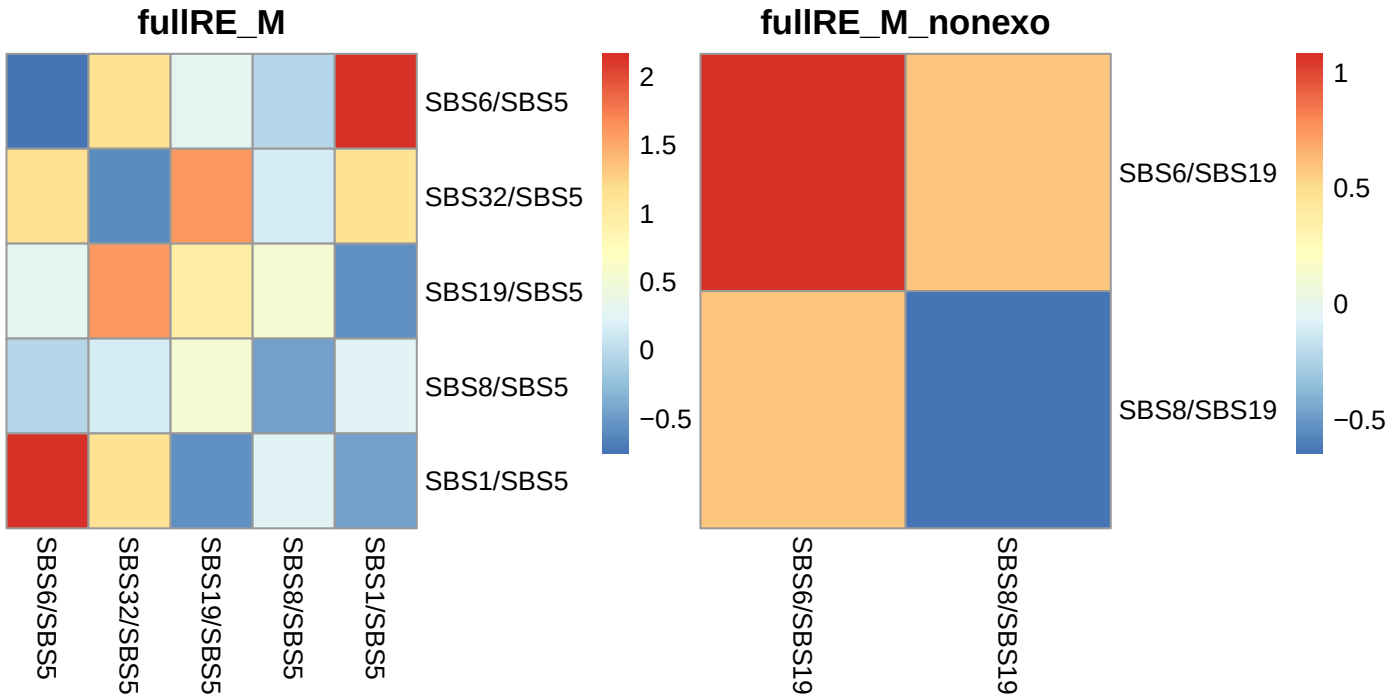

```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(sortedDM_MyeloidMPN)+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')), nrow=2)
```

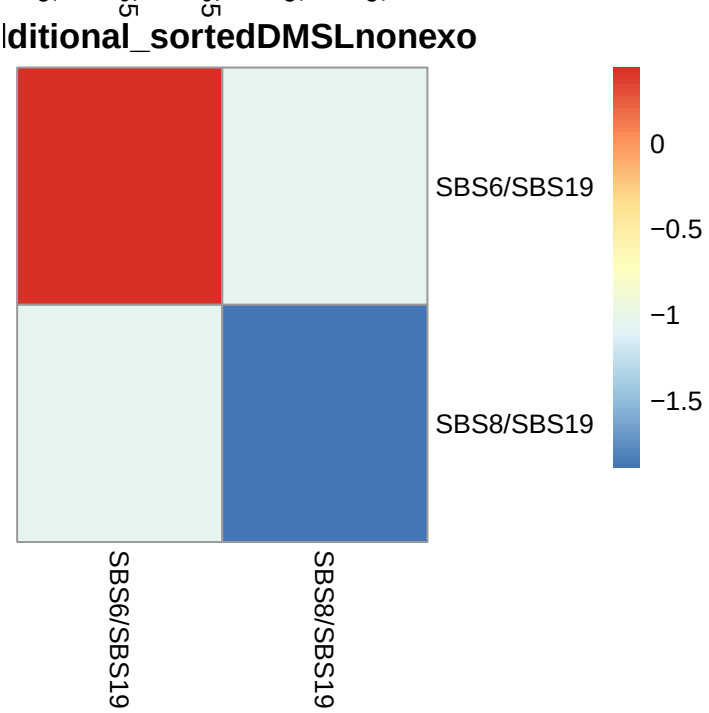

Myeloid−MPN
fullRE_M_nonexo
Intercept
Slope
Estimate
LogR


Myeloid−MPN
fullRE_DMSL_nonexo
Intercept
Slope
Estimate
LogR


Myeloid−MPN
diagRE_DMSL_nonexo
Intercept
Slope
Estimate
LogR

Covariance matrices

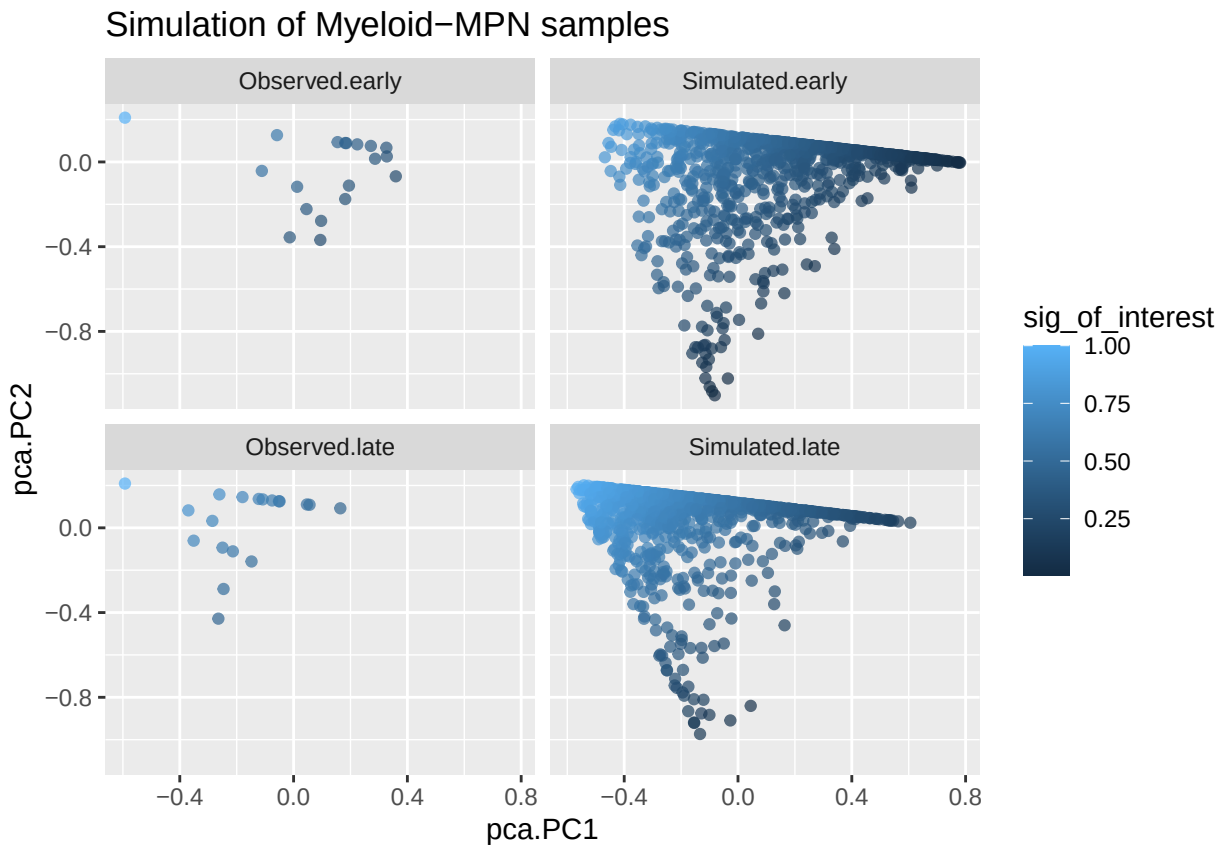




Simulation under inferred data

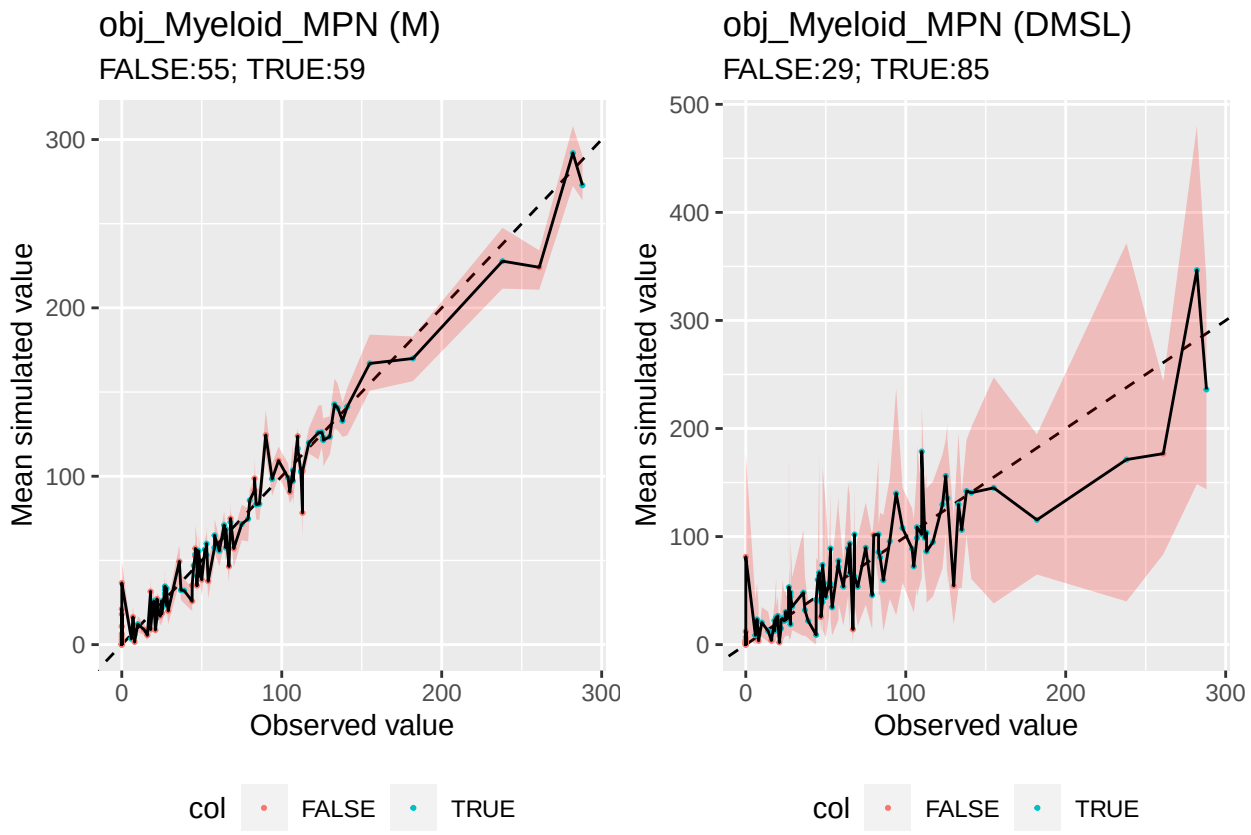
```
## [1] 19
```

```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```



Ranked plot for coverage

```
ct <- "Myeloid-MPN"
integer_overdispersion_param_DMSL <- 1
obj_Myeloid_MPN_nonexo <- (give_subset_sigs_TMBobj(obj_Myeloid_MPN, sigs_to_remove = nonexogenous$V1))
obj_Myeloid_MPN_nonexo_sorted <- sort_columns_TMB(give_subset_sigs_TMBobj(obj_Myeloid_MPN, sigs_to_remove
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                data_object = obj_Myeloid_MPN_nonexo,
                print_plot = F, nreps = 20, model = "M")), function(i){
                  lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                         rank_number=1:length(j)) )})[[1]],
                data_object = obj_Myeloid_MPN_nonexo,
                loglog = F, title = 'obj_Myeloid_MPN (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = sortedDM_Myeloi
                data_object = obj_Myeloid_MPN_nonexo_sorted,
                print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                  lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                         rank_number=1:length(j)) )})[[1]],
                data_object = obj_Myeloid_MPN_nonexo_sorted,
           loglog = F, title = 'obj_Myeloid_MPN (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

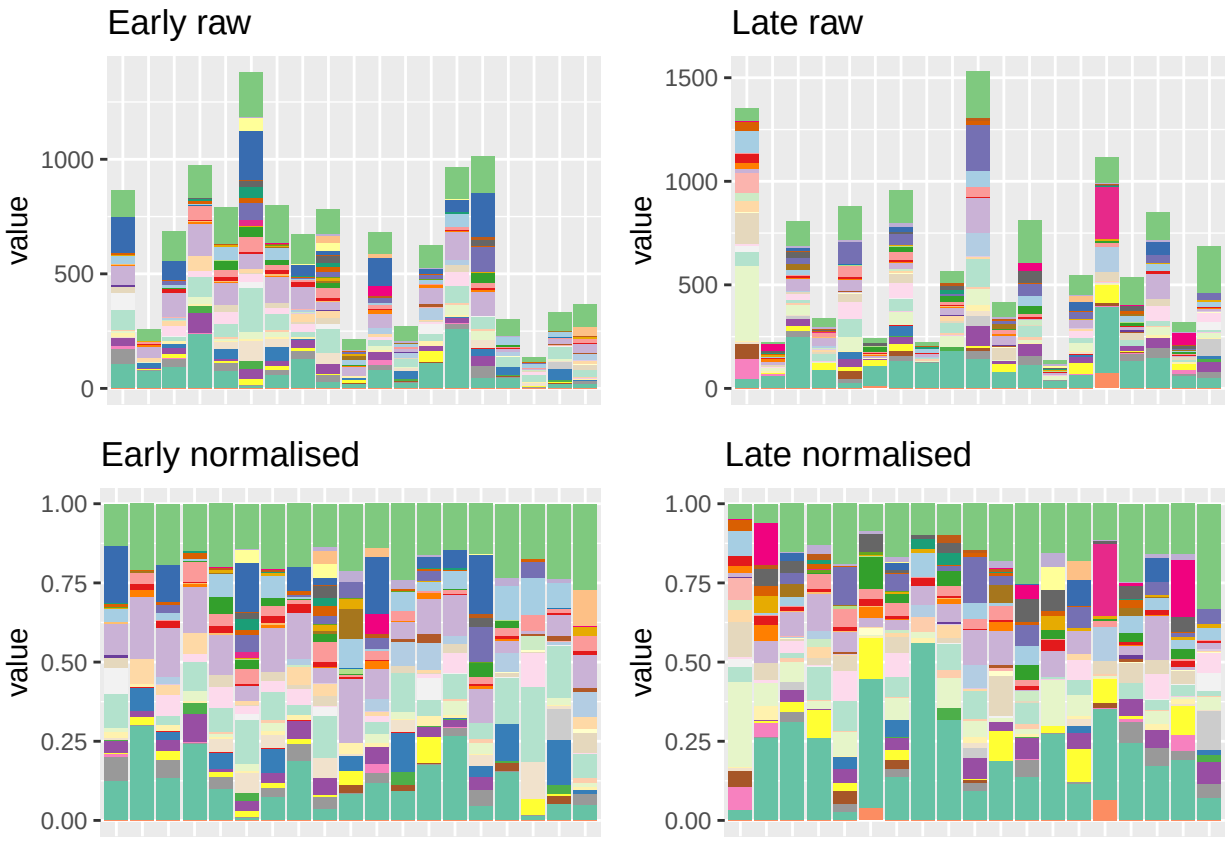
```
obj_Myeloid_MPN_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                   path_to_data = "../../data/")
```

```
## [1] 19
```

```
give_barplot_from_obj(obj = obj_Myeloid_MPN_mutSigExtractor, legend_on = FALSE)
```

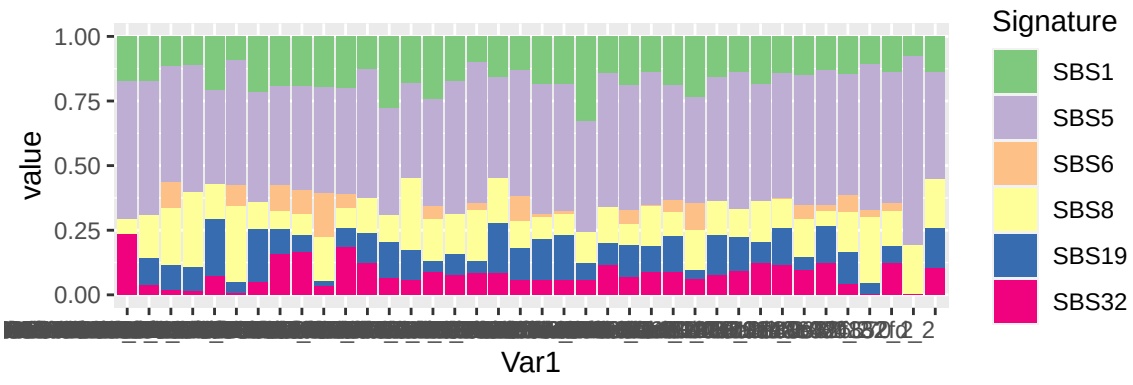
```
## Creating plot... it might take some time if the data are large. Number of samples: 19
## Creating plot... it might take some time if the data are large. Number of samples: 19
## Creating plot... it might take some time if the data are large. Number of samples: 19
## Creating plot... it might take some time if the data are large. Number of samples: 19
```

```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.

```
## Creating plot... it might take some time if the data are large. Number of samples: 38
```



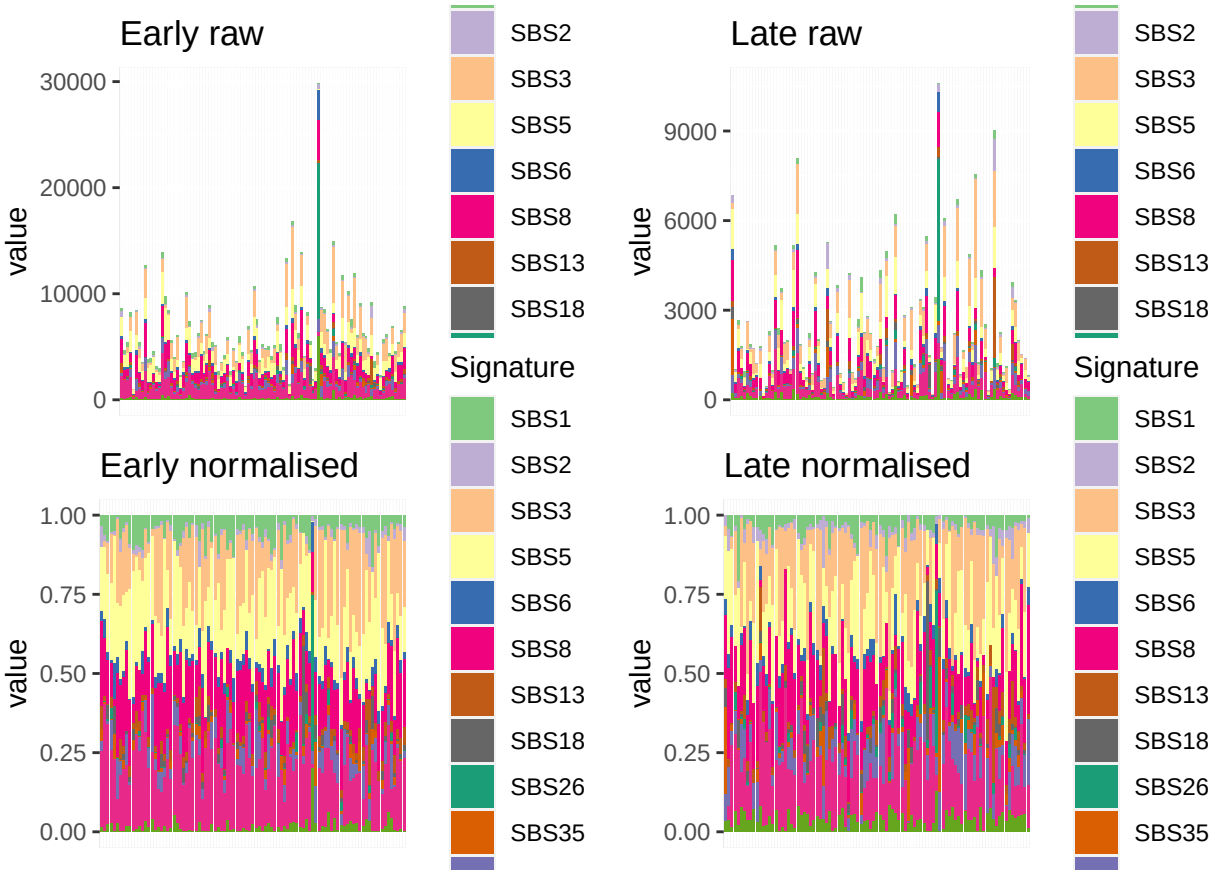
Ovary-AdenoCA

Barplot and general statistics

```
## [1] 97
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 97
## Creating plot... it might take some time if the data are large. Number of samples: 97
## Creating plot... it might take some time if the data are large. Number of samples: 97
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 97
```



The number of samples and signatures is:

```
## [1] 194  13
```

The signatures are:

```
##  [1] "SBS1"  "SBS2"  "SBS3"  "SBS5"  "SBS6"  "SBS8"  "SBS13" "SBS18" "SBS26"
## [10] "SBS35" "SBS39" "SBS40" "SBS41"
```

Convergence table

These are the results for the convergence of models fits. None of the all-signatures models converged (we do have many signatures!) but nonexo generally have, except fullRE_DMSL_nonexo.

```
##            value                                L2                 L1
## 1  Ovary-AdenoCA    hessian_positivedefinite_bool            diagRE_M
## 2  Ovary-AdenoCA hessian_nonpositivedefinite_bool            fullRE_M
## 3  Ovary-AdenoCA hessian_nonpositivedefinite_bool         diagRE_DMDL
## 4  Ovary-AdenoCA                          Timeout        fullRE_halfDM
## 5  Ovary-AdenoCA hessian_nonpositivedefinite_bool         fullRE_DMDL
## 6  Ovary-AdenoCA hessian_nonpositivedefinite_bool         diagRE_DMSL
## 7  Ovary-AdenoCA    hessian_positivedefinite_bool        sparseRE_DMSL
## 8  Ovary-AdenoCA    hessian_positivedefinite_bool         fullRE_DMSL
## 9  Ovary-AdenoCA    hessian_positivedefinite_bool    fullRE_DMSL_SBS1
```

```
## 10 Ovary-AdenoCA    hessian_positivedefinite_bool          fullRE_M_nonexo
## 11 Ovary-AdenoCA    hessian_positivedefinite_bool       diagRE_DMSL_nonexo
## 12 Ovary-AdenoCA    hessian_positivedefinite_bool     sparseRE_DMSL_nonexo
## 13 Ovary-AdenoCA hessian_nonpositivedefinite_bool       fullRE_DMSL_nonexo
## 14 Ovary-AdenoCA hessian_nonpositivedefinite_bool       fullRE_DMDL_nonexo
## 15 Ovary-AdenoCA                          Timeout fullRE_DMDL_sortednonexo
```

Re-running of fitting

Using fullRE_M_nonexo to fit fullRE_DMSL_nonexo.

If we use the values of the fullRE M exo as initial values for the fullRE DMSL exo do not yet converge:

```
## [1] FALSE
```

Potentially problematic signatures

We explore whether there are problematic signatures. There doesn't seem to be.

```
colSums(obj_Ovary_AdenoCA$Y == 0)/nrow(obj_Ovary_AdenoCA$Y)
```

```
##       SBS1       SBS2       SBS3       SBS5       SBS6       SBS8      SBS13
## 0.02061856 0.04639175 0.15463918 0.04639175 0.11855670 0.01546392 0.04123711
##      SBS18      SBS26      SBS35      SBS39      SBS40      SBS41
## 0.36597938 0.64432990 0.35567010 0.16494845 0.07216495 0.19587629
```

```
colSums(obj_Ovary_AdenoCA$Y)/sum(obj_Ovary_AdenoCA$Y)
```

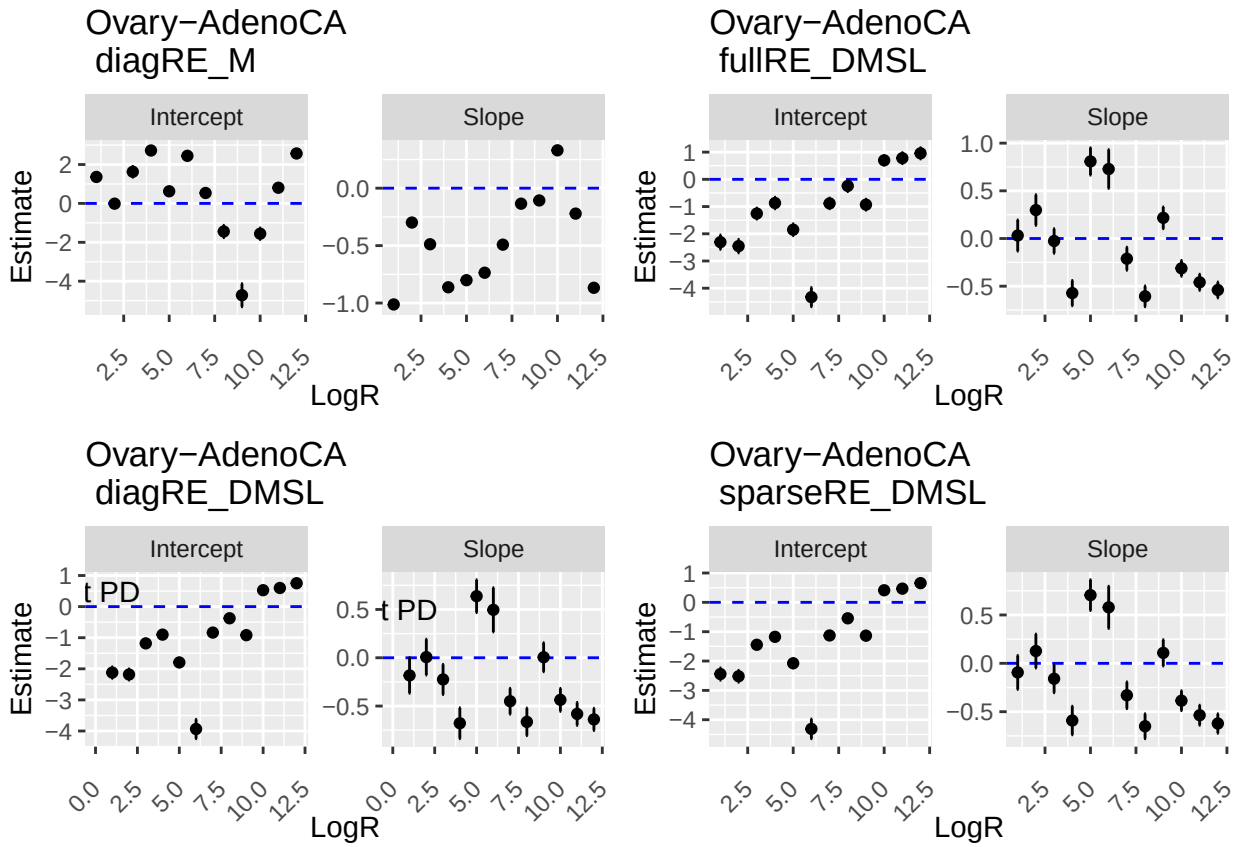
```
##       SBS1       SBS2       SBS3       SBS5       SBS6       SBS8      SBS13
## 0.04443406 0.01997521 0.18513114 0.18242339 0.02948011 0.16654912 0.03420887
##      SBS18      SBS26      SBS35      SBS39      SBS40      SBS41
## 0.01553666 0.03041662 0.01913467 0.06447749 0.17833631 0.02989634
```

Betas

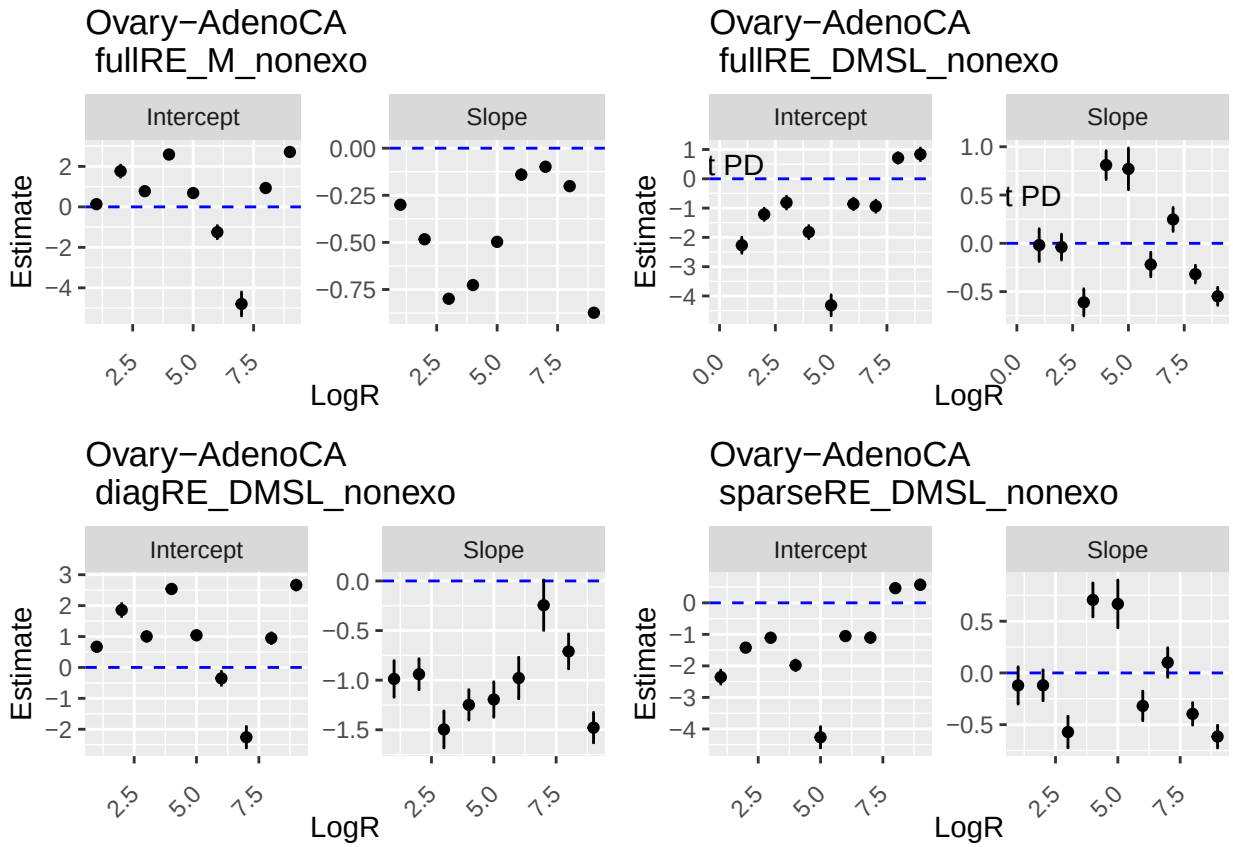
```
ct <- "Ovary-AdenoCA"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

```
## Warning in sqrt(as.numeric(object$diag.cov.random)): NaNs produced
```



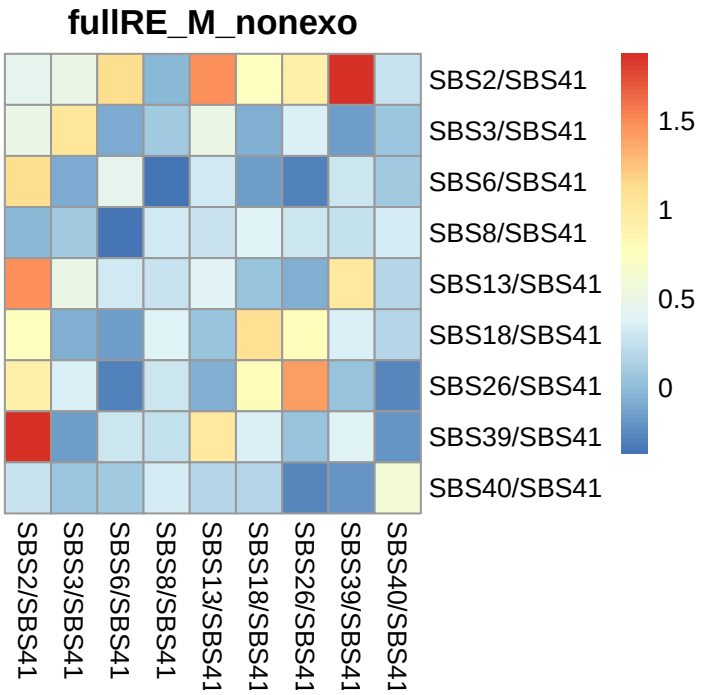

```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(sortedDM_OvaryAdenoCA)+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct

## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used

## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of $2.6852565 \times 10^{-28}$.

Covariance matrices



Keep in mind that fullRE DMSL nonexo has not converged.

Simulation under inferred data

Using diagRE DMSL nonexo.

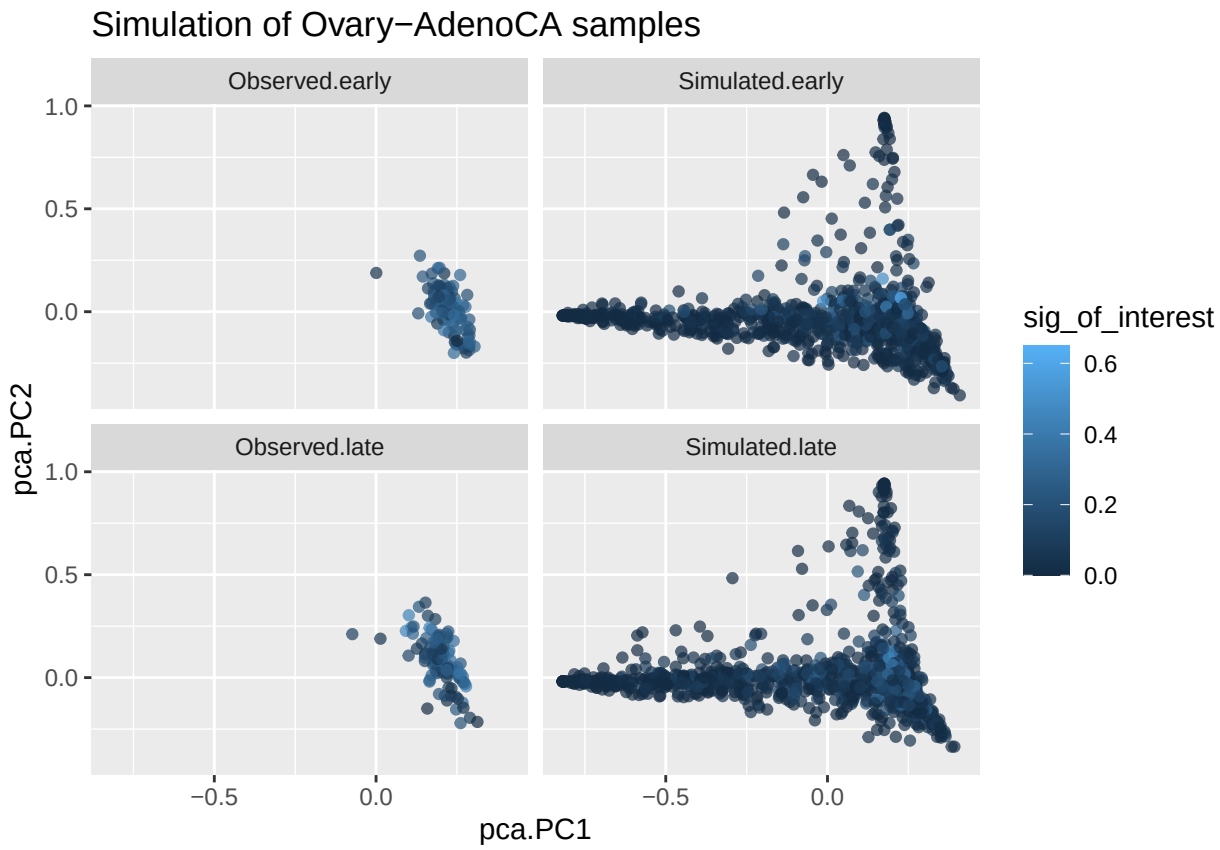
```
## [1] 97
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```

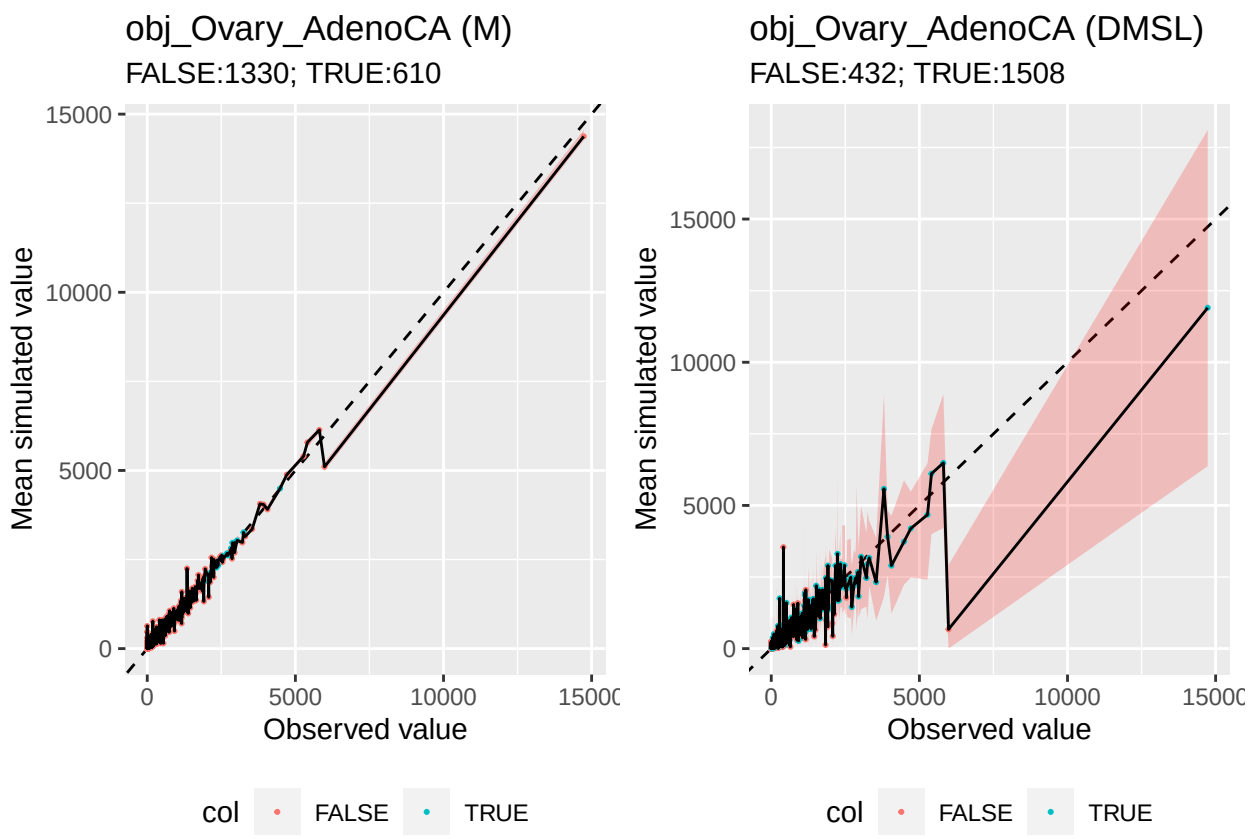
```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```



Ranked plot for coverage

```
ct <- "Ovary-AdenoCA"
integer_overdispersion_param_DMSL <- 1
obj_Ovary_AdenoCA_nonexo <- give_subset_sigs_TMBobj(obj_Ovary_AdenoCA, sigs_to_remove = nonexogenous$V1)
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                  data_object = obj_Ovary_AdenoCA_nonexo,
                  print_plot = F, nreps = 20, model = "M")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Ovary_AdenoCA_nonexo,
                  loglog = F, title = 'obj_Ovary_AdenoCA (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = diagRE_DMSL_nor
                  data_object = obj_Ovary_AdenoCA_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Ovary_AdenoCA_nonexo,
            loglog = F, title = 'obj_Ovary_AdenoCA (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

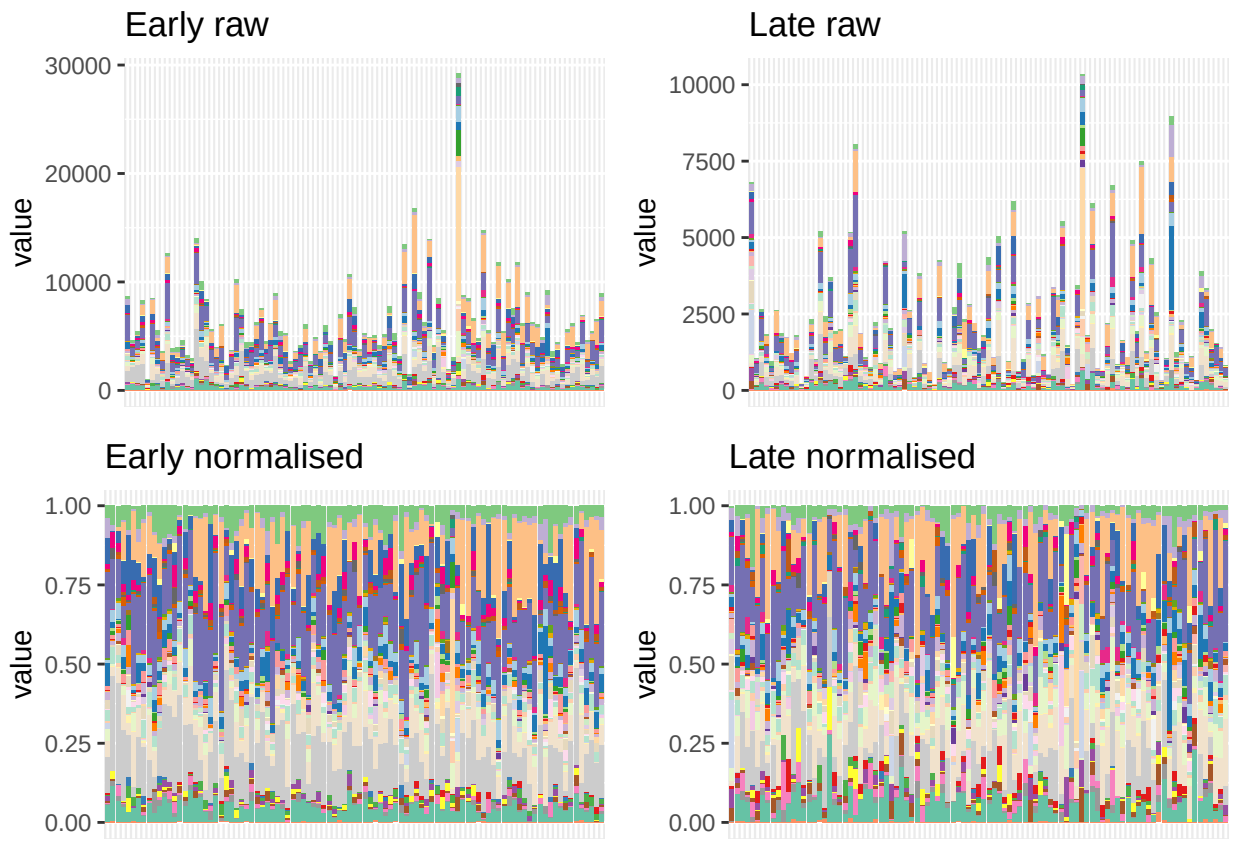
```
obj_Ovary_AdenoCA_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

```
## [1] 97
```

```
give_barplot_from_obj(obj = obj_Ovary_AdenoCA_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 97
## Creating plot... it might take some time if the data are large. Number of samples: 97
## Creating plot... it might take some time if the data are large. Number of samples: 97
## Creating plot... it might take some time if the data are large. Number of samples: 97
```

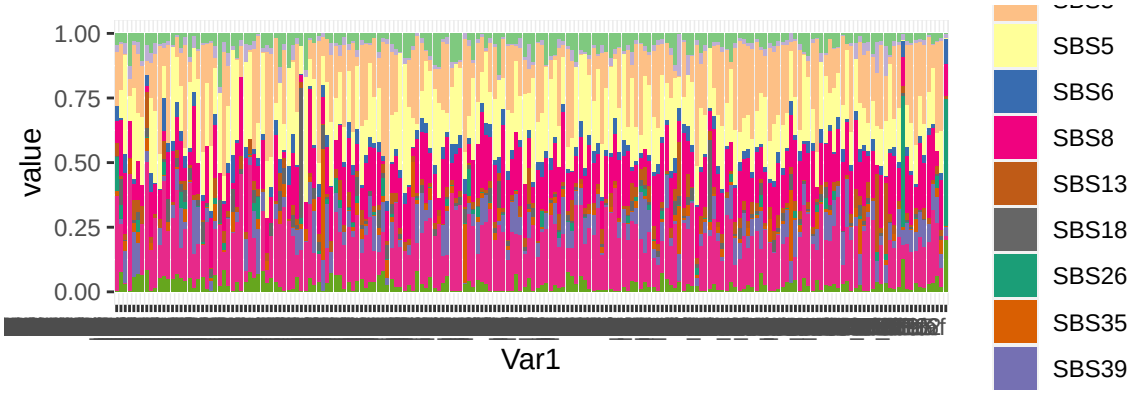
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Ovary_AdenoCA$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Ovary_AdenoCA$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 194
```

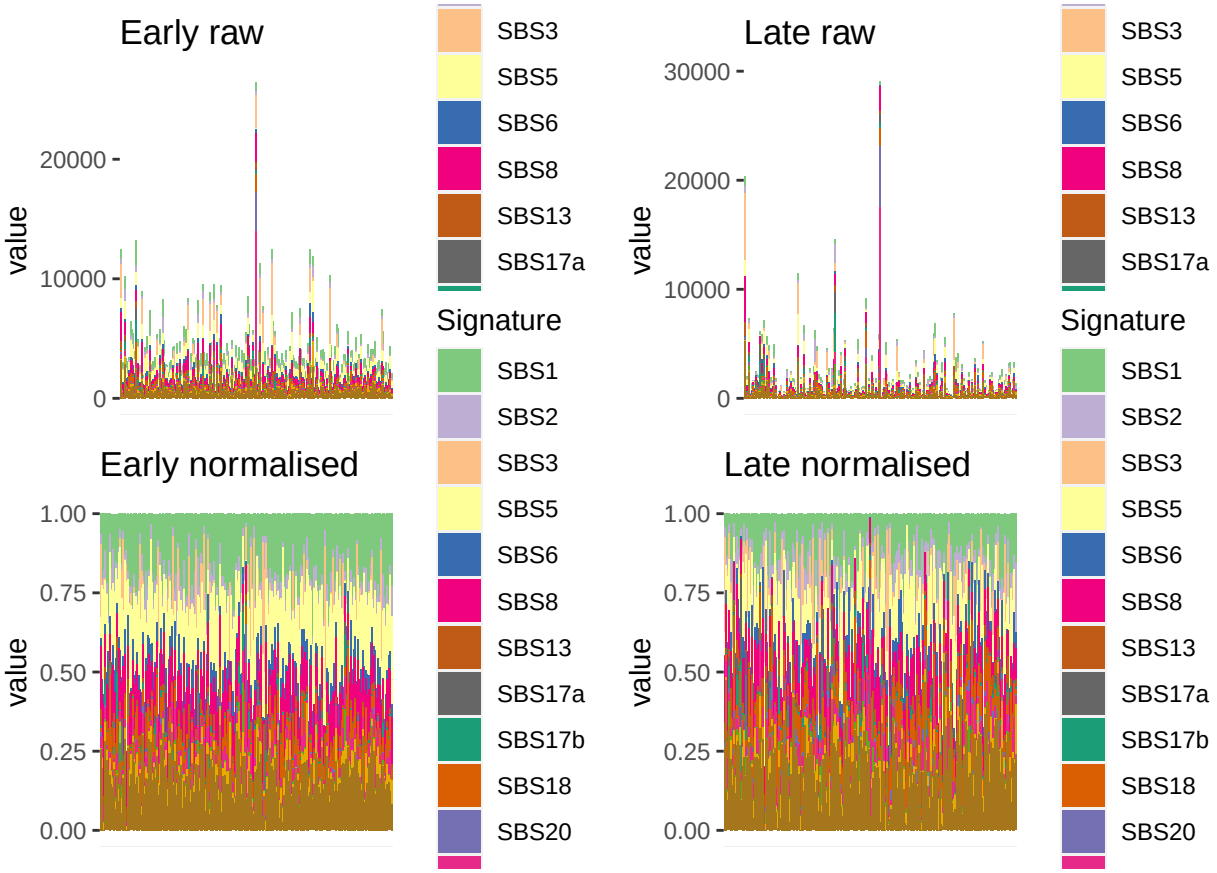


Panc-AdenoCA

Barplot and general statistics

```
## [1] 193
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 193
## Creating plot... it might take some time if the data are large. Number of samples: 193
## Creating plot... it might take some time if the data are large. Number of samples: 193
## Creating plot... it might take some time if the data are large. Number of samples: 193
```



The number of samples and signatures is:

```
## [1] 386  15
```

The signatures are:

```
##  [1] "SBS1"   "SBS2"   "SBS3"   "SBS5"   "SBS6"   "SBS8"   "SBS13"  "SBS17a"
##  [9] "SBS17b" "SBS18"  "SBS20"  "SBS26"  "SBS28"  "SBS30"  "SBS40"
```

Convergence table

These are the results for the convergence of models fits. Most runs have converged. fullRE_DMSL_nonexo hadn't run.

```
##           value                                L2                 L1
## 1  Panc-AdenoCA    hessian_positivedefinite_bool          diagRE_M
## 2  Panc-AdenoCA hessian_nonpositivedefinite_bool          fullRE_M
```

```
## 3  Panc-AdenoCA hessian_nonpositivedefinite_bool             diagRE_DMDL
## 4  Panc-AdenoCA                           Timeout            fullRE_halfDM
## 5  Panc-AdenoCA hessian_nonpositivedefinite_bool             fullRE_DMDL
## 6  Panc-AdenoCA    hessian_positivedefinite_bool             diagRE_DMSL
## 7  Panc-AdenoCA    hessian_positivedefinite_bool           sparseRE_DMSL
## 8  Panc-AdenoCA hessian_nonpositivedefinite_bool             fullRE_DMSL
## 9  Panc-AdenoCA hessian_nonpositivedefinite_bool        fullRE_DMSL_SBS1
## 10 Panc-AdenoCA    hessian_positivedefinite_bool         fullRE_M_nonexo
## 11 Panc-AdenoCA    hessian_positivedefinite_bool       diagRE_DMSL_nonexo
## 12 Panc-AdenoCA    hessian_positivedefinite_bool     sparseRE_DMSL_nonexo
## 13 Panc-AdenoCA                           Timeout       fullRE_DMSL_nonexo
## 14 Panc-AdenoCA hessian_nonpositivedefinite_bool       fullRE_DMDL_nonexo
## 15 Panc-AdenoCA    hessian_positivedefinite_bool fullRE_DMDL_sortednonexo
```

Re-running of fitting

Using fullRE_M_nonexo to fit fullRE_DMSL_nonexo. M hasn't converged.

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

Potentially problematic signatures

We explore whether there are problematic signatures. SBS17a is potentially problematic.

```
colSums(obj_Panc_AdenoCA$Y == 0)/nrow(obj_Panc_AdenoCA$Y)
```

```
##        SBS1        SBS2        SBS3        SBS5        SBS6        SBS8
## 0.000000000 0.012953368 0.634715026 0.051813472 0.069948187 0.005181347
##       SBS13      SBS17a      SBS17b       SBS18       SBS20       SBS26
## 0.036269430 0.575129534 0.183937824 0.093264249 0.647668394 0.134715026
##       SBS28       SBS30       SBS40
## 0.409326425 0.124352332 0.023316062
```

```
colSums(obj_Panc_AdenoCA$Y)/sum(obj_Panc_AdenoCA$Y)
```

```
##        SBS1        SBS2        SBS3        SBS5        SBS6        SBS8
## 0.146510755 0.044043854 0.068370611 0.164694624 0.043276473 0.126954041
##       SBS13      SBS17a      SBS17b       SBS18       SBS20       SBS26
## 0.035397768 0.009365890 0.021818955 0.052439007 0.011446261 0.054377412
##       SBS28       SBS30       SBS40
## 0.008232467 0.029313201 0.183758680
```

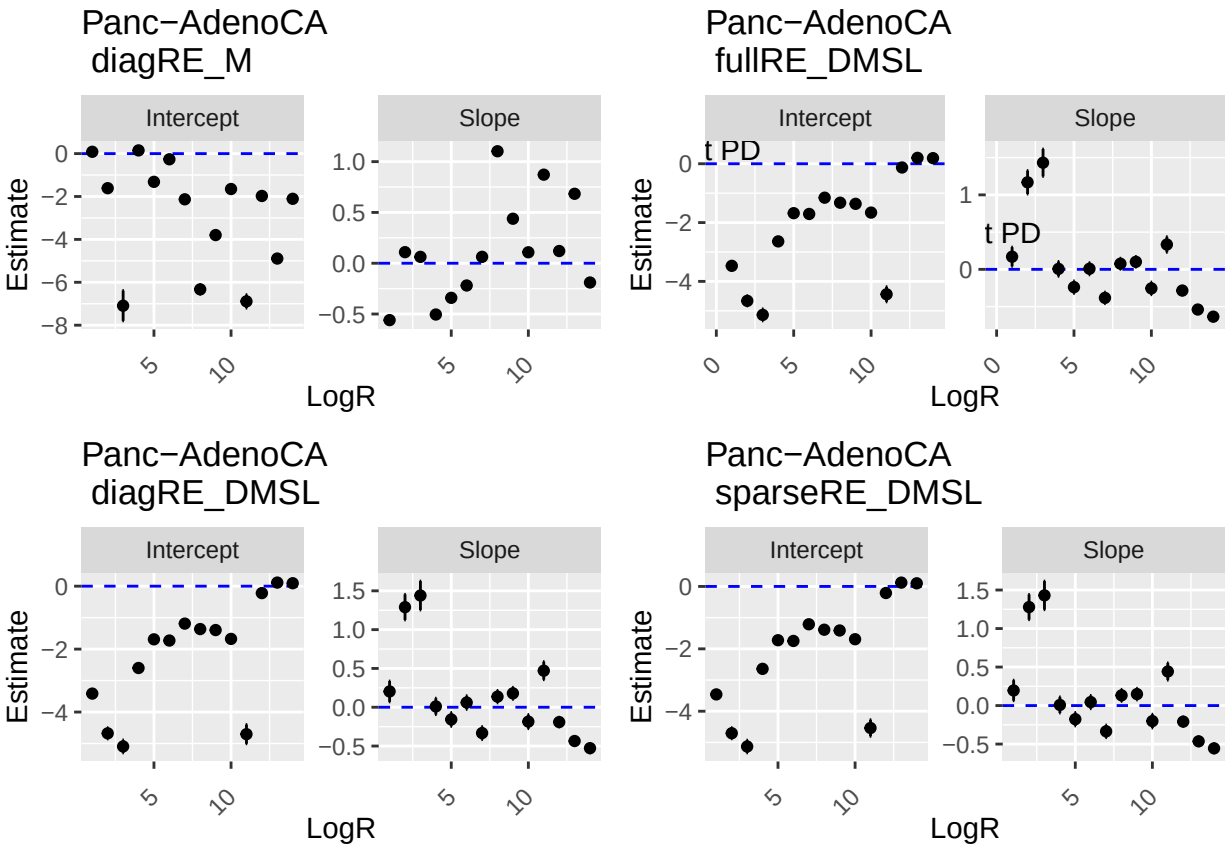
From the violin plot, none seem too problematic.

```
ggplot(melt(obj_Panc_AdenoCA$Y), aes(x=Var2, y=value+1))+geom_violin()+scale_y_continuous(trans = "log2")
```

Betas

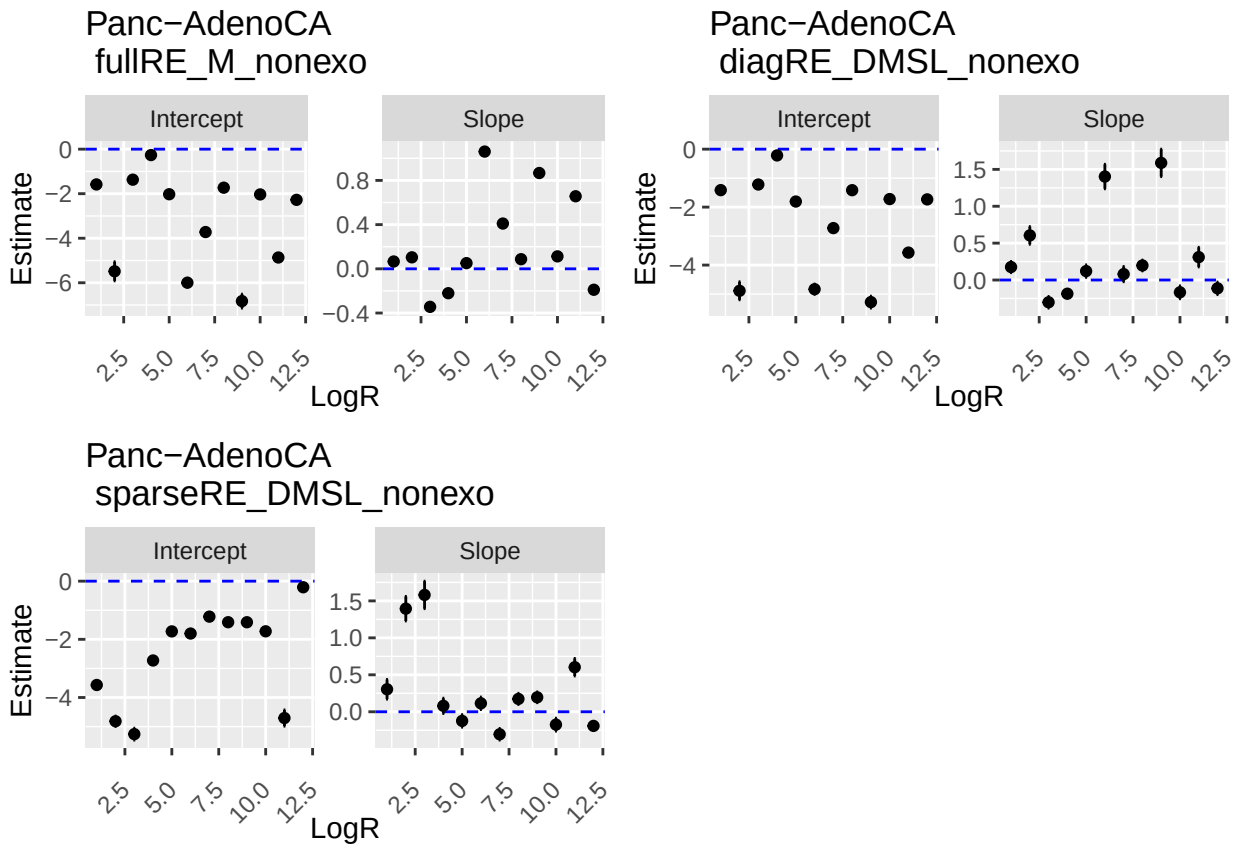
```
ct <- "Panc-AdenoCA"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```




```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
```

```
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```



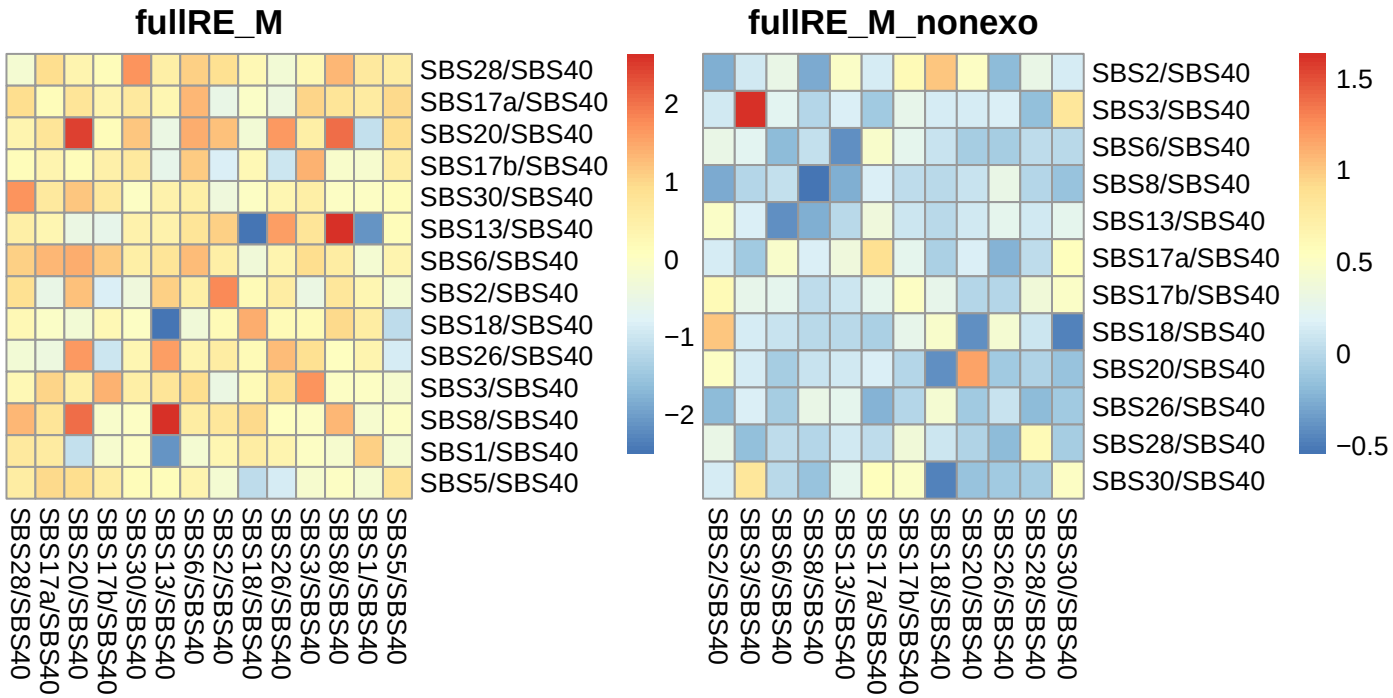

```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct
```

```
## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used
```

```
## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of $6.8710408 \times 10^{-46}$.

Covariance matrices



Simulation under inferred data

That's not a good simulation, using diagRE DMSL!

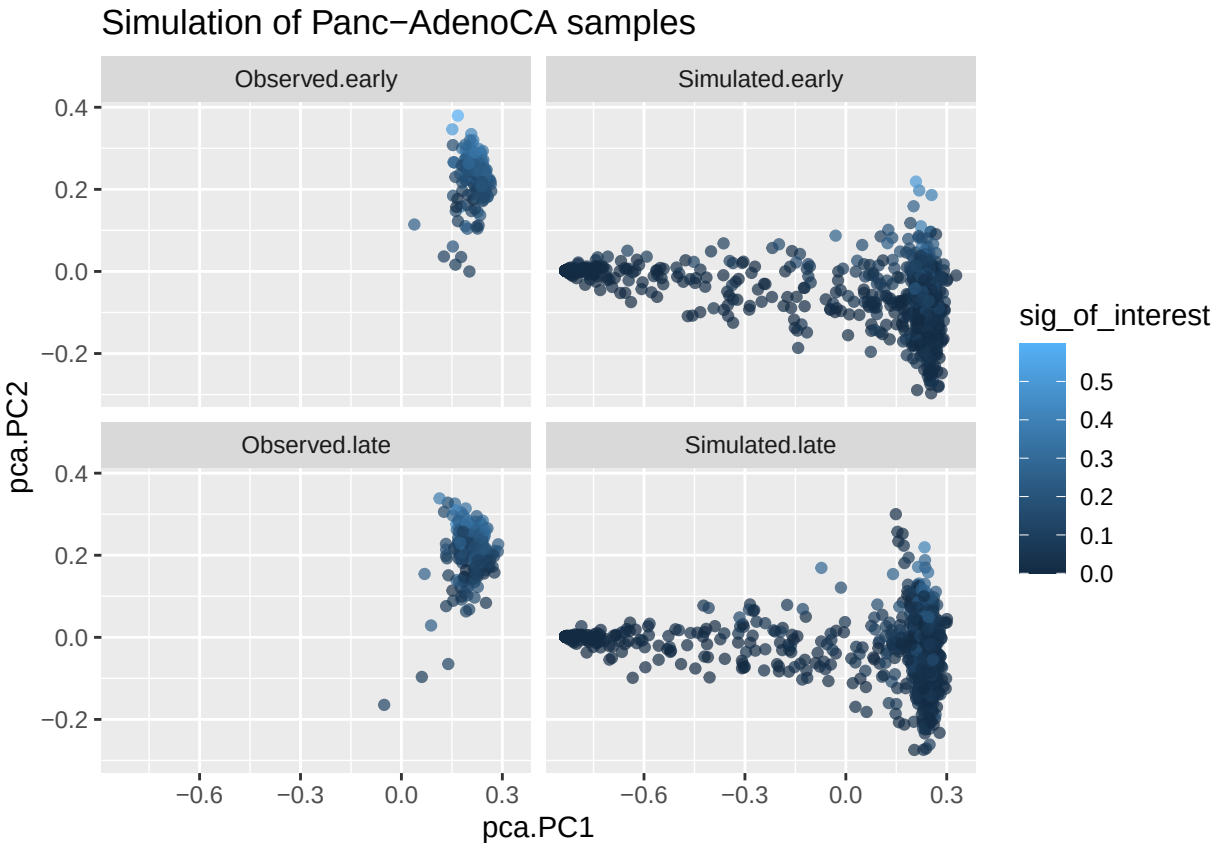
```
## [1] 193
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

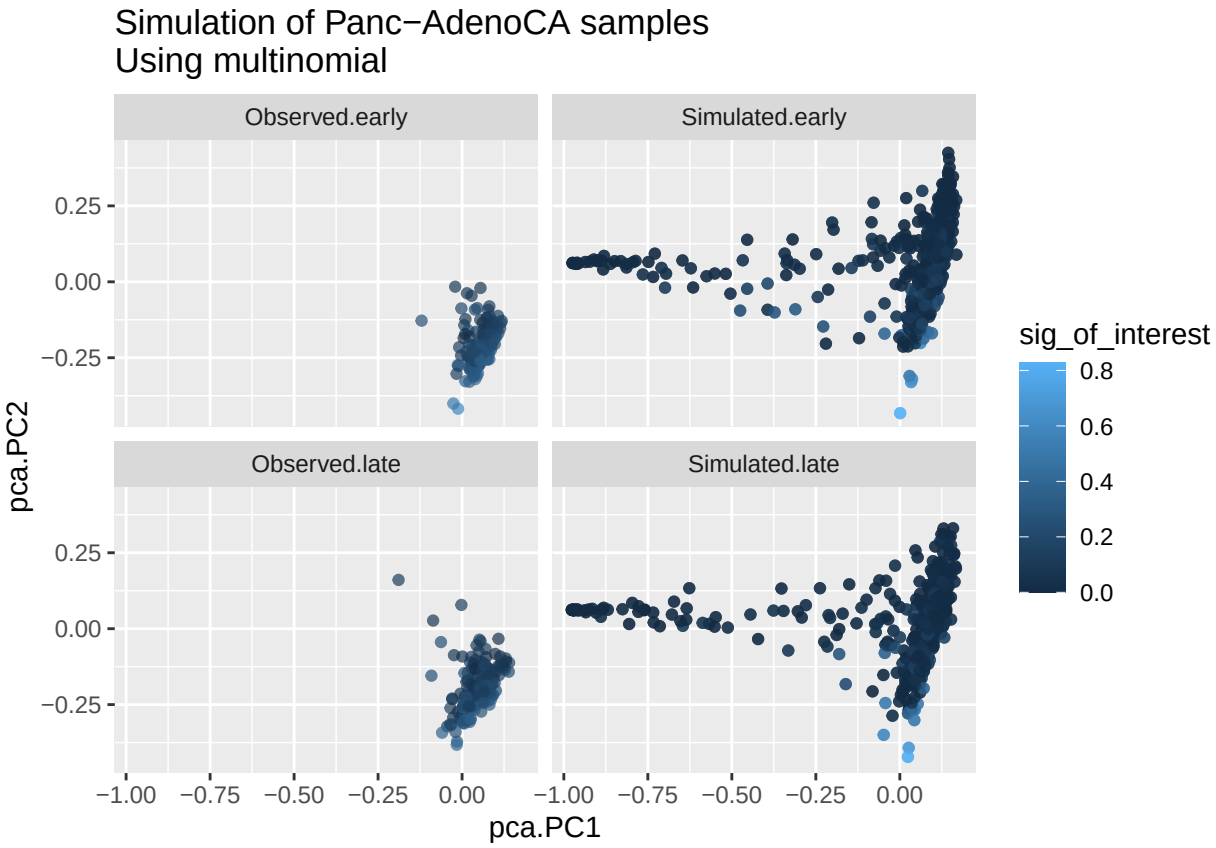
```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```



Multinomial doesn't look great either

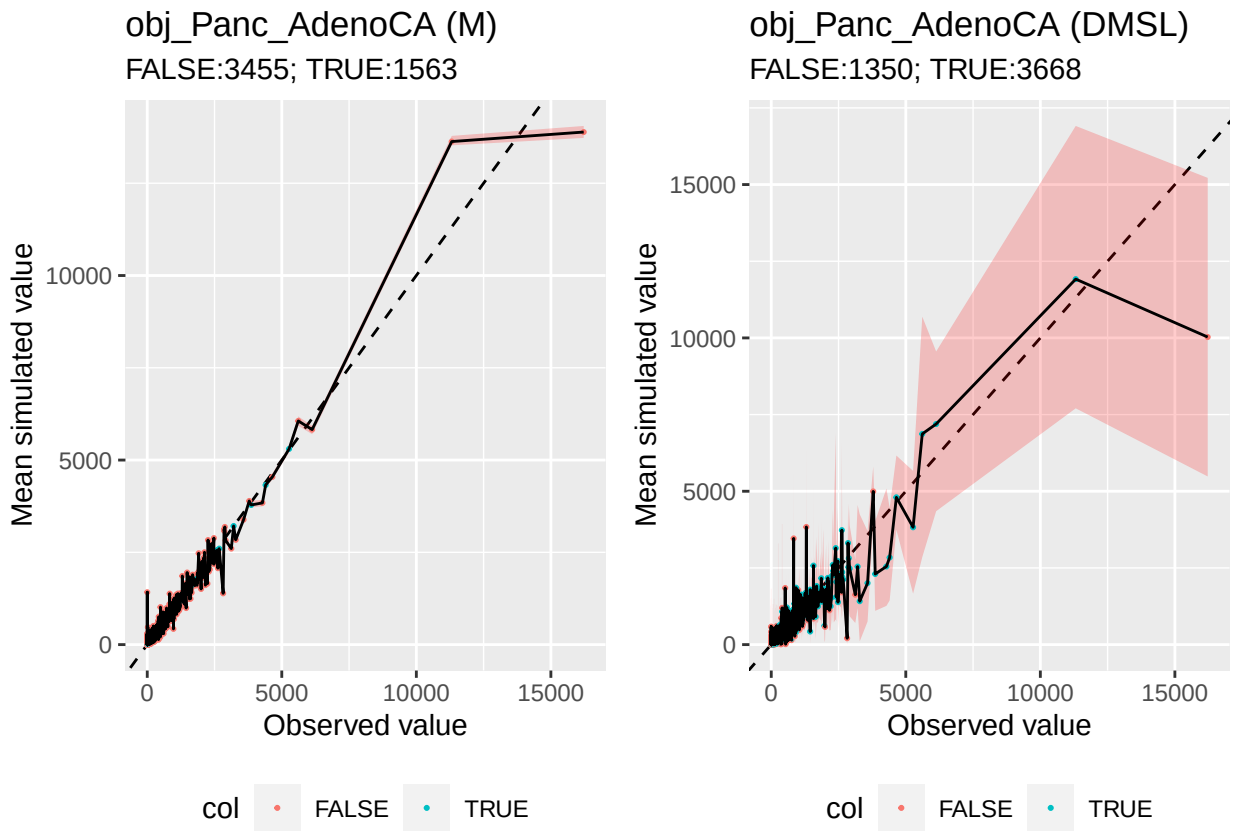
```
## [1] 193
```

```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```



Ranked plot for coverage

```
ct <- "Panc-AdenoCA"
integer_overdispersion_param_DMSL <- 1
obj_Panc_AdenoCA_nonexo <- give_subset_sigs_TMBobj(obj_Panc_AdenoCA, sigs_to_remove = nonexogenous$V1)
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                  data_object = obj_Panc_AdenoCA_nonexo,
                  print_plot = F, nreps = 20, model = "M")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Panc_AdenoCA_nonexo,
                  loglog = F, title = 'obj_Panc_AdenoCA (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = diagRE_DMSL_nor
                  data_object = obj_Panc_AdenoCA_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Panc_AdenoCA_nonexo,
           loglog = F, title = 'obj_Panc_AdenoCA (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

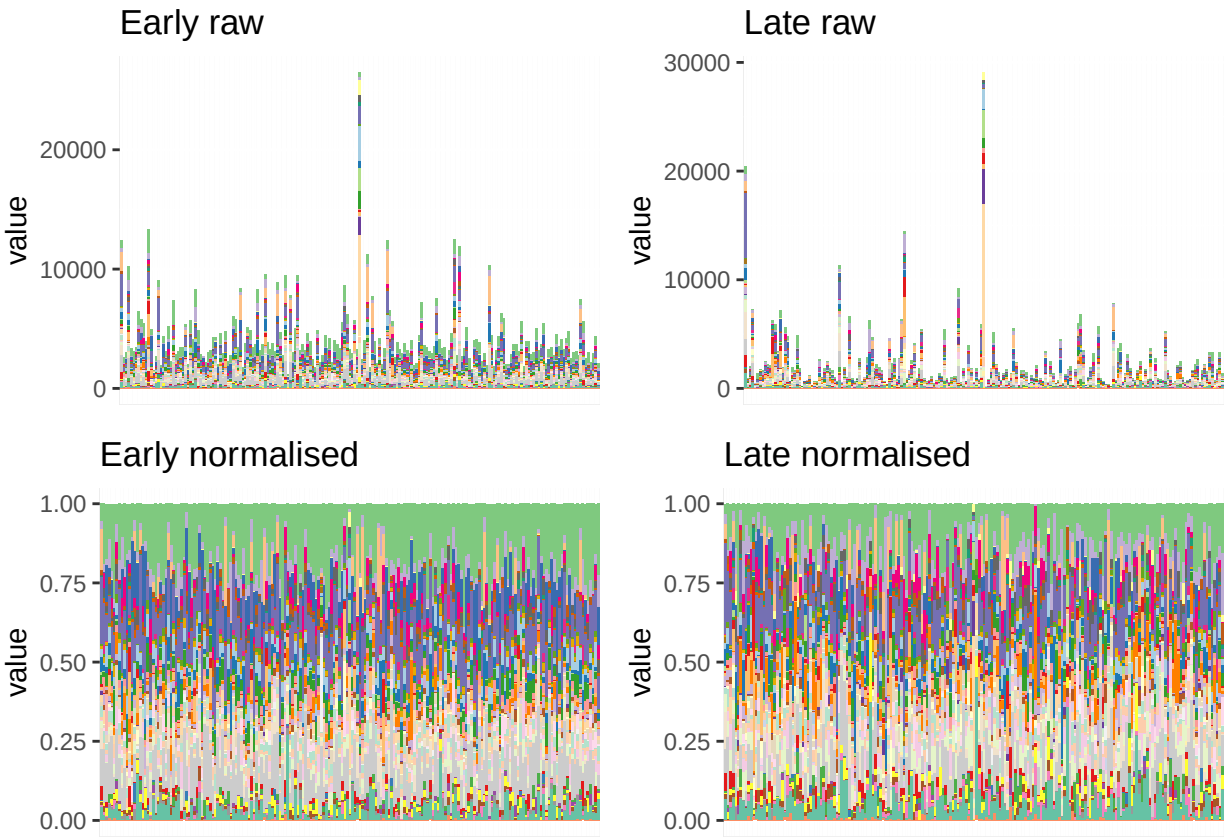
```
obj_Panc_AdenoCA_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

```
## [1] 193
```

```
give_barplot_from_obj(obj = obj_Panc_AdenoCA_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 193
## Creating plot... it might take some time if the data are large. Number of samples: 193
## Creating plot... it might take some time if the data are large. Number of samples: 193
## Creating plot... it might take some time if the data are large. Number of samples: 193
```

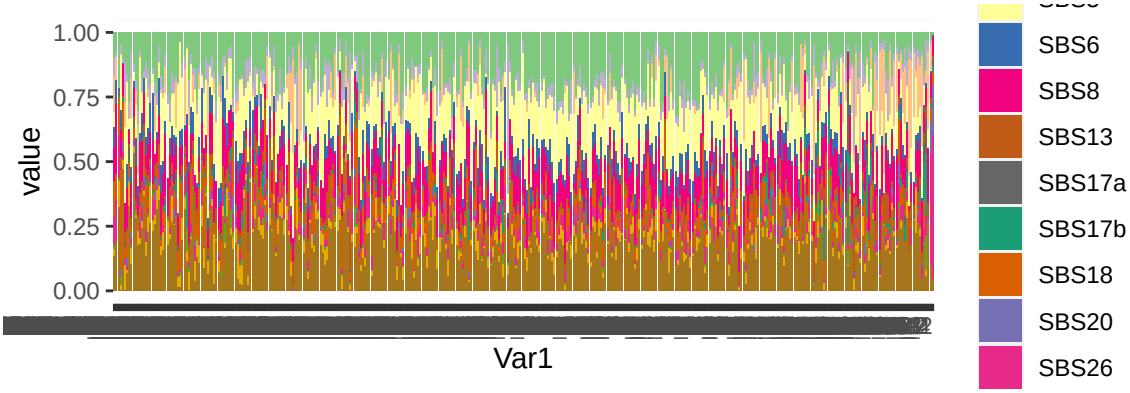
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Panc_AdenoCA$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Panc_AdenoCA$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 386
```

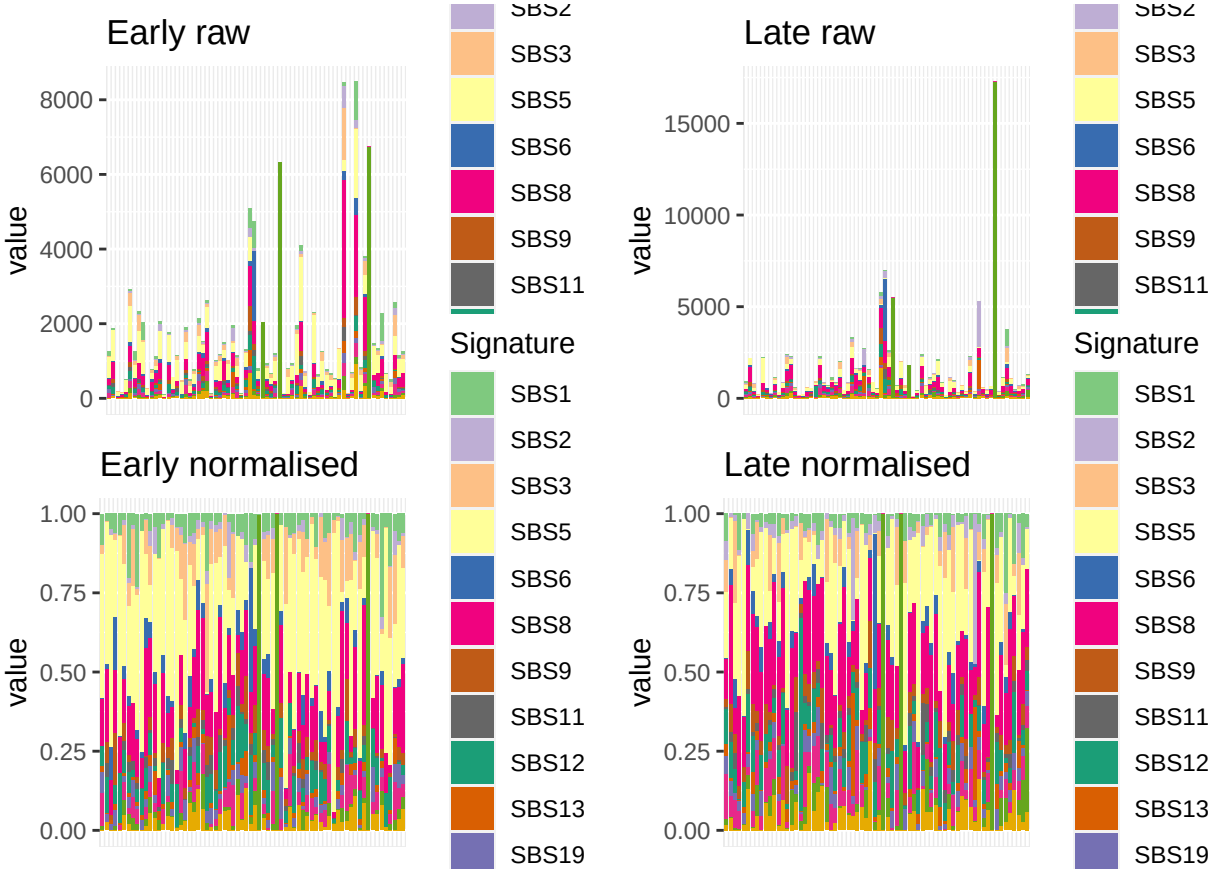


Panc-Endocrine

Barplot and general statistics

```
## [1] 70
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 70
## Creating plot... it might take some time if the data are large. Number of samples: 70
## Creating plot... it might take some time if the data are large. Number of samples: 70
## Creating plot... it might take some time if the data are large. Number of samples: 70
```



The number of samples and signatures is:

```
## [1] 140  14
```

The signatures are:

```
##  [1] "SBS1"  "SBS2"  "SBS3"  "SBS5"  "SBS6"  "SBS8"  "SBS9"  "SBS11" "SBS12"
## [10] "SBS13" "SBS19" "SBS30" "SBS36" "SBS39"
```

Convergence table

These are the results for the convergence of models fits. fullRE_DMSL and fullRE_DMSL_nonexo haven't.

```
##             value                                L2                  L1
## 1  Panc-Endocrine    hessian_positivedefinite_bool             diagRE_M
## 2  Panc-Endocrine hessian_nonpositivedefinite_bool             fullRE_M
## 3  Panc-Endocrine hessian_nonpositivedefinite_bool           diagRE_DMDL
```

```
## 4  Panc-Endocrine                          Timeout            fullRE_halfDM
## 5  Panc-Endocrine hessian_nonpositivedefinite_bool              fullRE_DMDL
## 6  Panc-Endocrine    hessian_positivedefinite_bool              diagRE_DMSL
## 7  Panc-Endocrine    hessian_positivedefinite_bool            sparseRE_DMSL
## 8  Panc-Endocrine hessian_nonpositivedefinite_bool              fullRE_DMSL
## 9  Panc-Endocrine hessian_nonpositivedefinite_bool         fullRE_DMSL_SBS1
## 10 Panc-Endocrine    hessian_positivedefinite_bool          fullRE_M_nonexo
## 11 Panc-Endocrine    hessian_positivedefinite_bool       diagRE_DMSL_nonexo
## 12 Panc-Endocrine    hessian_positivedefinite_bool     sparseRE_DMSL_nonexo
## 13 Panc-Endocrine hessian_nonpositivedefinite_bool       fullRE_DMSL_nonexo
## 14 Panc-Endocrine hessian_nonpositivedefinite_bool       fullRE_DMDL_nonexo
## 15 Panc-Endocrine                          Timeout fullRE_DMDL_sortednonexo
```

Re-running of fitting

Using fullRE_M_nonexo to fit fullRE_DMSL_nonexo.

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

If we use the values of the fullRE M exo as initial values for the fullRE DMSL exo doesn't converge:

```
## [1] FALSE
```

Potentially problematic signatures

We explore whether there are problematic signatures:

```
colSums(obj_Panc_Endocrine$Y == 0)/nrow(obj_Panc_Endocrine$Y)
```

```
##       SBS1       SBS2       SBS3       SBS5       SBS6       SBS8       SBS9
## 0.08571429 0.20714286 0.43571429 0.09285714 0.35714286 0.05000000 0.14285714
##      SBS11      SBS12      SBS13      SBS19      SBS30      SBS36      SBS39
## 0.32142857 0.12142857 0.13571429 0.18571429 0.25000000 0.35000000 0.26428571
```

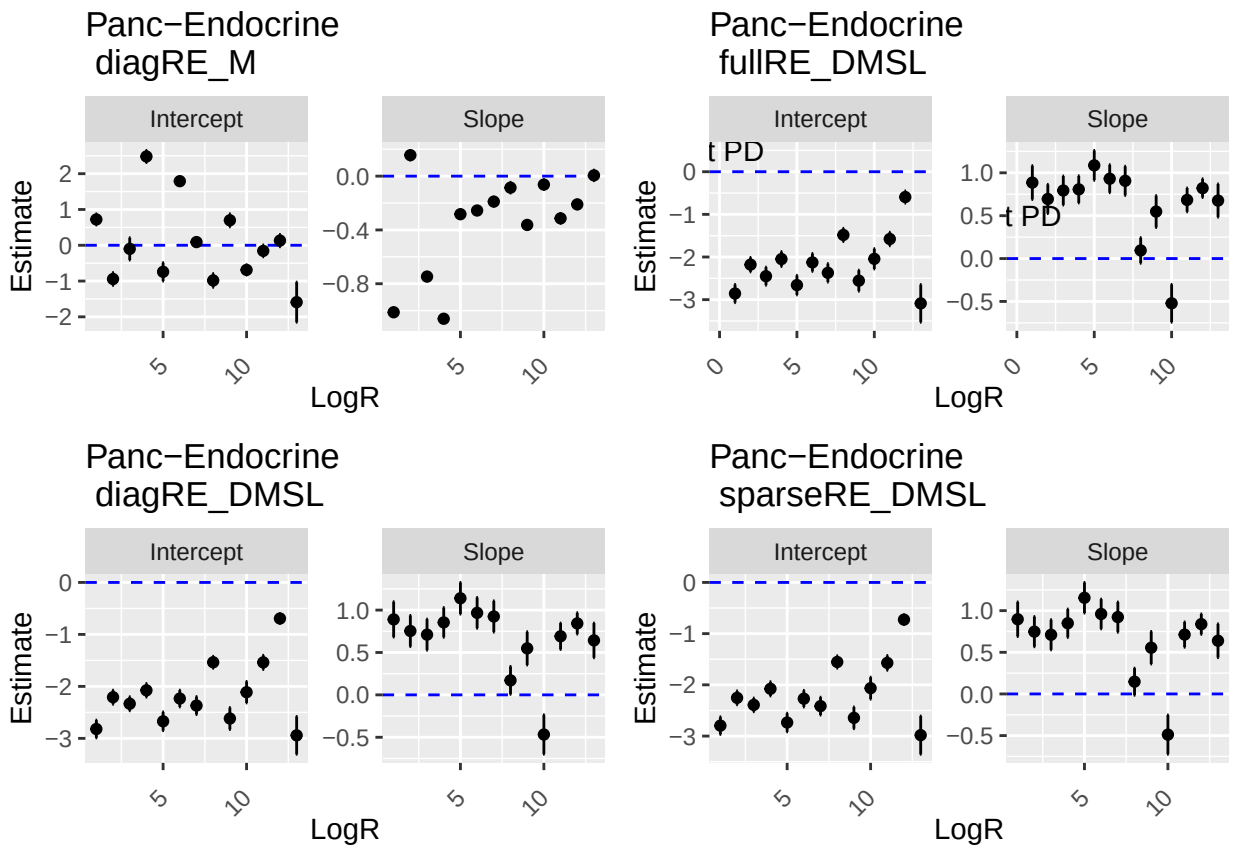
```
colSums(obj_Panc_Endocrine$Y)/sum(obj_Panc_Endocrine$Y)
```

```
##       SBS1       SBS2       SBS3       SBS5       SBS6       SBS8       SBS9
## 0.04497473 0.03735807 0.05104230 0.19581878 0.04501764 0.17414887 0.03565881
##      SBS11      SBS12      SBS13      SBS19      SBS30      SBS36      SBS39
## 0.01924975 0.05892071 0.03124330 0.02551471 0.04475588 0.19146763 0.04482883
```

Betas

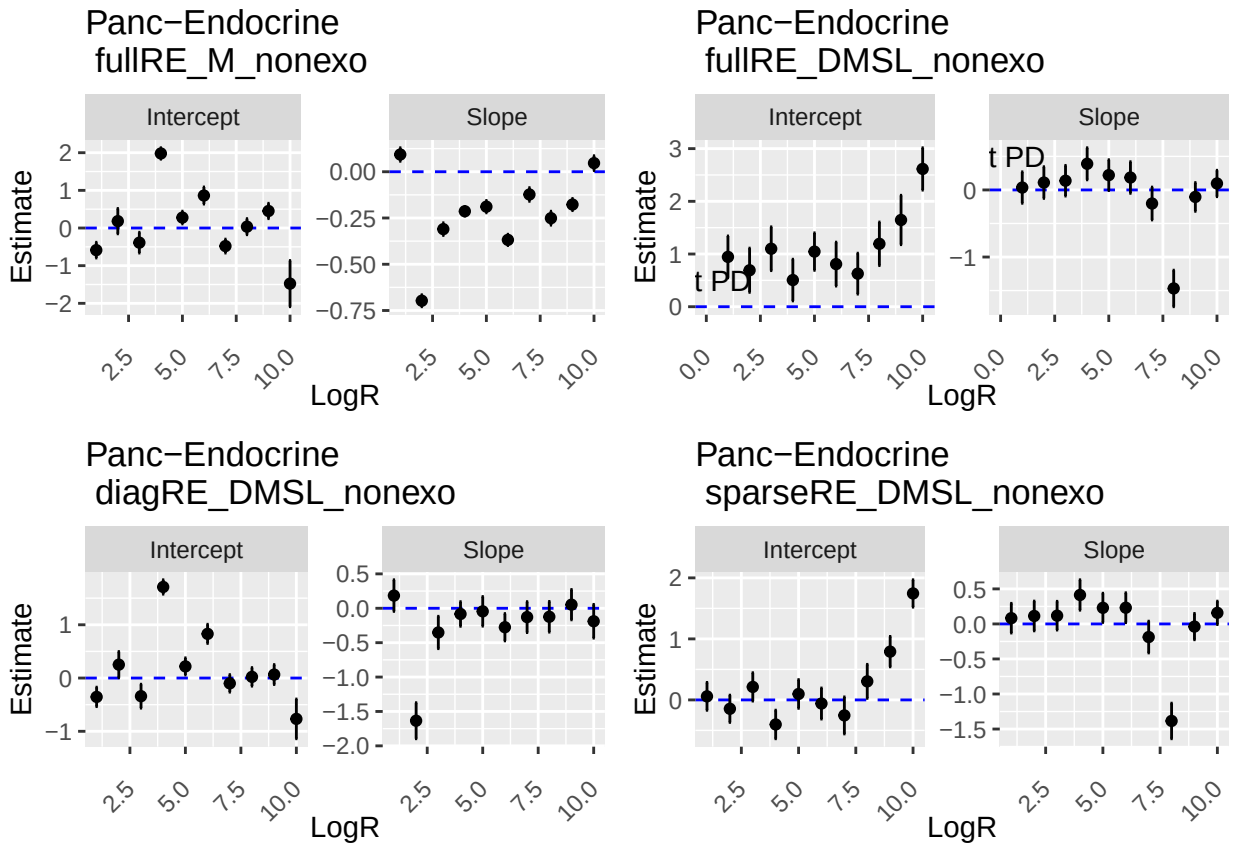
```
ct <- "Panc-Endocrine"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```




```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(sortedDM_PancEndocrine)+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```

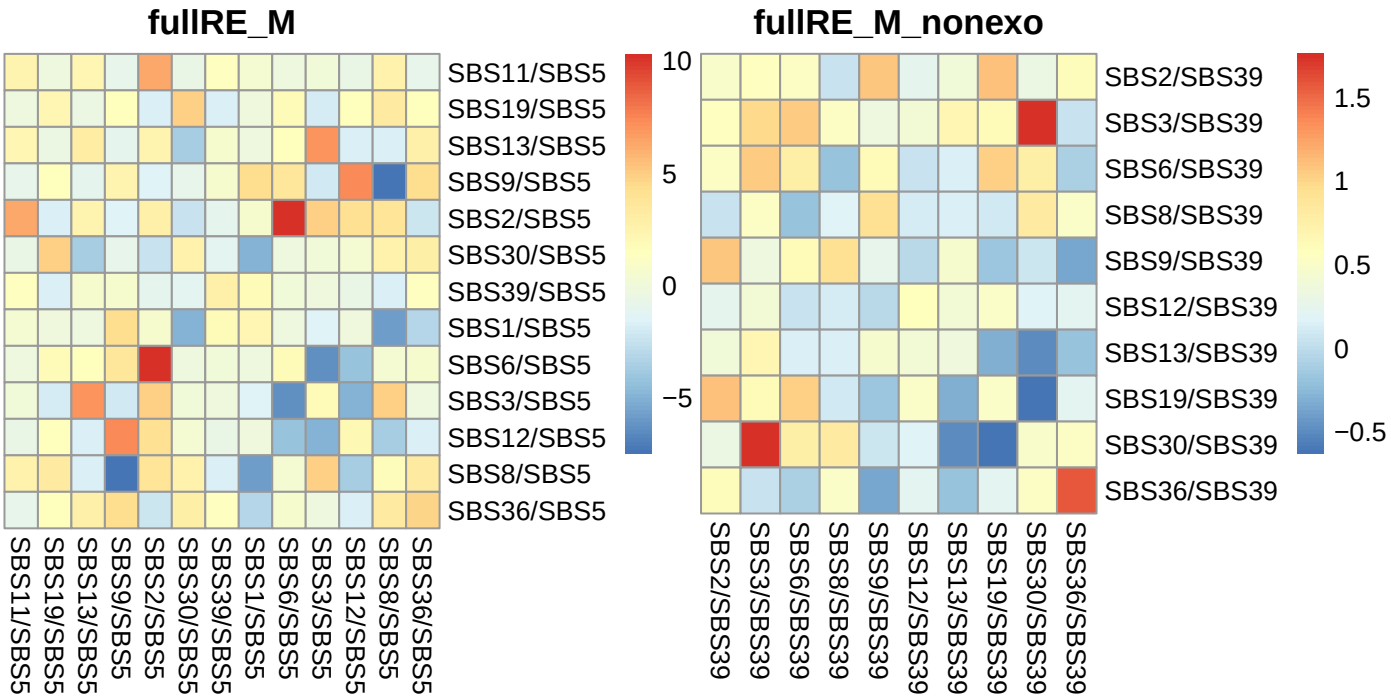
```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct

## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used

## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of 1.9645842×10^{-9}.

Covariance matrices



Simulation under inferred data

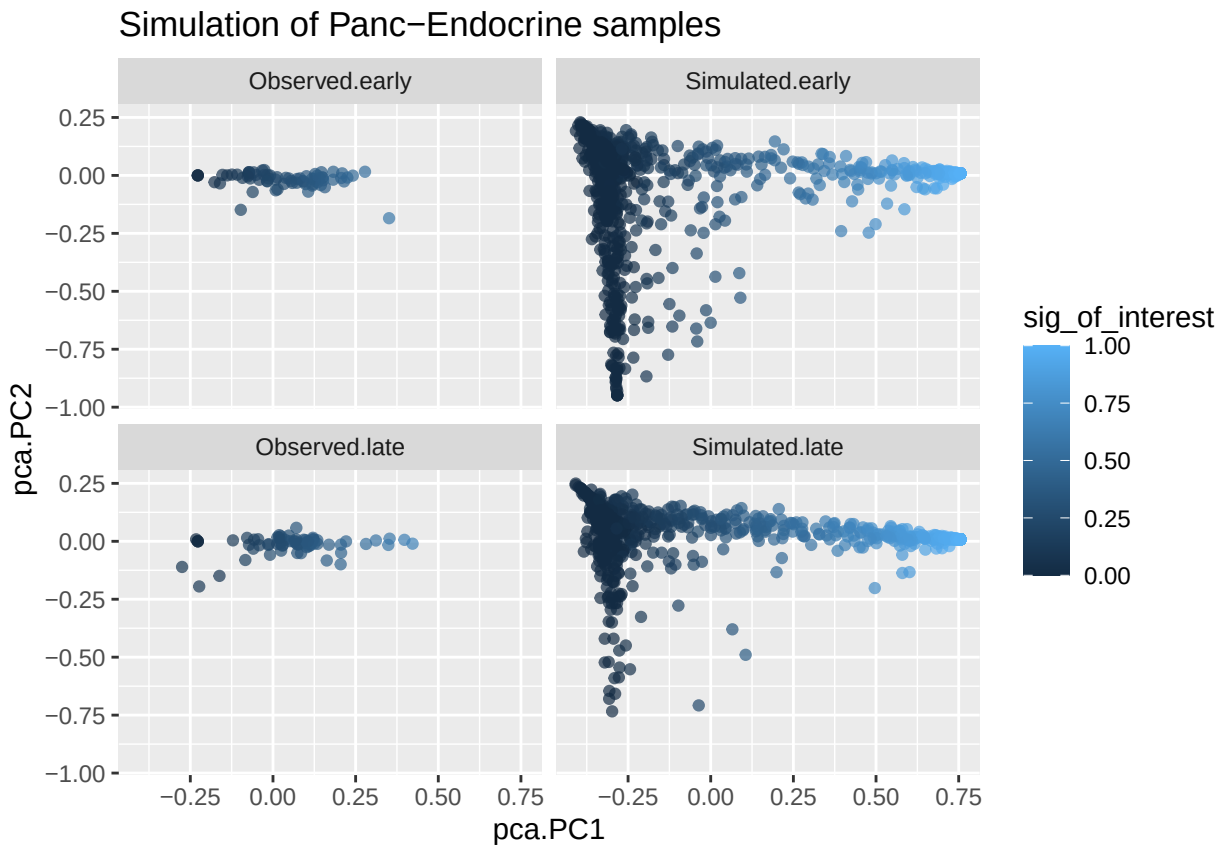
```
## [1] 70
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```

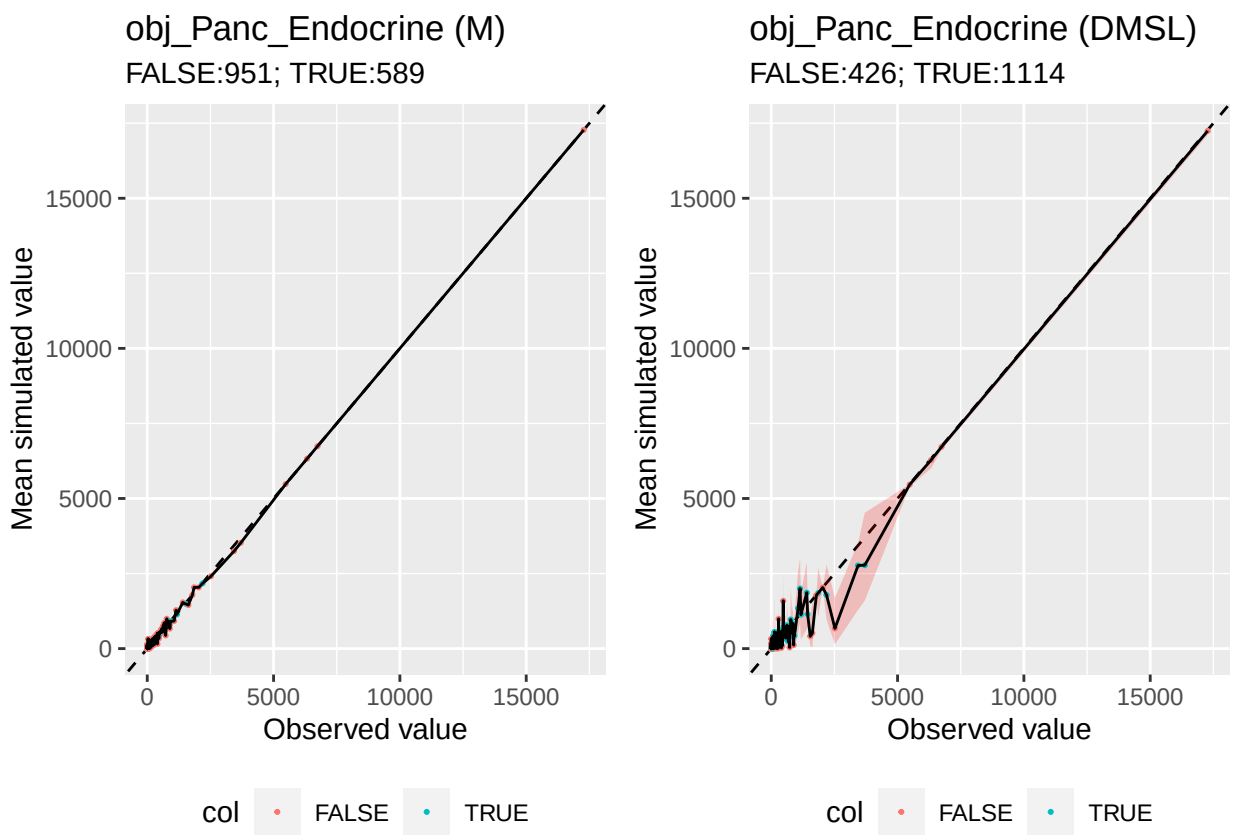
```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```



Ranked plot for coverage

```
ct <- "Panc-Endocrine"
integer_overdispersion_param_DMSL <- 1
obj_Panc_Endocrine_nonexo <- give_subset_sigs_TMBobj(obj_Panc_Endocrine, sigs_to_remove = nonexogenous$V1
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                data_object = obj_Panc_Endocrine_nonexo,
                print_plot = F, nreps = 20, model = "M")), function(i){
                  lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                         rank_number=1:length(j)) )})[[1]],
                data_object = obj_Panc_Endocrine_nonexo,
                loglog = F, title = 'obj_Panc_Endocrine (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = diagRE_DMSL_nor
                data_object = obj_Panc_Endocrine_nonexo,
                print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                  lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                         rank_number=1:length(j)) )})[[1]],
                data_object = obj_Panc_Endocrine_nonexo,
           loglog = F, title = 'obj_Panc_Endocrine (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

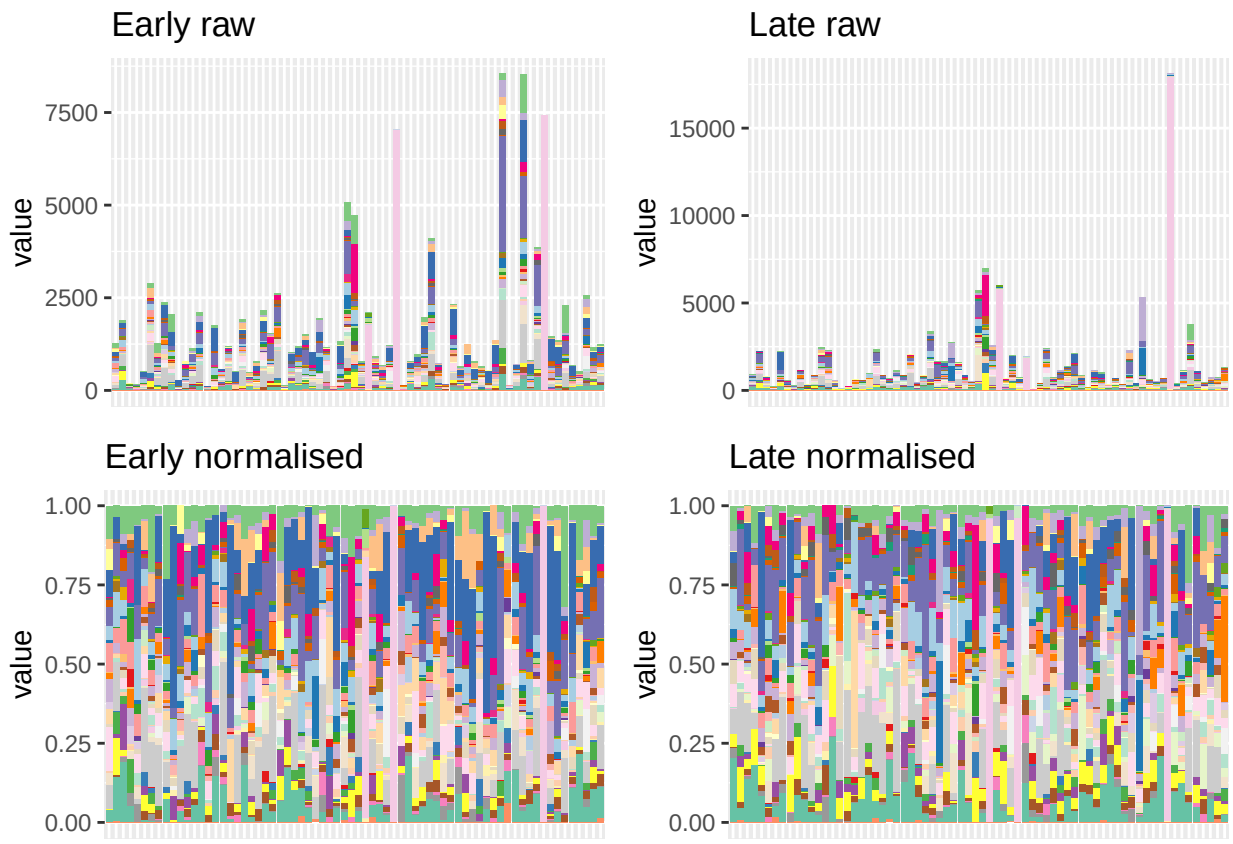
```
obj_Panc_Endocrine_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

```
## [1] 70
```

```
give_barplot_from_obj(obj = obj_Panc_Endocrine_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 70
## Creating plot... it might take some time if the data are large. Number of samples: 70
## Creating plot... it might take some time if the data are large. Number of samples: 70
## Creating plot... it might take some time if the data are large. Number of samples: 70
```

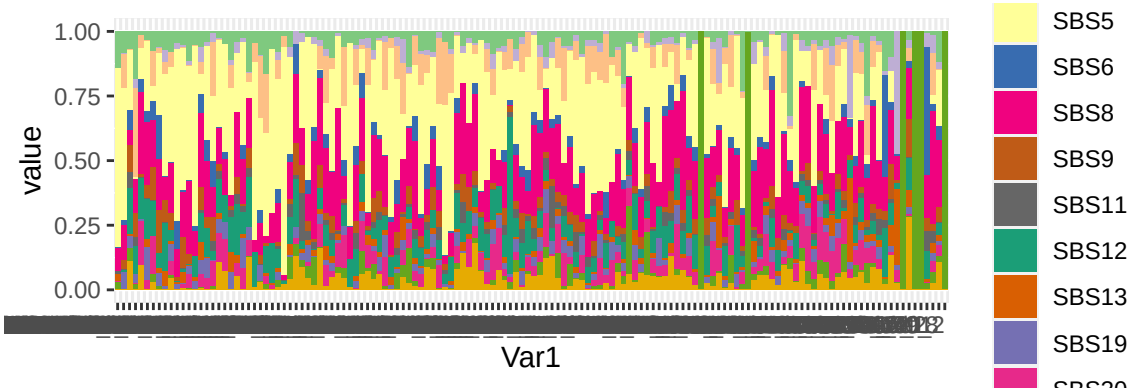
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: there is a trend with one signature only being present, and in very large amounts, in hyeprmutated samples.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Panc_Endocrine$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Panc_Endocrine$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 140
```

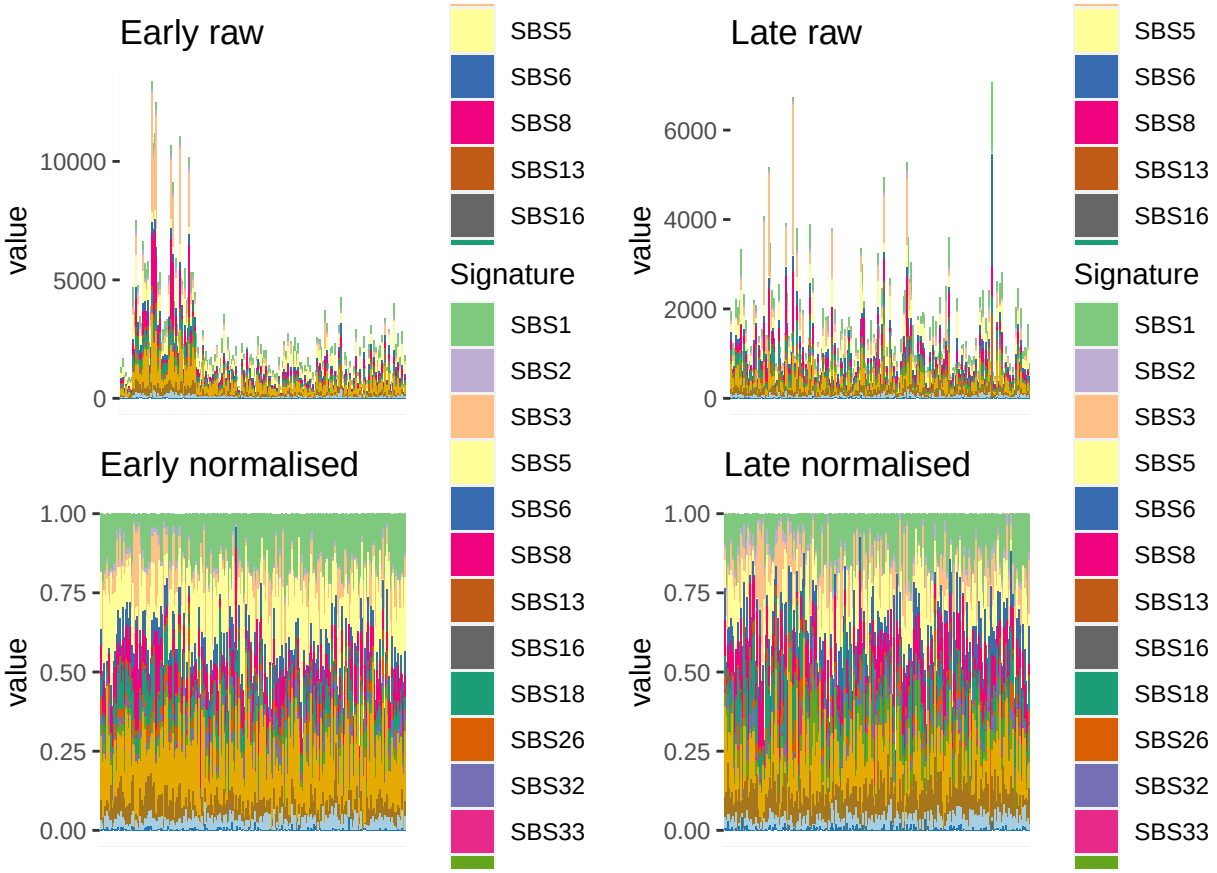


Prost-AdenoCA

Barplot and general statistics

```
## [1] 208
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 208
## Creating plot... it might take some time if the data are large. Number of samples: 208
## Creating plot... it might take some time if the data are large. Number of samples: 208
## Creating plot... it might take some time if the data are large. Number of samples: 208
```



The number of samples and signatures is:

```
## [1] 416  17
```

The signatures are:

```
##  [1] "SBS1"  "SBS2"  "SBS3"  "SBS5"  "SBS6"  "SBS8"  "SBS13" "SBS16" "SBS18"
## [10] "SBS26" "SBS32" "SBS33" "SBS37" "SBS40" "SBS41" "SBS50" "SBS52"
```

Convergence table

These are the results for the convergence of models fits. Most have converged. fullRE_DMSL_nonexo hasn't run and needs to be re-run.

```
##            value                                 L2                 L1
## 1  Prost-AdenoCA    hessian_positivedefinite_bool          diagRE_M
## 2  Prost-AdenoCA hessian_nonpositivedefinite_bool          fullRE_M
```

```
## 3  Prost-AdenoCA hessian_nonpositivedefinite_bool             diagRE_DMDL
## 4  Prost-AdenoCA                          Timeout            fullRE_halfDM
## 5  Prost-AdenoCA                          Timeout              fullRE_DMDL
## 6  Prost-AdenoCA    hessian_positivedefinite_bool              diagRE_DMSL
## 7  Prost-AdenoCA    hessian_positivedefinite_bool            sparseRE_DMSL
## 8  Prost-AdenoCA hessian_nonpositivedefinite_bool              fullRE_DMSL
## 9  Prost-AdenoCA hessian_nonpositivedefinite_bool         fullRE_DMSL_SBS1
## 10 Prost-AdenoCA    hessian_positivedefinite_bool          fullRE_M_nonexo
## 11 Prost-AdenoCA    hessian_positivedefinite_bool       diagRE_DMSL_nonexo
## 12 Prost-AdenoCA    hessian_positivedefinite_bool     sparseRE_DMSL_nonexo
## 13 Prost-AdenoCA                          Timeout       fullRE_DMSL_nonexo
## 14 Prost-AdenoCA    hessian_positivedefinite_bool       fullRE_DMDL_nonexo
## 15 Prost-AdenoCA hessian_nonpositivedefinite_bool fullRE_DMDL_sortednonexo
```

Re-running of fitting

Using fullRE_M_nonexo to fit fullRE_DMSL_nonexo.

But DMSL hasn't:

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

```
## [1] FALSE
```

Potentially problematic signatures

We explore whether there are problematic signatures. None seem to be, although SBS33 is absent in 60% of samples.

```
colSums(obj_Prost_AdenoCA$Y == 0)/nrow(obj_Prost_AdenoCA$Y)
```

```
##        SBS1        SBS2        SBS3        SBS5        SBS6        SBS8
## 0.007211538 0.040865385 0.225961538 0.108173077 0.033653846 0.052884615
##       SBS13       SBS16       SBS18       SBS26       SBS32       SBS33
## 0.259615385 0.331730769 0.043269231 0.317307692 0.100961538 0.665865385
##       SBS37       SBS40       SBS41       SBS50       SBS52
## 0.257211538 0.086538462 0.026442308 0.057692308 0.427884615
```

```
colSums(obj_Prost_AdenoCA$Y)/sum(obj_Prost_AdenoCA$Y)
```

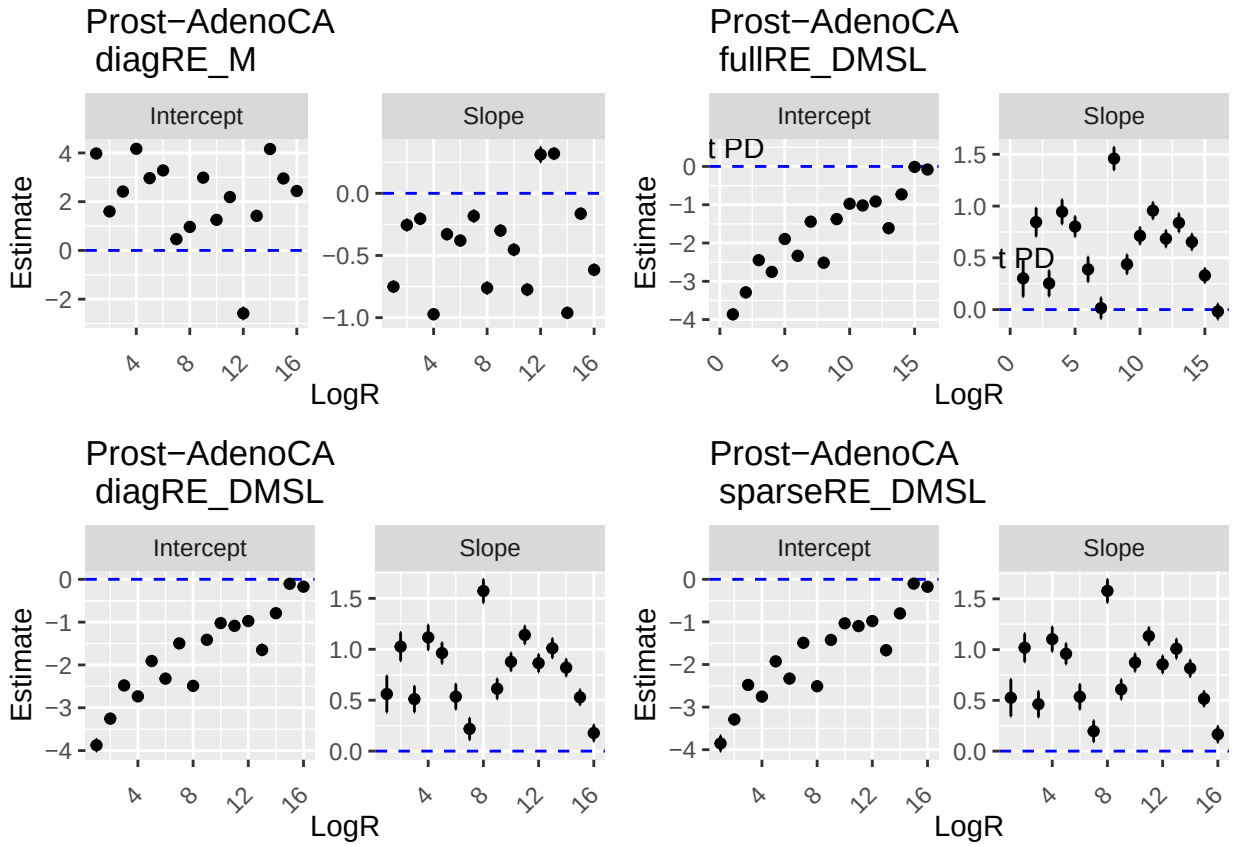
```
##        SBS1        SBS2        SBS3        SBS5        SBS6        SBS8
## 0.123798623 0.018138349 0.101489206 0.145492714 0.063352195 0.110930563
##       SBS13       SBS16       SBS18       SBS26       SBS32       SBS33
## 0.011721046 0.011380527 0.071927318 0.022167235 0.022482663 0.003387275
##       SBS37       SBS40       SBS41       SBS50       SBS52
## 0.028615602 0.166680208 0.065069131 0.029925110 0.003442236
```

Betas

```
ct <- "Prost-AdenoCA"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```

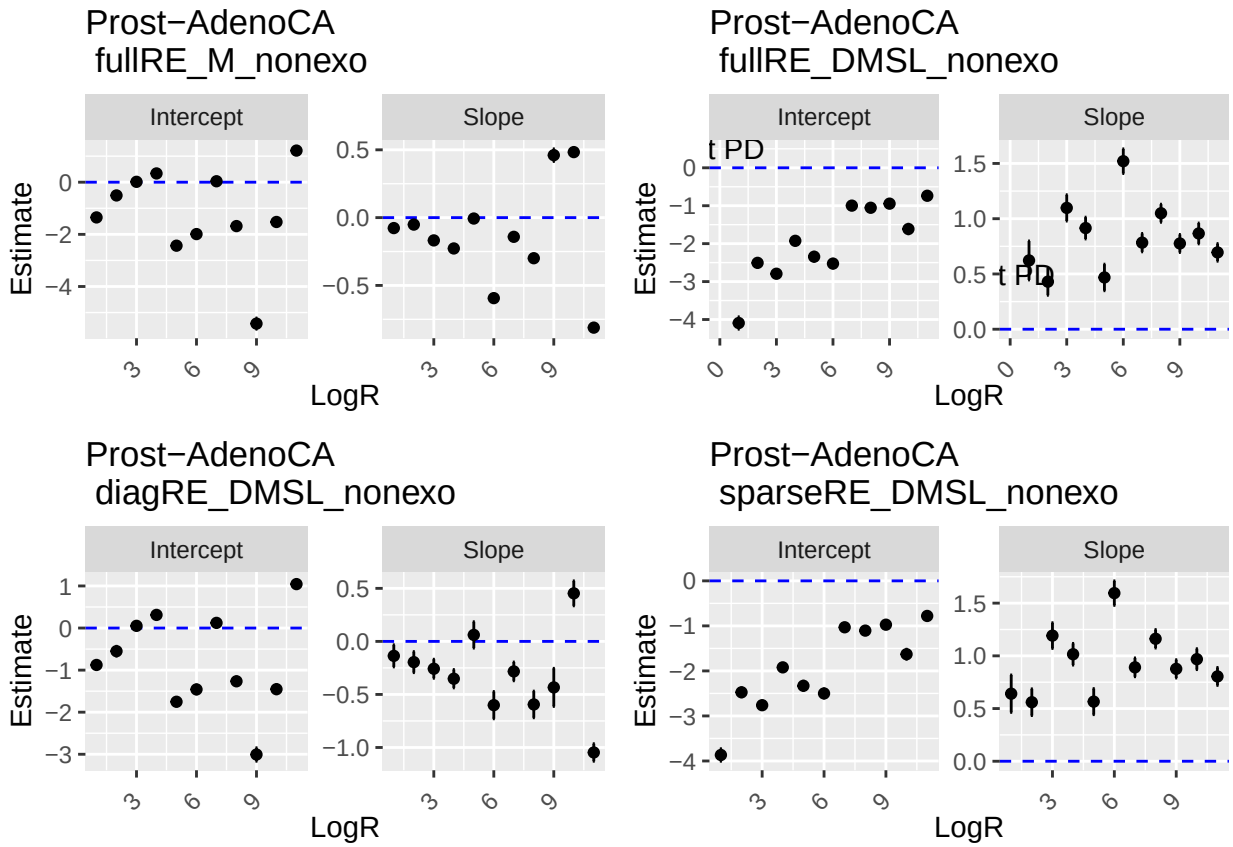
```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

```
## Warning in sqrt(as.numeric(object$diag.cov.random)): NaNs produced
```




```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(sortedDM_ProstAdenoCA)+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```



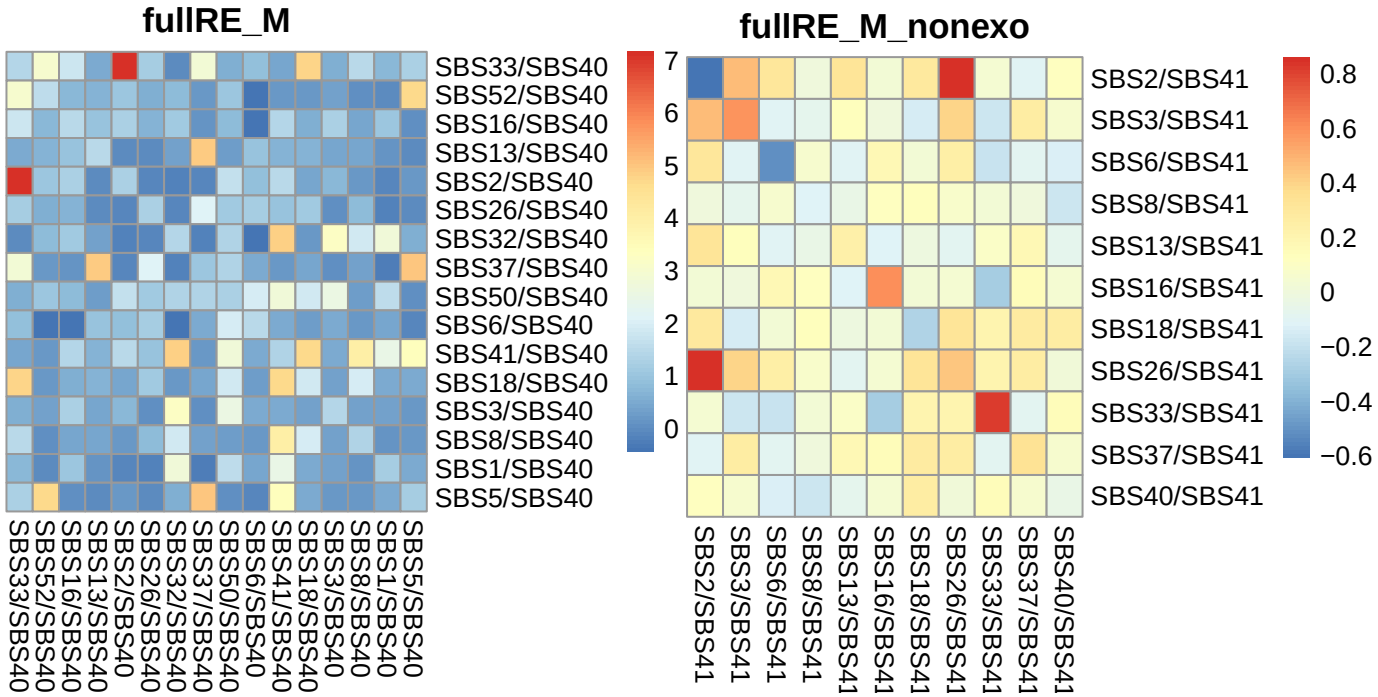

```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct
```

```
## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used
```

```
## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of 5.142907×10^{-58}.

Covariance matrices



Simulation under inferred data

It doesn't look great! Both seem quite different

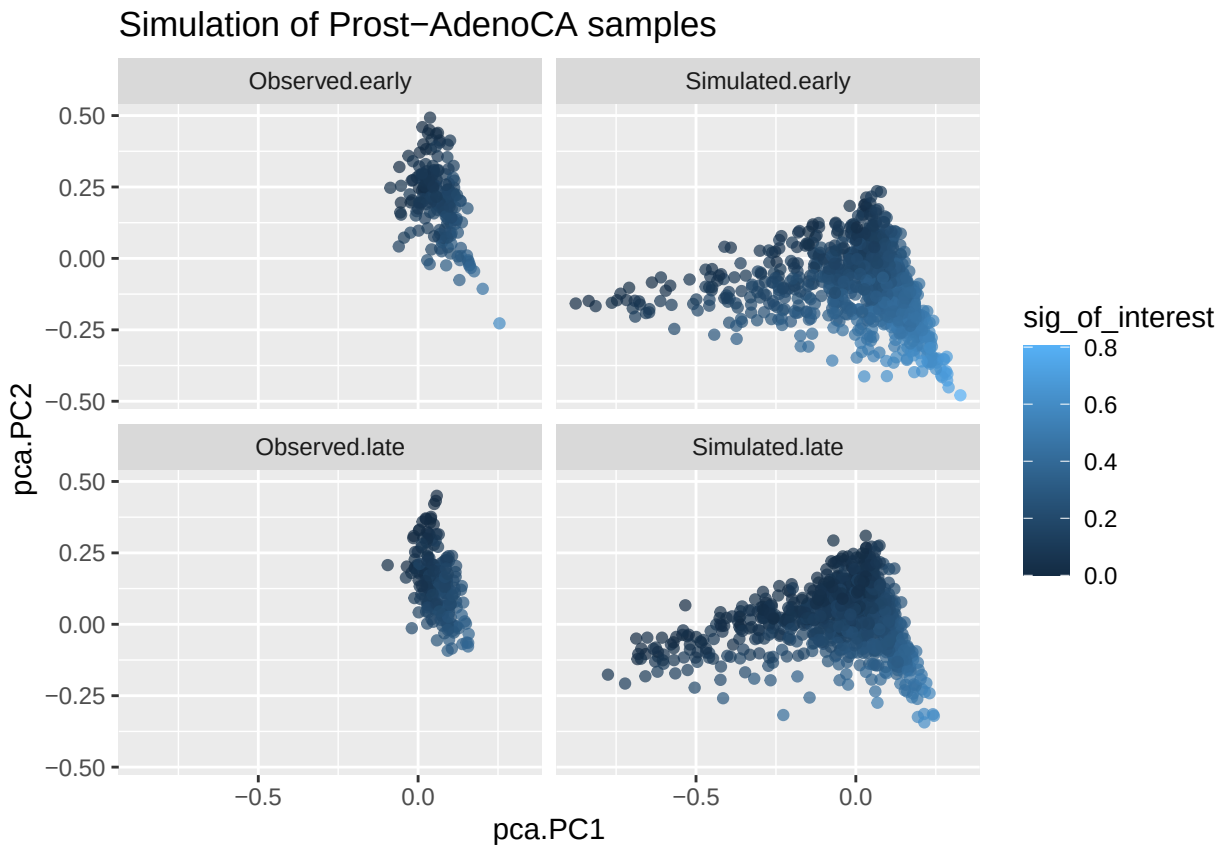
```
## [1] 208
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```

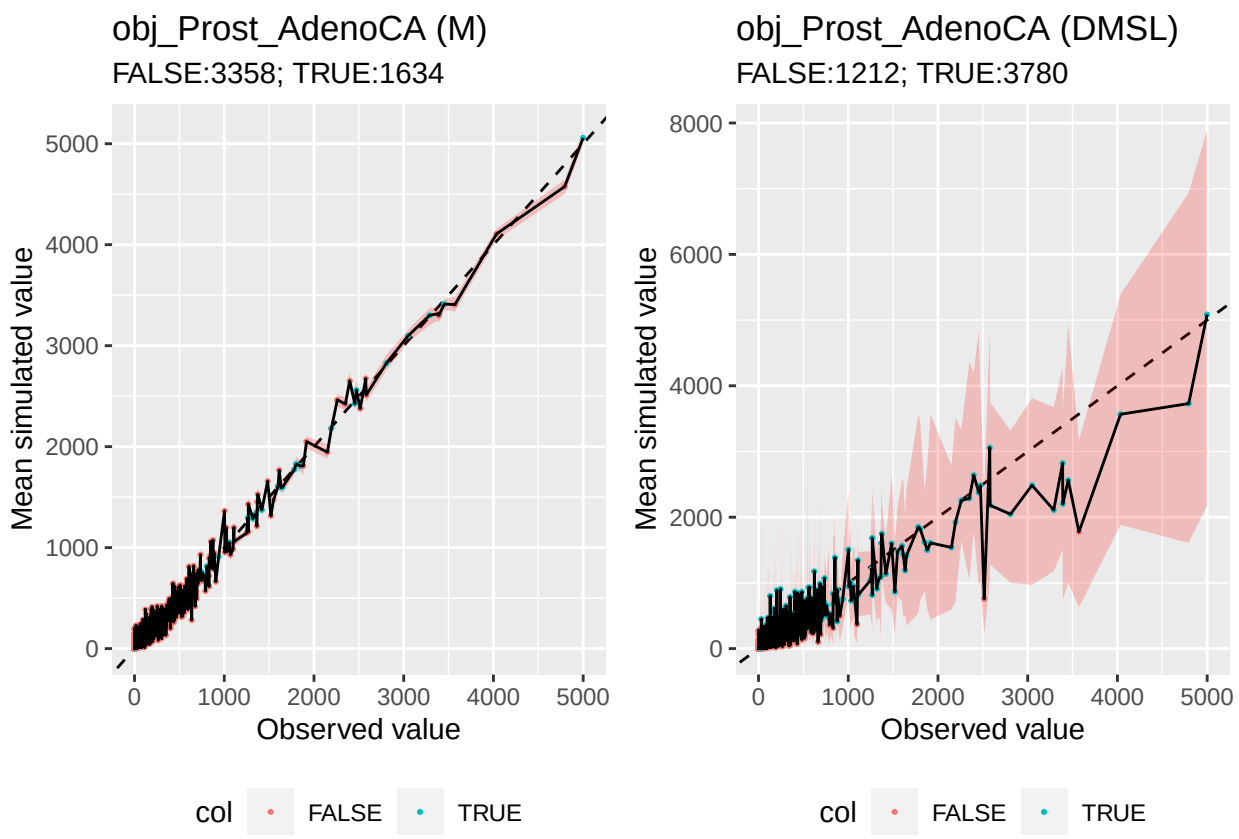
```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```



Ranked plot for coverage

```
ct <- "Prost-AdenoCA"
integer_overdispersion_param_DMSL <- 1
obj_Prost_AdenoCA_nonexo <- give_subset_sigs_TMBobj(obj_Prost_AdenoCA, sigs_to_remove = nonexogenous$V1)
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                  data_object = obj_Prost_AdenoCA_nonexo,
                  print_plot = F, nreps = 20, model = "M")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Prost_AdenoCA_nonexo,
                  loglog = F, title = 'obj_Prost_AdenoCA (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = diagRE_DMSL_nor
                  data_object = obj_Prost_AdenoCA_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Prost_AdenoCA_nonexo,
           loglog = F, title = 'obj_Prost_AdenoCA (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

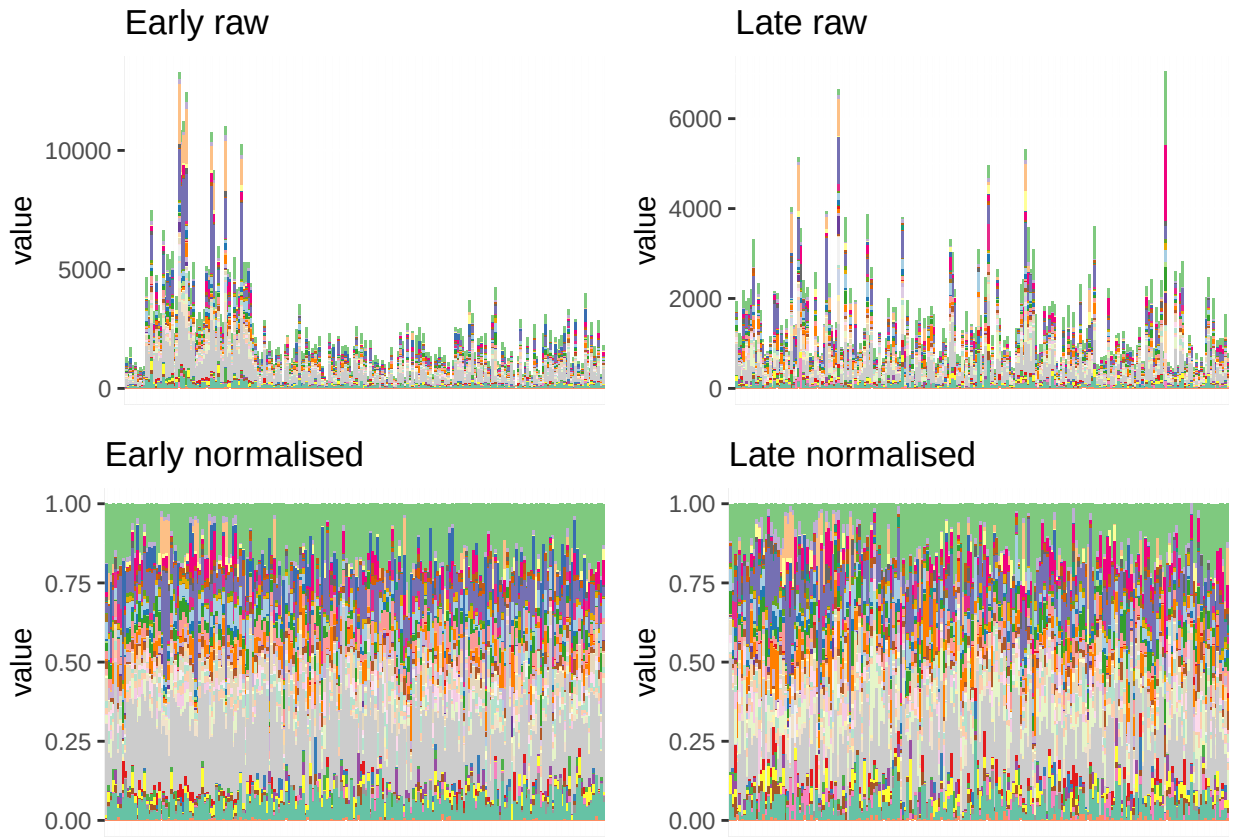
```
obj_Prost_AdenoCA_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

```
## [1] 208
```

```
give_barplot_from_obj(obj = obj_Prost_AdenoCA_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 208
## Creating plot... it might take some time if the data are large. Number of samples: 208
## Creating plot... it might take some time if the data are large. Number of samples: 208
## Creating plot... it might take some time if the data are large. Number of samples: 208
```

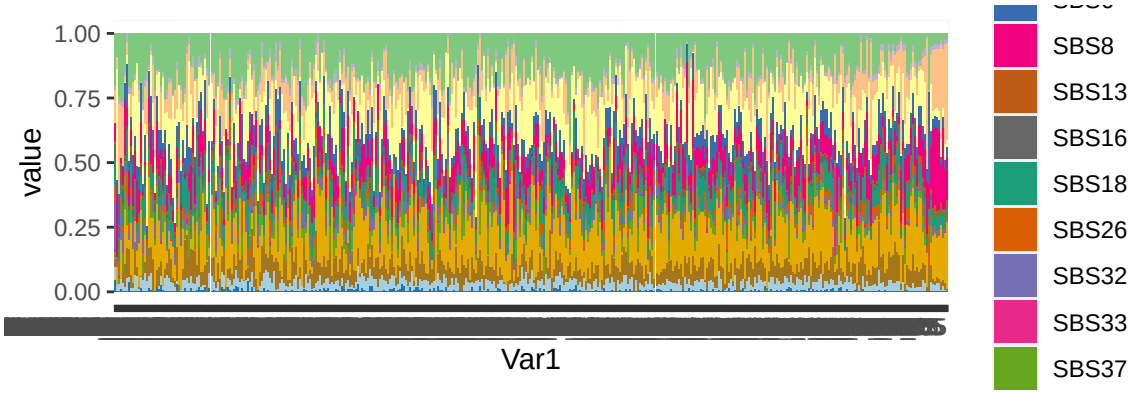
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations, except perhaps SBS3 in the hypermutated ones.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Prost_AdenoCA$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Prost_AdenoCA$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 416
```

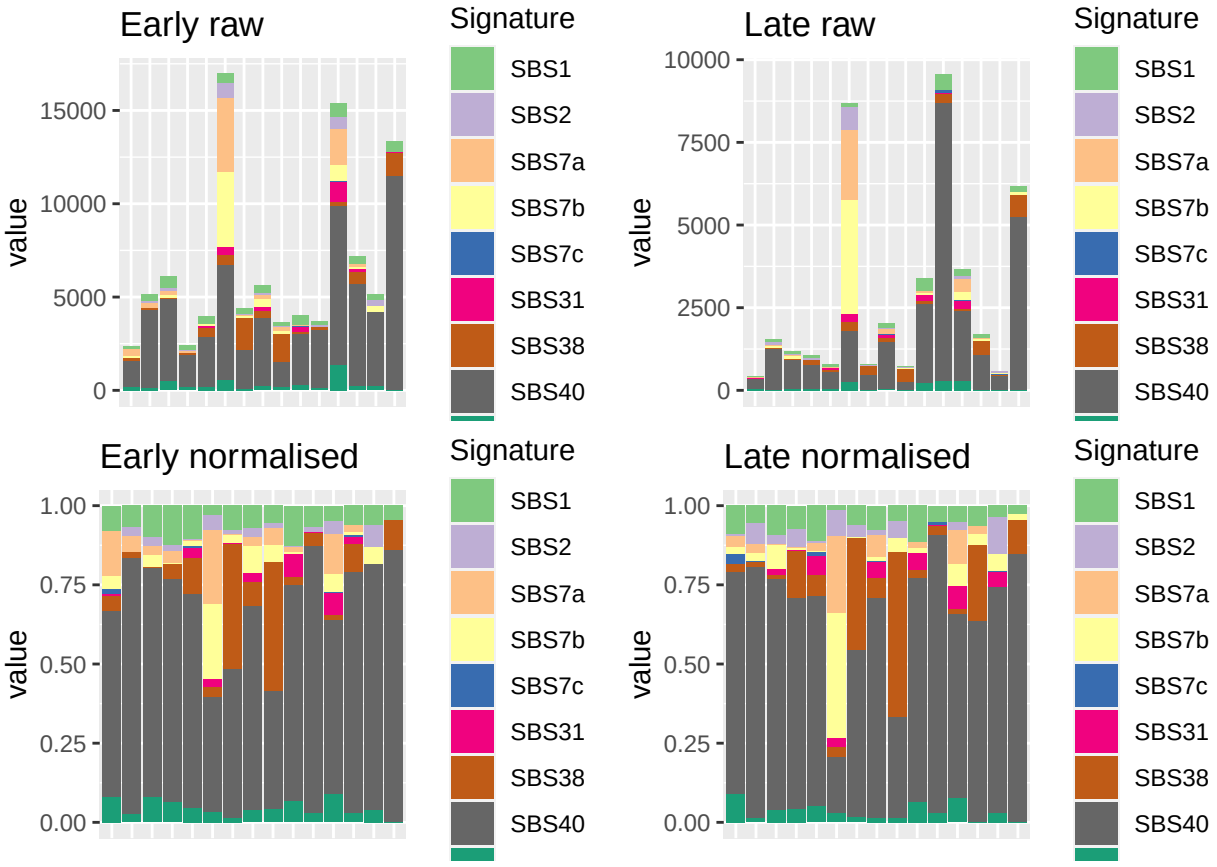


Skin-Melanoma.acral

Barplot and general statistics

```
## [1] 15
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 15
## Creating plot... it might take some time if the data are large. Number of samples: 15
## Creating plot... it might take some time if the data are large. Number of samples: 15
## Creating plot... it might take some time if the data are large. Number of samples: 15
```



The number of samples and signatures is:

```
## [1] 30  9
```

The signatures are:

```
## [1] "SBS1"  "SBS2"  "SBS7a" "SBS7b" "SBS7c" "SBS31" "SBS38" "SBS40" "SBS58"
```

Convergence table

These are the results for the convergence of models fits. They have converged even though very clearly we have very few observations and too many parameters. I thought I would have excluded this cancer type? In CT_sufficient_samples.txt it does appear but shouldn't - I don't continue the analyses for this cancer type.

```
##                  value                              L2
## 1  Skin-Melanoma.acral    hessian_positivedefinite_bool
## 2  Skin-Melanoma.acral    hessian_positivedefinite_bool
```

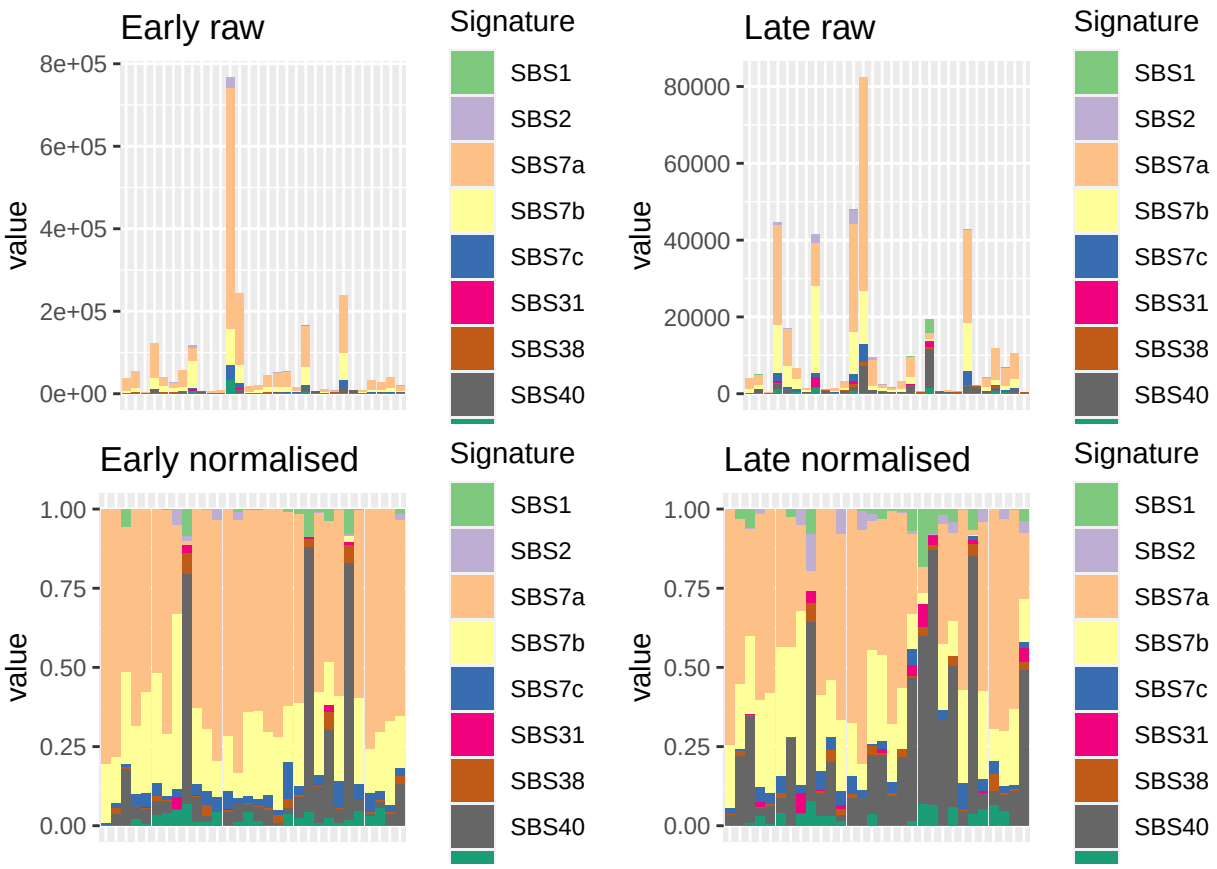
```
## 3  Skin-Melanoma.acral hessian_nonpositivedefinite_bool
## 4  Skin-Melanoma.acral                          Timeout
## 5  Skin-Melanoma.acral hessian_nonpositivedefinite_bool
## 6  Skin-Melanoma.acral    hessian_positivedefinite_bool
## 7  Skin-Melanoma.acral    hessian_positivedefinite_bool
## 8  Skin-Melanoma.acral hessian_nonpositivedefinite_bool
## 9  Skin-Melanoma.acral hessian_nonpositivedefinite_bool
## 10 Skin-Melanoma.acral    hessian_positivedefinite_bool
## 11 Skin-Melanoma.acral    hessian_positivedefinite_bool
## 12 Skin-Melanoma.acral                          Timeout
## 13 Skin-Melanoma.acral    hessian_positivedefinite_bool
## 14 Skin-Melanoma.acral    hessian_positivedefinite_bool
## 15 Skin-Melanoma.acral                          Timeout
##                           L1
## 1                    diagRE_M
## 2                    fullRE_M
## 3                  diagRE_DMDL
## 4                fullRE_halfDM
## 5                  fullRE_DMDL
## 6                  diagRE_DMSL
## 7                sparseRE_DMSL
## 8                  fullRE_DMSL
## 9            fullRE_DMSL_SBS1
## 10            fullRE_M_nonexo
## 11         diagRE_DMSL_nonexo
## 12       sparseRE_DMSL_nonexo
## 13         fullRE_DMSL_nonexo
## 14         fullRE_DMDL_nonexo
## 15 fullRE_DMDL_sortednonexo
```

Skin-Melanoma.cutaneous

Barplot and general statistics

```
## [1] 30
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
```



The number of samples and signatures is:

```
## [1] 60  9
```

The signatures are:

```
## [1] "SBS1"  "SBS2"  "SBS7a" "SBS7b" "SBS7c" "SBS31" "SBS38" "SBS40" "SBS58"
```

Convergence table

These are the results for the convergence of models fits. fullRE_DMSL have not converged.

```
##                       value                                L2
## 1  Skin-Melanoma.cutaneous    hessian_positivedefinite_bool
## 2  Skin-Melanoma.cutaneous hessian_nonpositivedefinite_bool
## 3  Skin-Melanoma.cutaneous    hessian_positivedefinite_bool
## 4  Skin-Melanoma.cutaneous                          Timeout
## 5  Skin-Melanoma.cutaneous hessian_nonpositivedefinite_bool
## 6  Skin-Melanoma.cutaneous    hessian_positivedefinite_bool
## 7  Skin-Melanoma.cutaneous    hessian_positivedefinite_bool
## 8  Skin-Melanoma.cutaneous hessian_nonpositivedefinite_bool
## 9  Skin-Melanoma.cutaneous hessian_nonpositivedefinite_bool
## 10 Skin-Melanoma.cutaneous    hessian_positivedefinite_bool
## 11 Skin-Melanoma.cutaneous    hessian_positivedefinite_bool
## 12 Skin-Melanoma.cutaneous                          Timeout
## 13 Skin-Melanoma.cutaneous                          Timeout
```

```
## 14 Skin-Melanoma.cutaneous hessian_nonpositivedefinite_bool
## 15 Skin-Melanoma.cutaneous    hessian_positivedefinite_bool
##                            L1
## 1                    diagRE_M
## 2                    fullRE_M
## 3                 diagRE_DMDL
## 4              fullRE_halfDM
## 5                 fullRE_DMDL
## 6                 diagRE_DMSL
## 7              sparseRE_DMSL
## 8                 fullRE_DMSL
## 9           fullRE_DMSL_SBS1
## 10           fullRE_M_nonexo
## 11        diagRE_DMSL_nonexo
## 12     sparseRE_DMSL_nonexo
## 13        fullRE_DMSL_nonexo
## 14        fullRE_DMDL_nonexo
## 15 fullRE_DMDL_sortednonexo
```

Re-running of fitting

Using fullRE_M_nonexo to fit fullRE_DMSL_nonexo.

If we use the values of the fullRE M exo as initial values for the fullRE DMSL exo do converge:

```
## [1] TRUE
```

It has converged.

Potentially problematic signatures

We explore whether there are problematic signatures; there are none.

```
colSums(obj_Skin_Melanomacutaneous$Y == 0)/nrow(obj_Skin_Melanomacutaneous$Y)
```

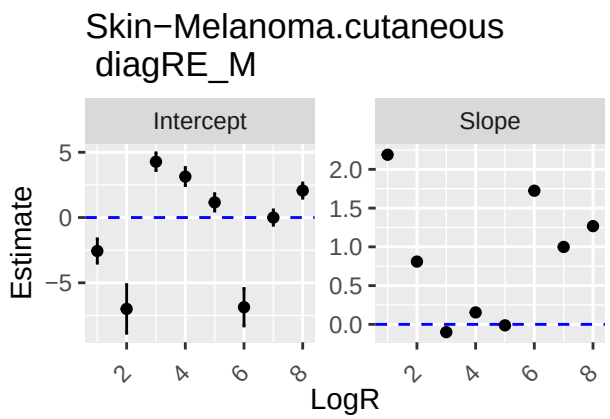
```
##       SBS1       SBS2      SBS7a      SBS7b      SBS7c      SBS31      SBS38
## 0.31666667 0.68333333 0.03333333 0.06666667 0.13333333 0.71666667 0.11666667
##      SBS40      SBS58
## 0.05000000 0.25000000
```

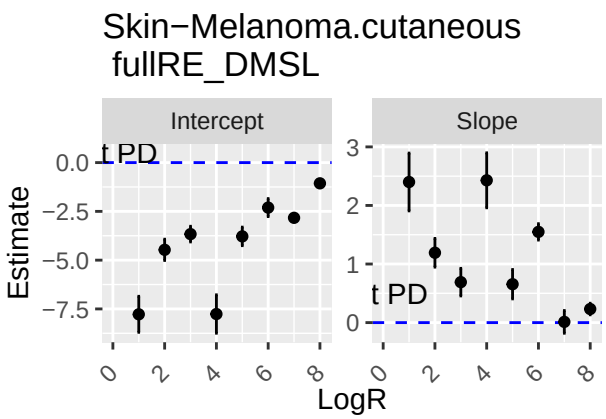
```
colSums(obj_Skin_Melanomacutaneous$Y)/sum(obj_Skin_Melanomacutaneous$Y)
```

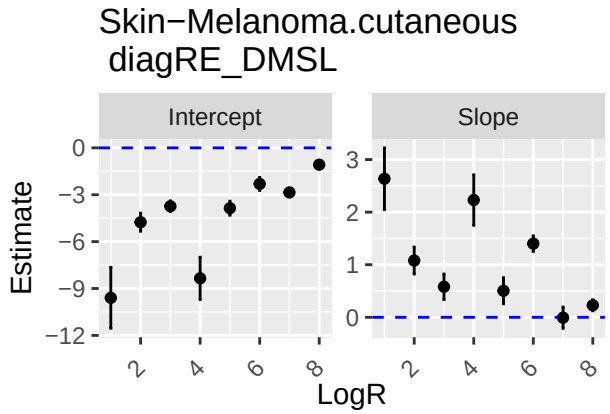
```
##        SBS1        SBS2       SBS7a       SBS7b       SBS7c       SBS31
## 0.004433478 0.015369819 0.652197003 0.207691993 0.044244244 0.003864520
##       SBS38       SBS40       SBS58
## 0.005701701 0.042679042 0.023818200
```

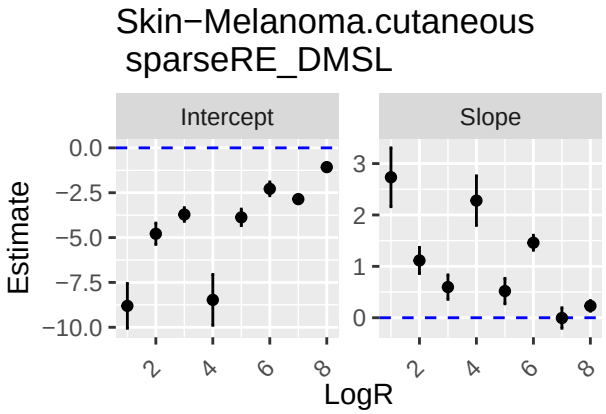
Betas

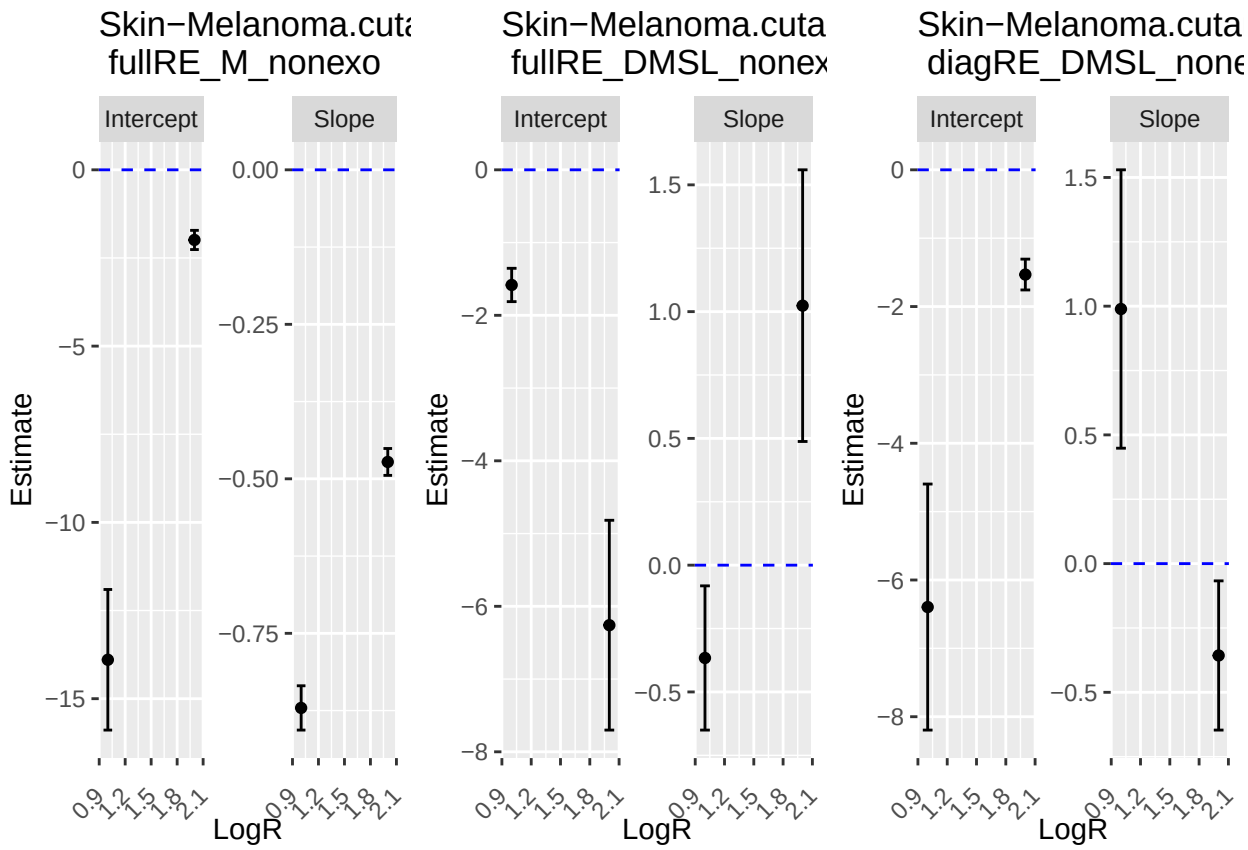
```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```


Skin−Melanoma.cutaneous
diagRE_M
Intercept
Slope
Estimate
LogR


Skin−Melanoma.cutaneous
fullRE_DMSL
Intercept
Slope
t PD
t PD
Estimate
LogR


Skin−Melanoma.cutaneous
diagRE_DMSL
Intercept
Slope
Estimate
LogR


Skin−Melanoma.cutaneous
sparseRE_DMSL
Intercept
Slope
Estimate
LogR



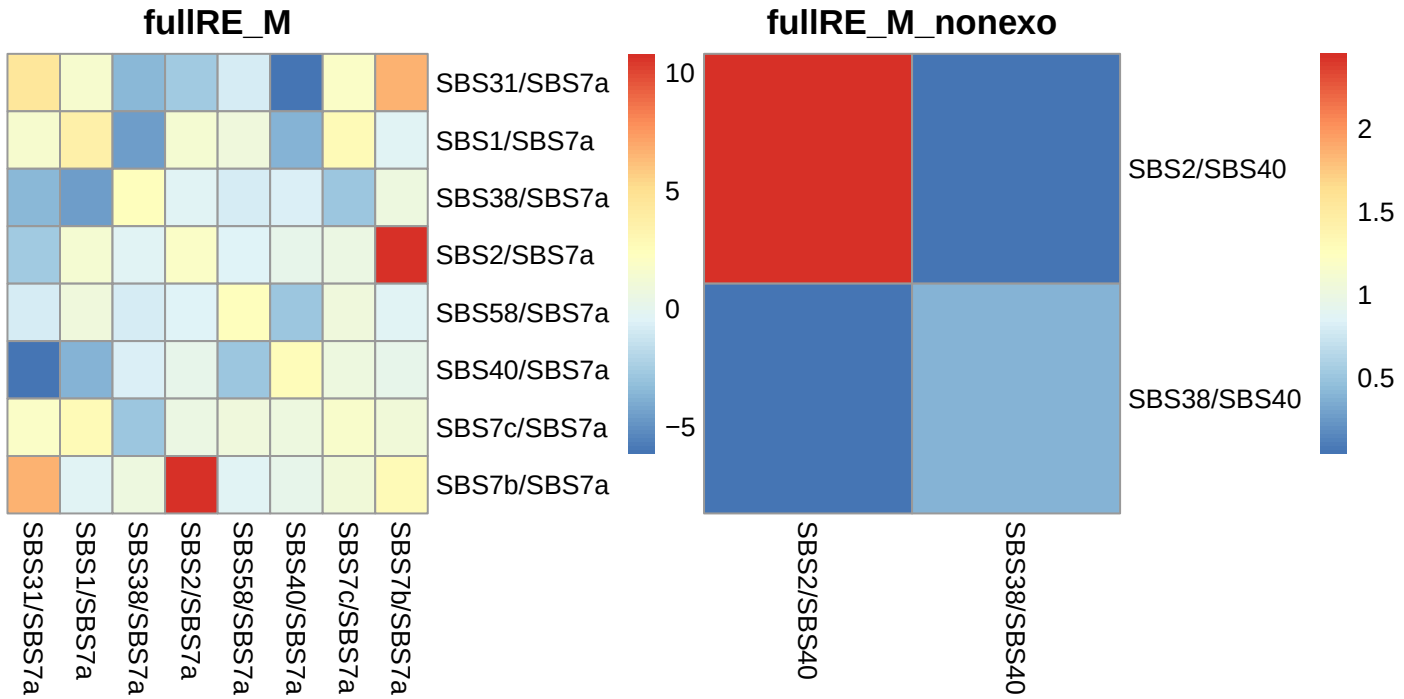

```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct
```

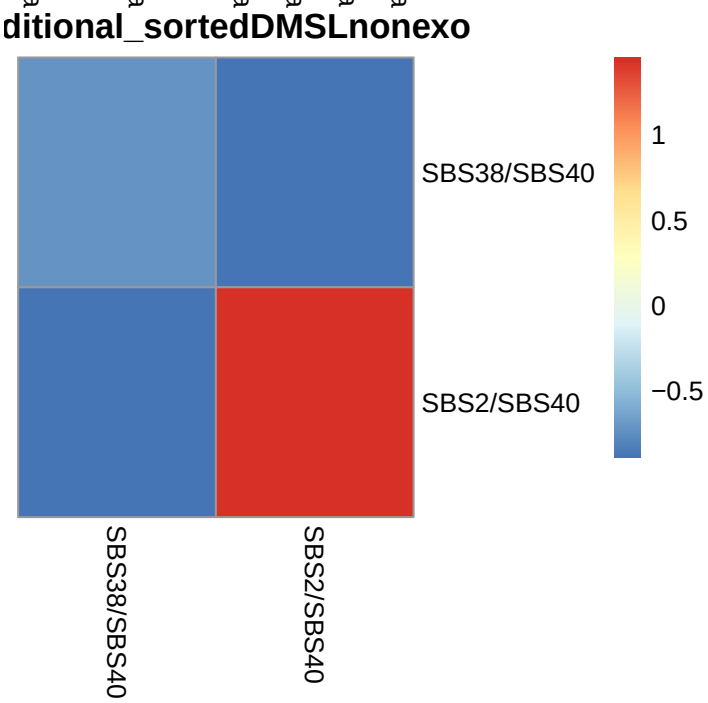
```
## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used
```

```
## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 0.0628799.

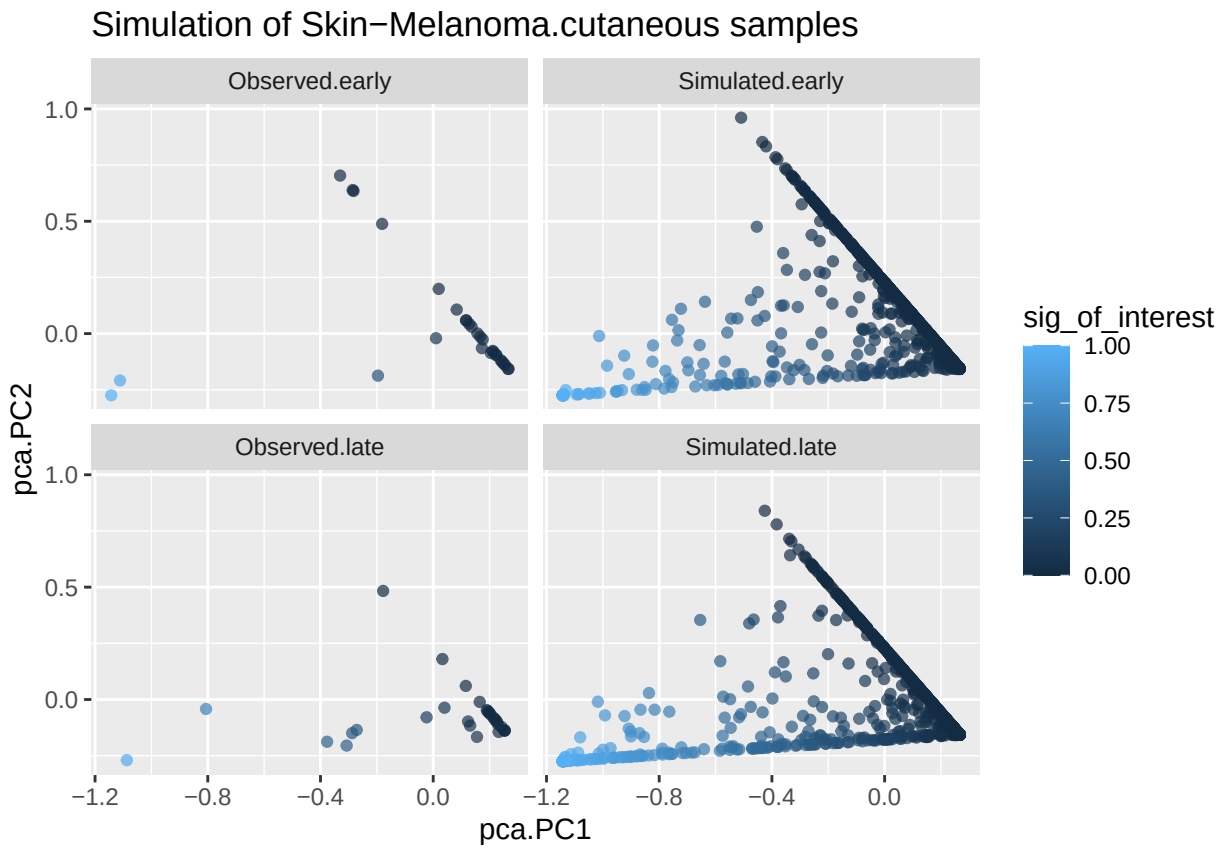
Covariance matrices





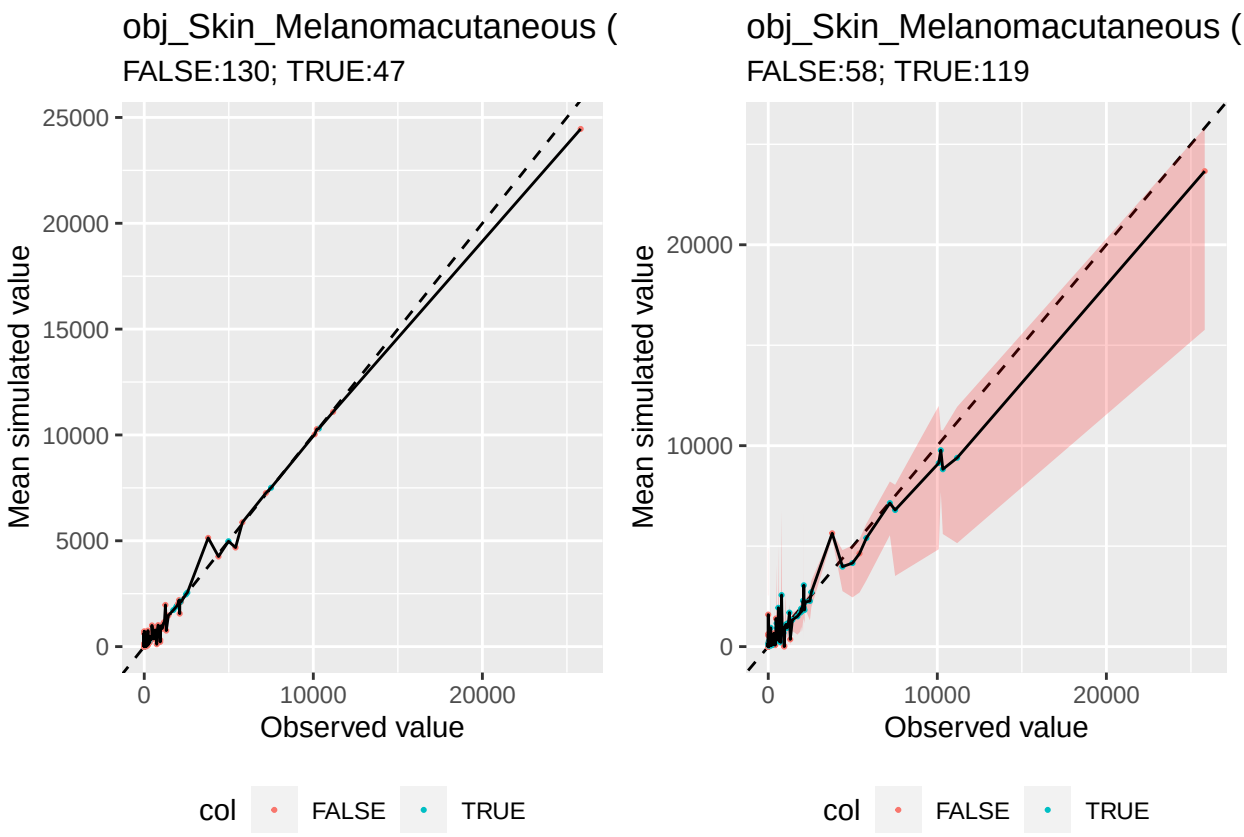
Simulation under inferred data

```
## [1] 30
```



Ranked plot for coverage

```
ct <- "Skin-Melanoma.cutaneous"
integer_overdispersion_param_DMSL <- 1
obj_Skin_Melanomacutaneous_nonexo <- give_subset_sigs_TMBobj(obj_Skin_Melanomacutaneous, sigs_to_remove =
obj_Skin_Melanomacutaneous_nonexo_sorted <- sort_columns_TMB(give_subset_sigs_TMBobj(obj_Skin_Melanomacut
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                data_object = obj_Skin_Melanomacutaneous_nonexo,
                print_plot = F, nreps = 20, model = "M")), function(i){
                  lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                         rank_number=1:length(j)) )})[[1]],
                data_object = obj_Skin_Melanomacutaneous_nonexo,
                loglog = F, title = 'obj_Skin_Melanomacutaneous (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = sortedDM_SkinMe
                data_object = obj_Skin_Melanomacutaneous_nonexo_sorted,
                print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                  lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                         rank_number=1:length(j)) )})[[1]],
                data_object = obj_Skin_Melanomacutaneous_nonexo_sorted,
           loglog = F, title = 'obj_Skin_Melanomacutaneous (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

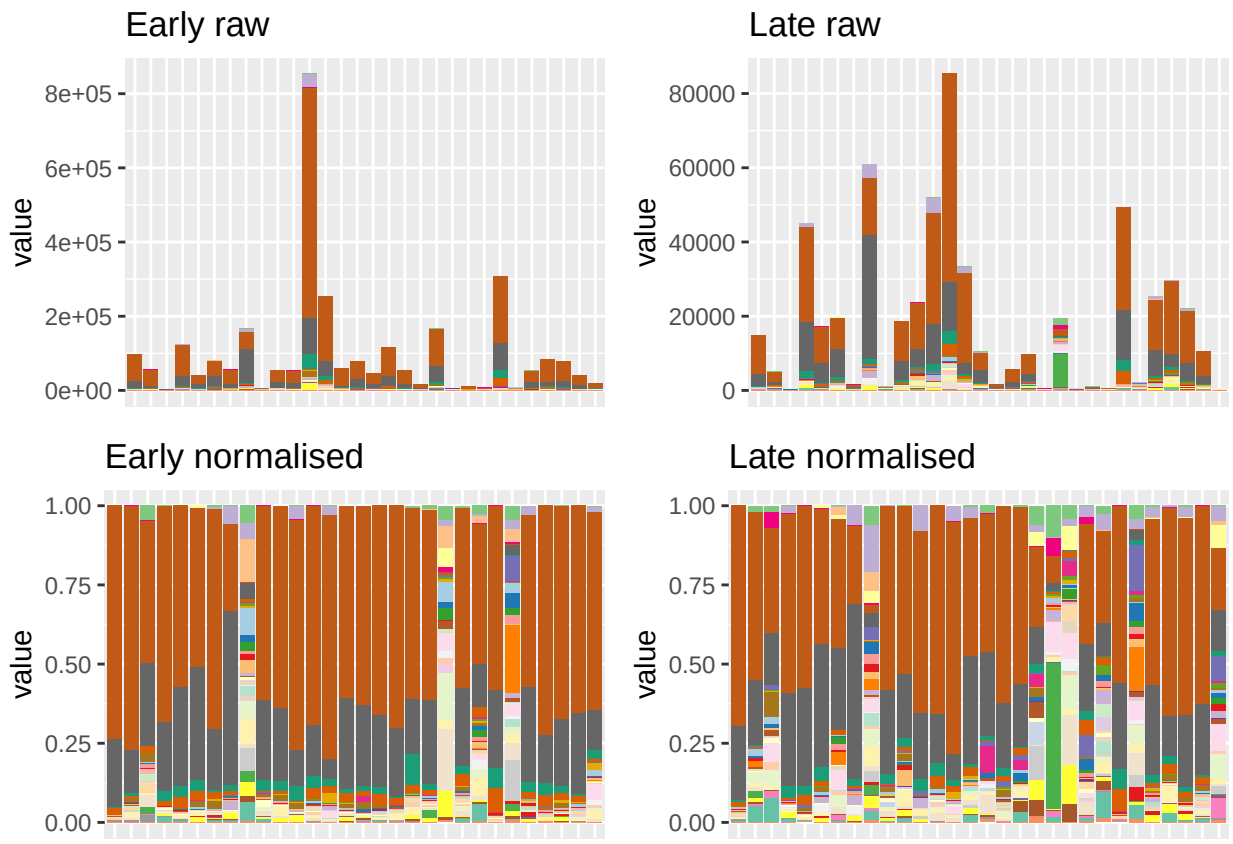
```
obj_Skin_Melanomacutaneous_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

```
## [1] 30
```

```
give_barplot_from_obj(obj = obj_Skin_Melanomacutaneous_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
```

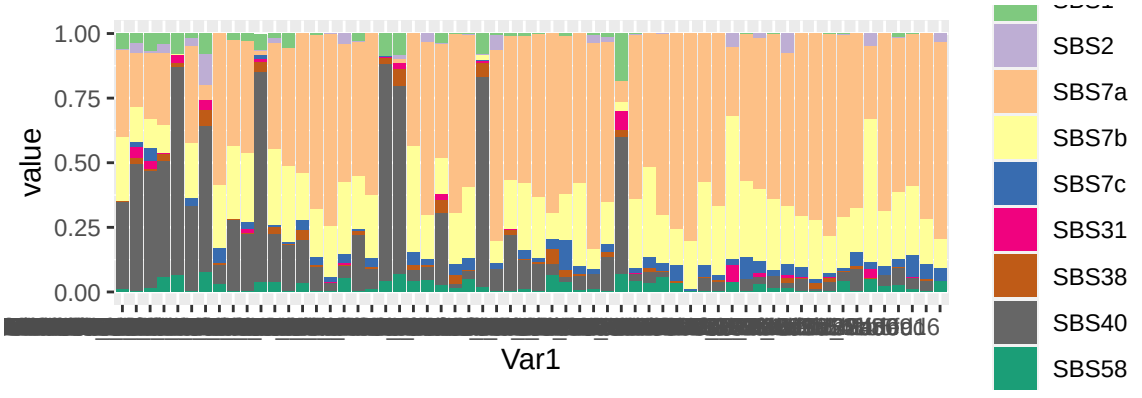
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: SBS40 is crearly prevalent in samples with few mutations.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Skin_Melanomacutaneous$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Skin_Melanomacutaneous$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 60
```

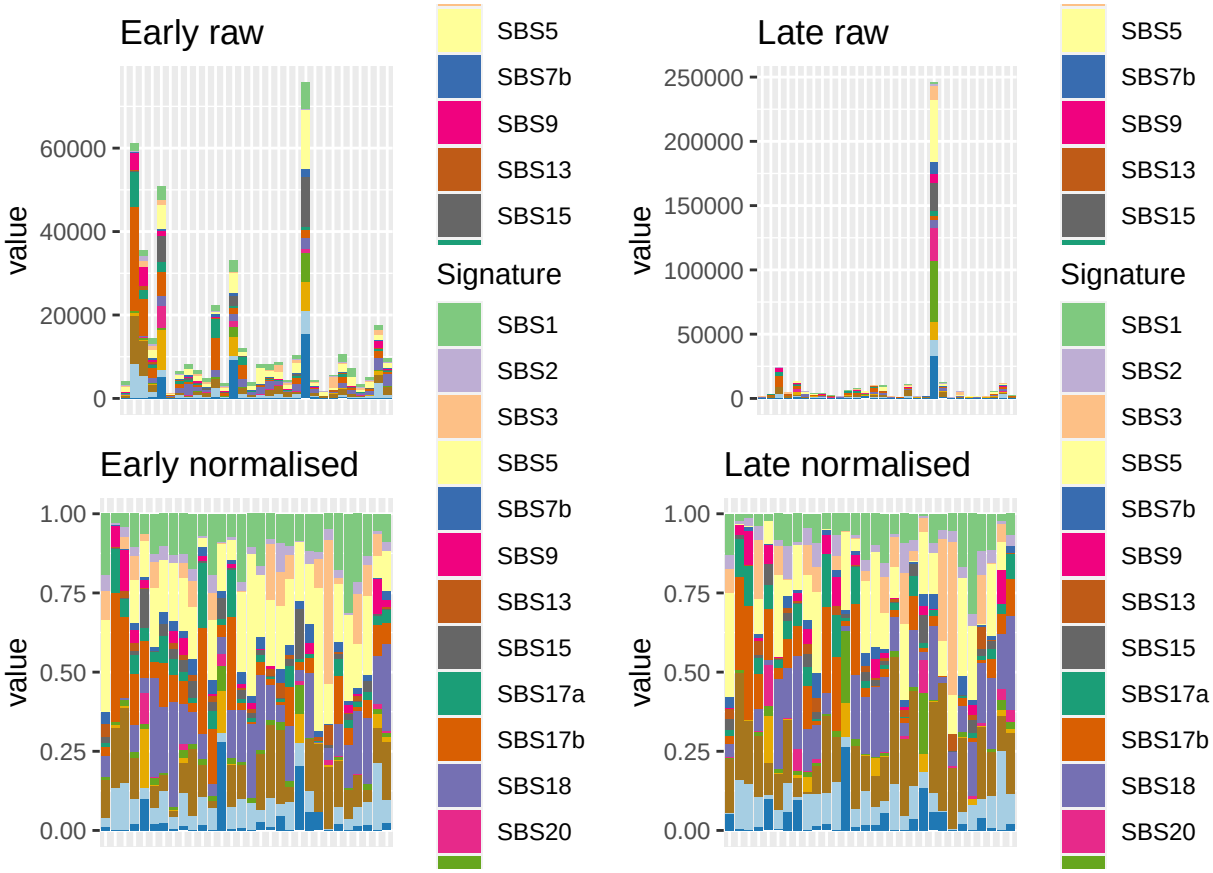


Stomach-AdenoCA

Barplot and general statistics

```
## [1] 30
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
```



The number of samples and signatures is:

```
## [1] 60 17
```

The signatures are:

```
##  [1] "SBS1"   "SBS2"   "SBS3"   "SBS5"   "SBS7b"  "SBS9"   "SBS13"  "SBS15"
##  [9] "SBS17a" "SBS17b" "SBS18"  "SBS20"  "SBS21"  "SBS26"  "SBS40"  "SBS41"
## [17] "SBS44"
```

Convergence table

These are the results for the convergence of models fits. Besides fullRE_DMSL_nonexo, we have convergence with almost everything.

```
##              value                                L2                 L1
## 1  Stomach-AdenoCA    hessian_positivedefinite_bool            diagRE_M
## 2  Stomach-AdenoCA hessian_nonpositivedefinite_bool            fullRE_M
## 3  Stomach-AdenoCA hessian_nonpositivedefinite_bool          diagRE_DMDL
## 4  Stomach-AdenoCA                         Timeout         fullRE_halfDM
## 5  Stomach-AdenoCA                         Timeout           fullRE_DMDL
```

```
## 6  Stomach-AdenoCA    hessian_positivedefinite_bool             diagRE_DMSL
## 7  Stomach-AdenoCA    hessian_positivedefinite_bool           sparseRE_DMSL
## 8  Stomach-AdenoCA                          Timeout             fullRE_DMSL
## 9  Stomach-AdenoCA hessian_nonpositivedefinite_bool        fullRE_DMSL_SBS1
## 10 Stomach-AdenoCA hessian_nonpositivedefinite_bool         fullRE_M_nonexo
## 11 Stomach-AdenoCA    hessian_positivedefinite_bool      diagRE_DMSL_nonexo
## 12 Stomach-AdenoCA    hessian_positivedefinite_bool    sparseRE_DMSL_nonexo
## 13 Stomach-AdenoCA                          Timeout      fullRE_DMSL_nonexo
## 14 Stomach-AdenoCA hessian_nonpositivedefinite_bool      fullRE_DMDL_nonexo
## 15 Stomach-AdenoCA hessian_nonpositivedefinite_bool fullRE_DMDL_sortednonexo
```

Re-running of fitting

Using fullRE_M_nonexo to fit fullRE_DMSL_nonexo, but M hasn't converged. We should include fewer signatures.

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

Potentially problematic signatures

We explore whether there are problematic signatures:

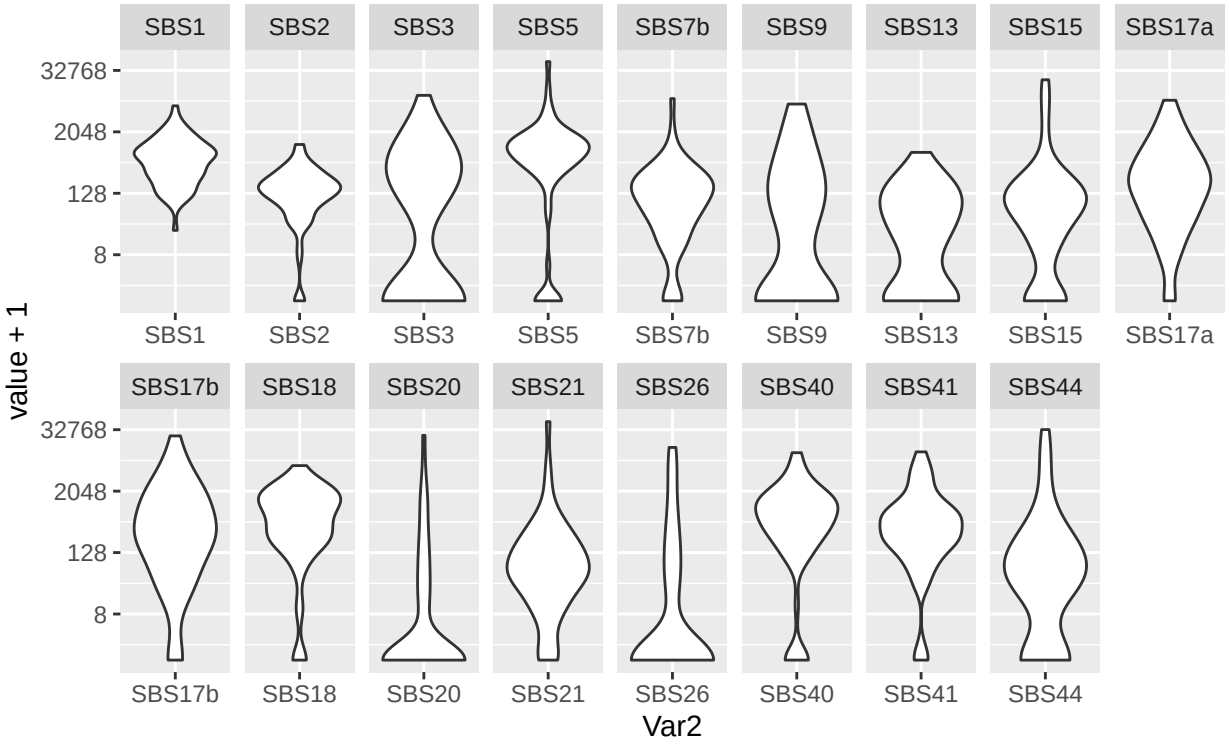
```
colSums(obj_Stomach_AdenoCA$Y == 0)/nrow(obj_Stomach_AdenoCA$Y)
```

```
##       SBS1       SBS2       SBS3       SBS5      SBS7b       SBS9      SBS13
## 0.00000000 0.05000000 0.45000000 0.13333333 0.08333333 0.41666667 0.30000000
##      SBS15     SBS17a     SBS17b      SBS18      SBS20      SBS21      SBS26
## 0.21666667 0.05000000 0.06666667 0.06666667 0.70000000 0.06666667 0.68333333
##      SBS40      SBS41      SBS44
## 0.11666667 0.05000000 0.26666667
```

```
colSums(obj_Stomach_AdenoCA$Y)/sum(obj_Stomach_AdenoCA$Y)
```

```
##        SBS1        SBS2        SBS3        SBS5       SBS7b        SBS9
## 0.060565293 0.014095732 0.036577106 0.141513807 0.023236523 0.033484479
##       SBS13       SBS15      SBS17a      SBS17b       SBS18       SBS20
## 0.005394089 0.054607746 0.047754477 0.106132160 0.070925941 0.041749297
##       SBS21       SBS26       SBS40       SBS41       SBS44
## 0.074860849 0.047217740 0.084139891 0.076236383 0.081508486
```

```
ggplot(melt(obj_Stomach_AdenoCA$Y), aes(x=Var2, y=value+1))+geom_violin()+scale_y_continuous(trans = "log
```

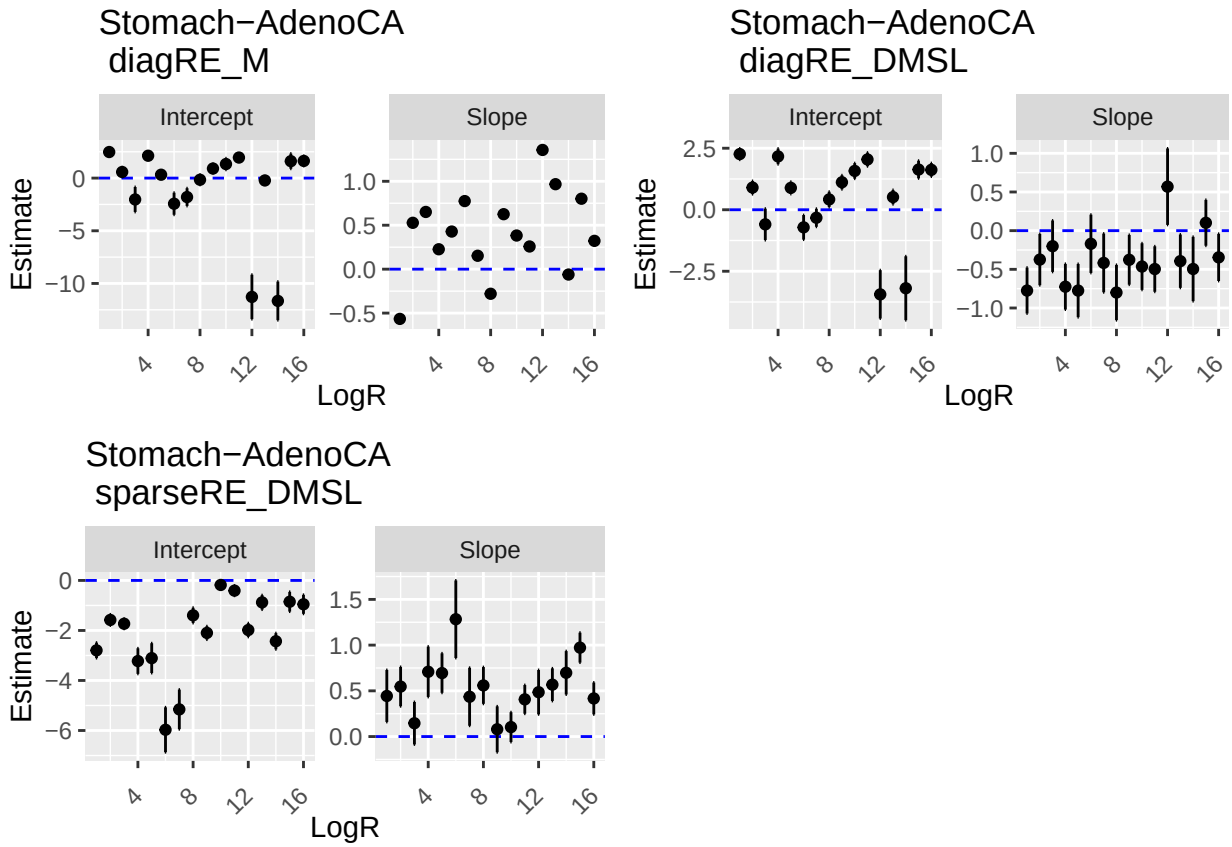


- Removing SBS20, SBS26, fullM still hasn't converged
- Removing SBS20, SBS26, SBS9 fullM still hasn't converged
- Removing SBS20, SBS26, SBS9, SBS13 fullM still hasn't converged
- Removing SBS20, SBS26, SBS9, SBS13, SBS44 fullM still hasn't converged

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

Betas

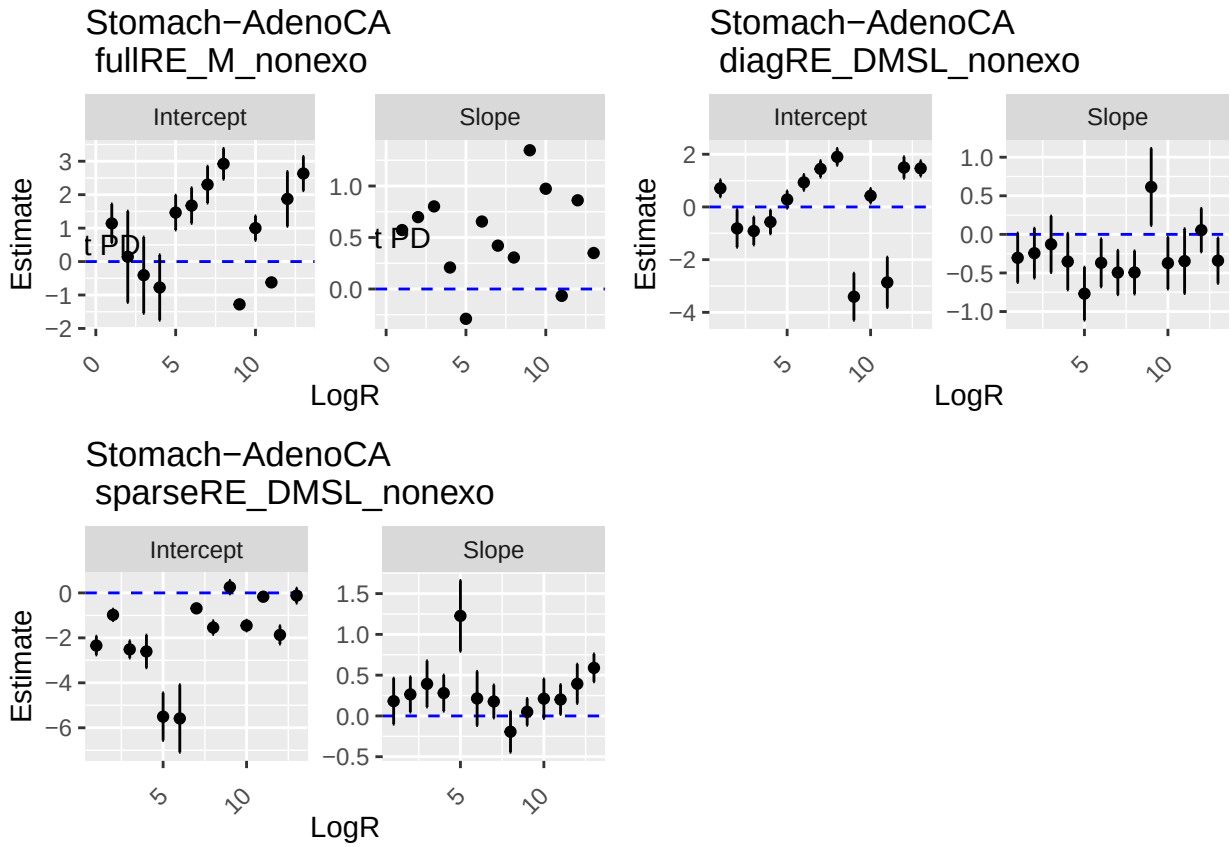
```
ct <- "Stomach-AdenoCA"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```




```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

```
## Warning in sqrt(as.numeric(object$diag.cov.random)): NaNs produced
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct
```

```
## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used
```

```
## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of 0.047603.

Covariance matrices

I do not include this section as I have had to use ony diagonal matrices.

Simulation under inferred data

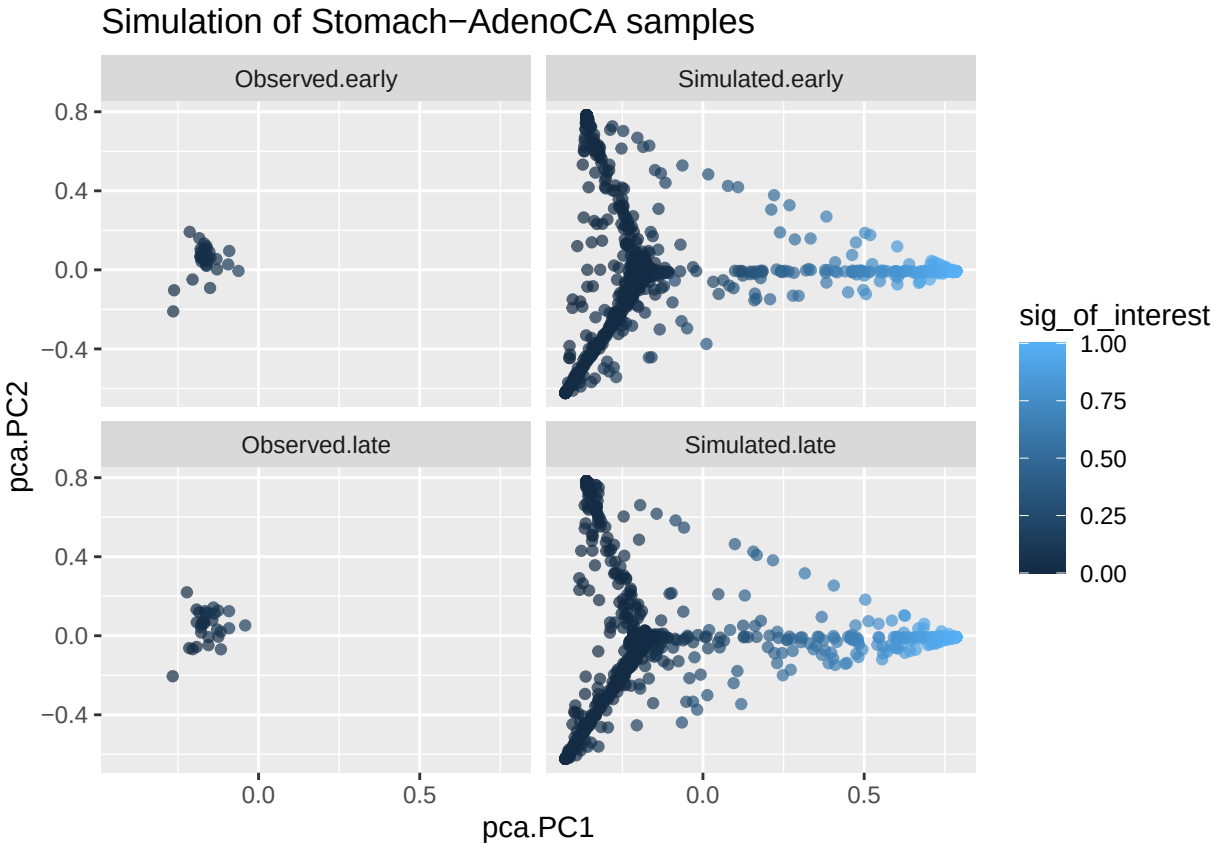
```
## [1] 30
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```

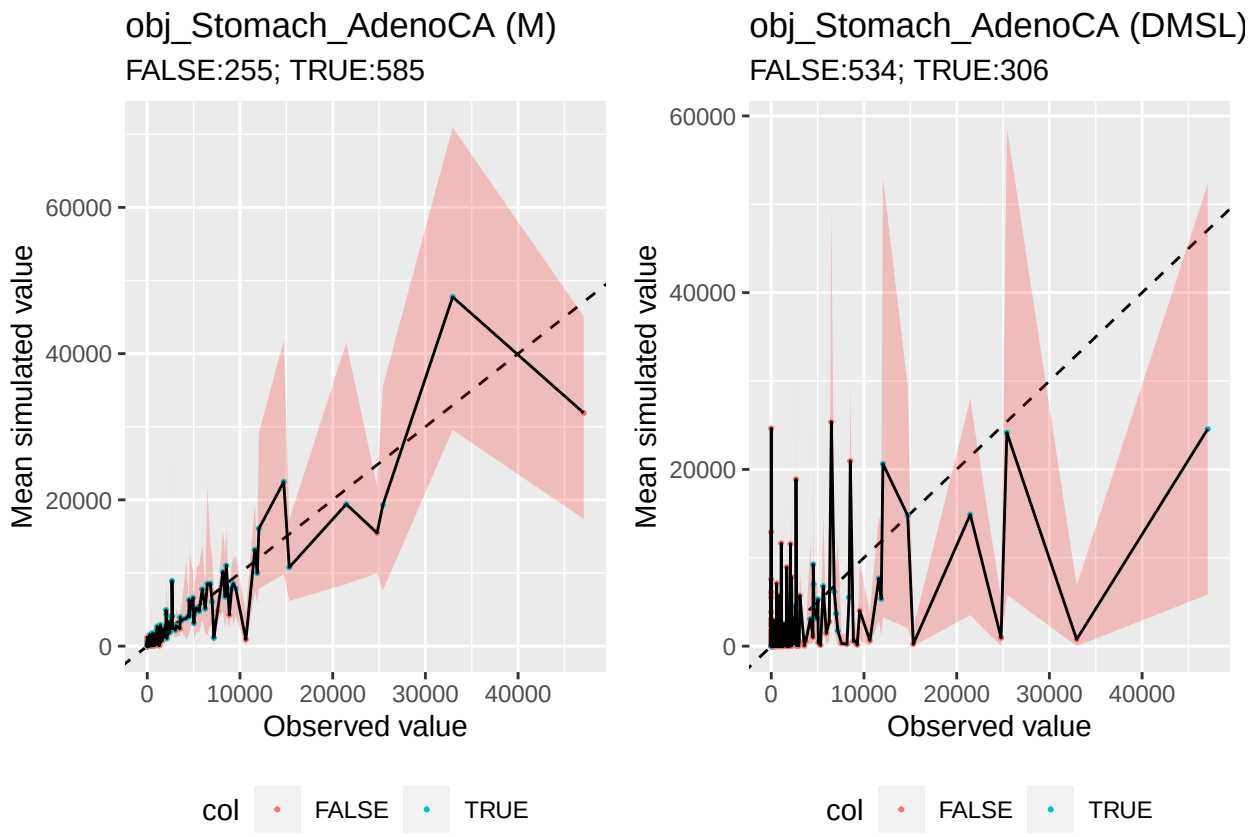


Ranked plot for coverage

Comparing for now only diagRE_DMSL_nonexo and sparse for nonexo. It doesn't look good.

```
ct <- "Stomach-AdenoCA"
integer_overdispersion_param_DMSL <- 1
obj_Stomach_AdenoCA_nonexo <- sort_columns_TMB(give_subset_sigs_TMBobj(obj_Stomach_AdenoCA, sigs_to_remov
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = spa
                  data_object = obj_Stomach_AdenoCA_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Stomach_AdenoCA_nonexo,
                  loglog = F, title = 'obj_Stomach_AdenoCA (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = diagRE_DMSL_non
                  data_object = obj_Stomach_AdenoCA_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Stomach_AdenoCA_nonexo,
```

```
          loglog = F, title = 'obj_Stomach_AdenoCA (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

```
obj_Stomach_AdenoCA_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

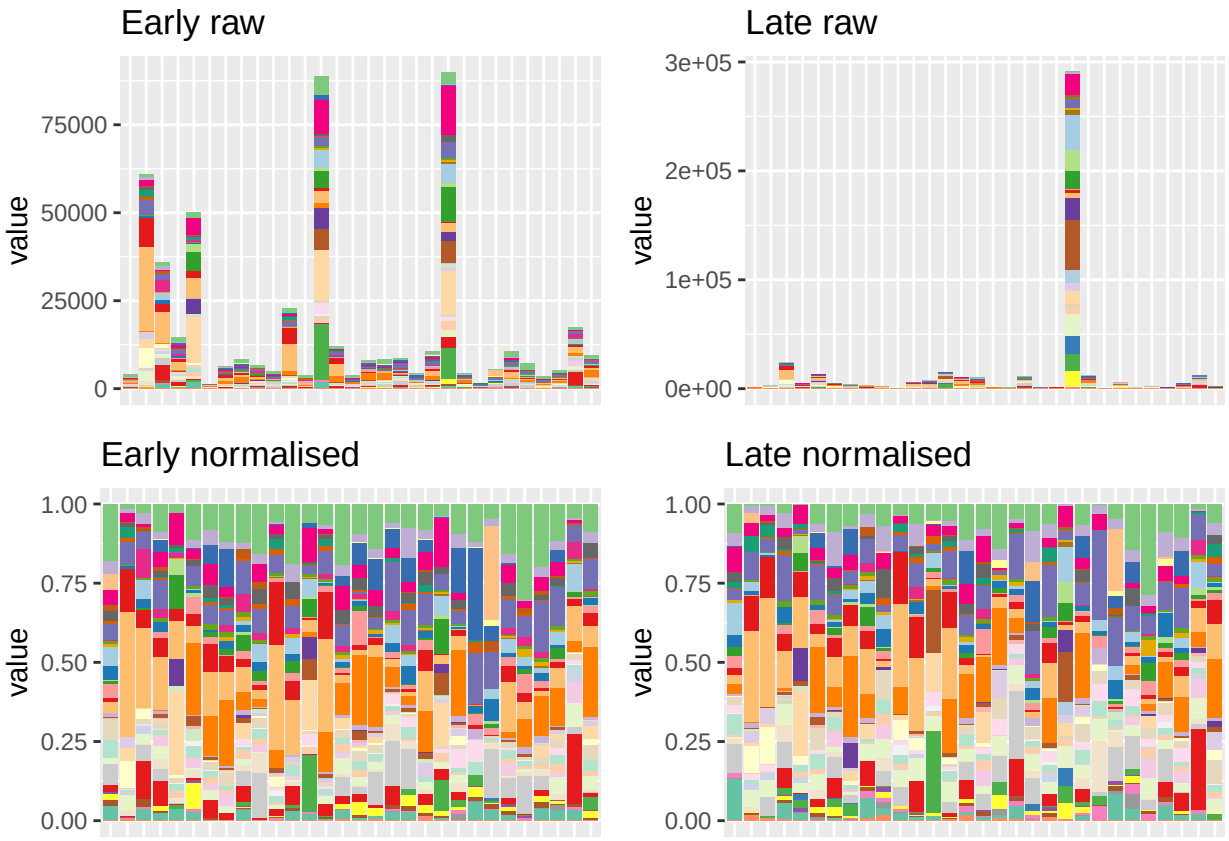
```
## [1] 30
```

```
give_barplot_from_obj(obj = obj_Stomach_AdenoCA_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
## Creating plot... it might take some time if the data are large. Number of samples: 30
```

```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```

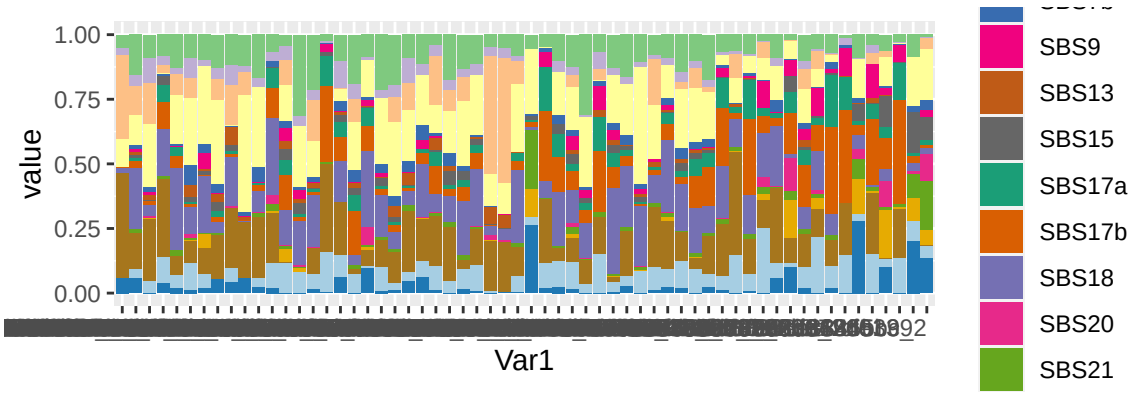
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: there is no clear trend of signatures being associated with the number of mutations.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Stomach_AdenoCA$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Stomach_AdenoCA$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 60
```

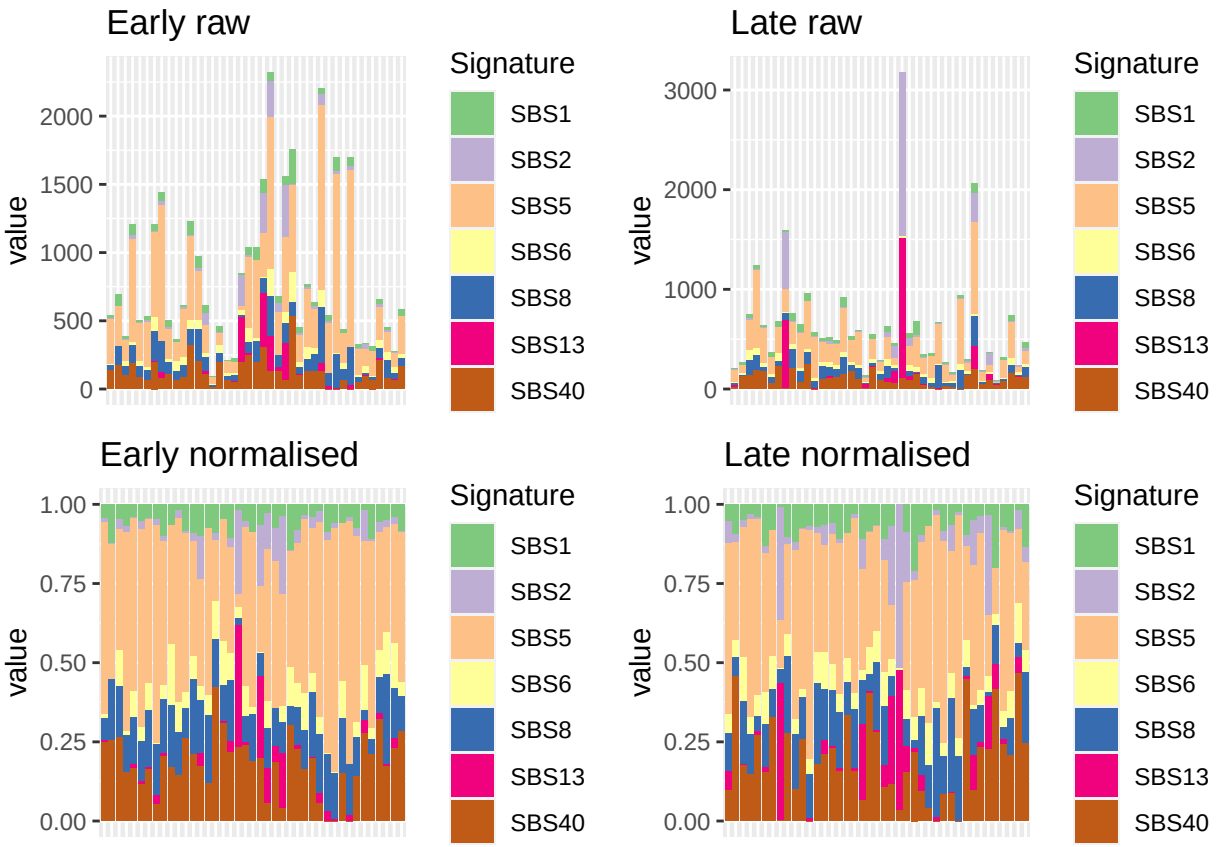


Thy-AdenoCA

Barplot and general statistics

```
## [1] 41
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 41
## Creating plot... it might take some time if the data are large. Number of samples: 41
## Creating plot... it might take some time if the data are large. Number of samples: 41
## Creating plot... it might take some time if the data are large. Number of samples: 41
```



The number of samples and signatures is:

```
## [1] 82  7
```

The signatures are:

```
## [1] "SBS1"  "SBS2"  "SBS5"  "SBS6"  "SBS8"  "SBS13" "SBS40"
```

Convergence table

These are the results for the convergence of models fits. Practically everything timed-out.

```
##          value                                L2                  L1
## 1  Thy-AdenoCA    hessian_positivedefinite_bool             diagRE_M
## 2  Thy-AdenoCA    hessian_positivedefinite_bool             fullRE_M
## 3  Thy-AdenoCA    hessian_positivedefinite_bool           diagRE_DMDL
## 4  Thy-AdenoCA                          Timeout         fullRE_halfDM
## 5  Thy-AdenoCA hessian_nonpositivedefinite_bool           fullRE_DMDL
```

```
## 6  Thy-AdenoCA    hessian_positivedefinite_bool             diagRE_DMSL
## 7  Thy-AdenoCA    hessian_positivedefinite_bool           sparseRE_DMSL
## 8  Thy-AdenoCA                          Timeout             fullRE_DMSL
## 9  Thy-AdenoCA                          Timeout        fullRE_DMSL_SBS1
## 10 Thy-AdenoCA                          Timeout         fullRE_M_nonexo
## 11 Thy-AdenoCA    hessian_positivedefinite_bool      diagRE_DMSL_nonexo
## 12 Thy-AdenoCA    hessian_positivedefinite_bool    sparseRE_DMSL_nonexo
## 13 Thy-AdenoCA                          Timeout      fullRE_DMSL_nonexo
## 14 Thy-AdenoCA                          Timeout      fullRE_DMDL_nonexo
## 15 Thy-AdenoCA                          Timeout fullRE_DMDL_sortednonexo
```

Re-running of fitting

Using fullRE_M_nonexo to fit fullRE_DMSL_nonexo.

If we use the values of the fullRE M exo as initial values for the fullRE DMSL exo do not converge, even though there aren't many signatures:

```
## [1] FALSE
```

Potentially problematic signatures

We explore whether there are problematic signatures:

```
colSums(obj_Thy_AdenoCA$Y == 0)/nrow(obj_Thy_AdenoCA$Y)
```

```
##       SBS1       SBS2       SBS5       SBS6       SBS8      SBS13      SBS40
## 0.01219512 0.12195122 0.01219512 0.06097561 0.01219512 0.35365854 0.07317073
```

```
colSums(obj_Thy_AdenoCA$Y)/sum(obj_Thy_AdenoCA$Y)
```

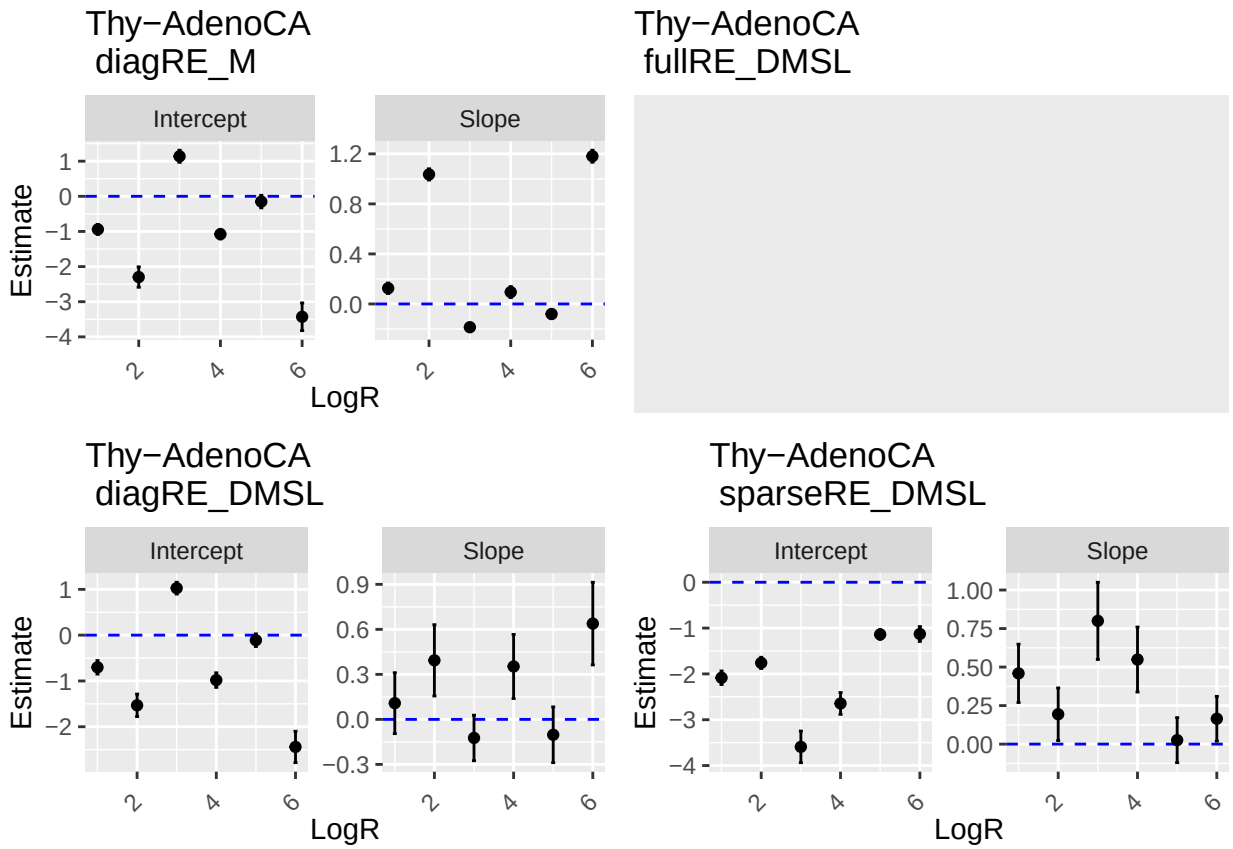
```
##       SBS1       SBS2       SBS5       SBS6       SBS8      SBS13      SBS40
## 0.06120959 0.08303459 0.44489809 0.05581557 0.12930691 0.07239594 0.15333931
```

```
ggplot(melt(obj_Thy_AdenoCA$Y), aes(x=Var2, y=value+1))+geom_violin()+scale_y_continuous(trans = "log2")
```

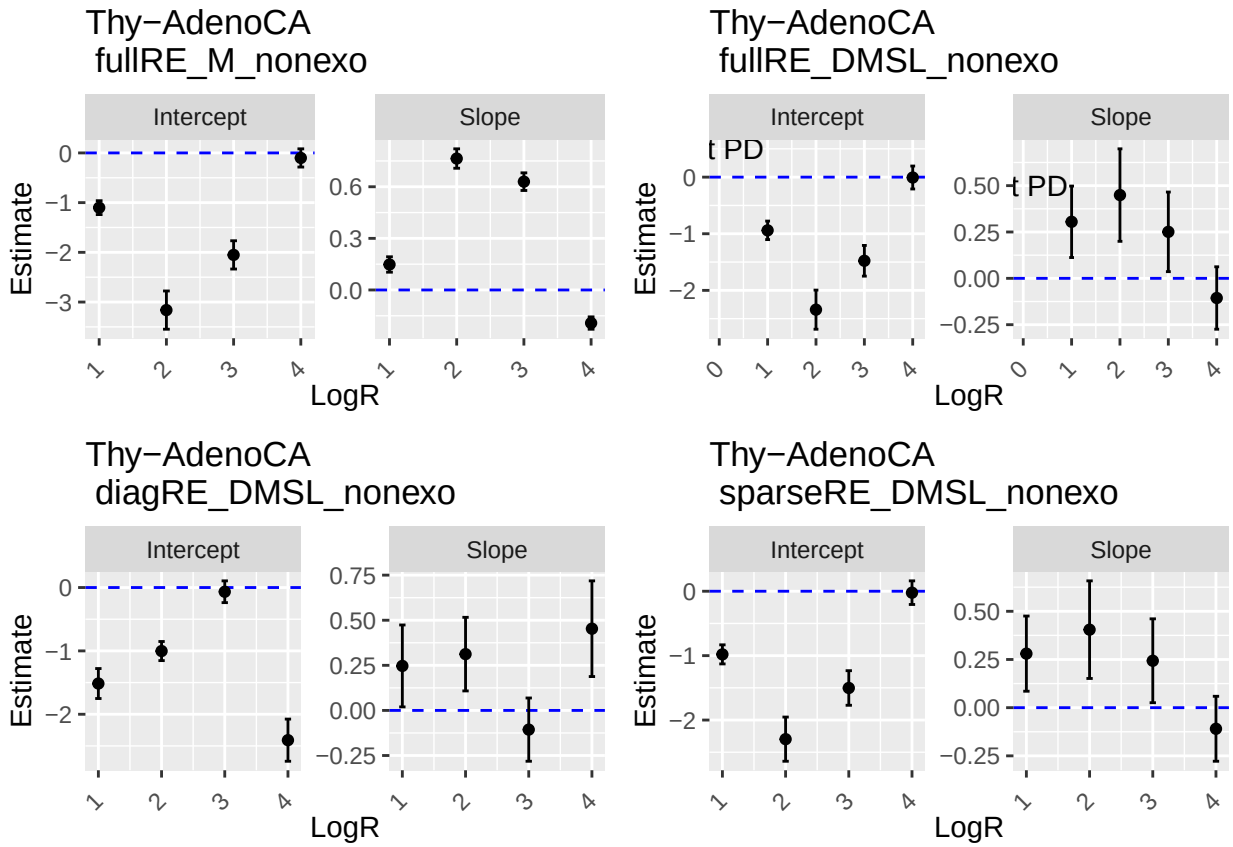
Betas

```
ct <- "Thy-AdenoCA"

grid.arrange(plot_betas(diagRE_M[[ct]])+ggtitle(paste0(ct, '\n diagRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
```

```
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```




```
grid.arrange(
  plot_betas(sortedM_ThyAdenoCA)+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(sortedDM_ThyAdenoCA)+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct
```

```
## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used
```

```
## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of 0.1064332.

Covariance matrices

I do not include those.

Simulation under inferred data

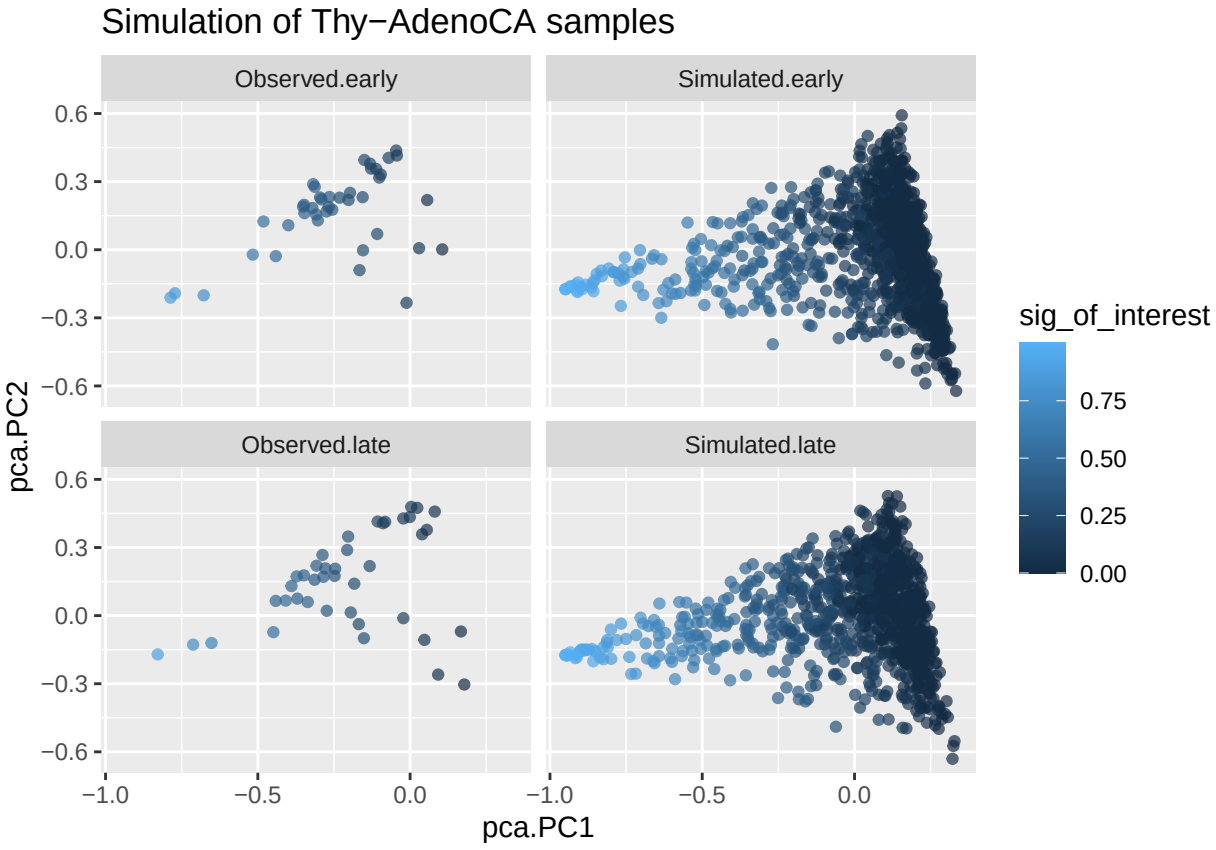
```
## [1] 41
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

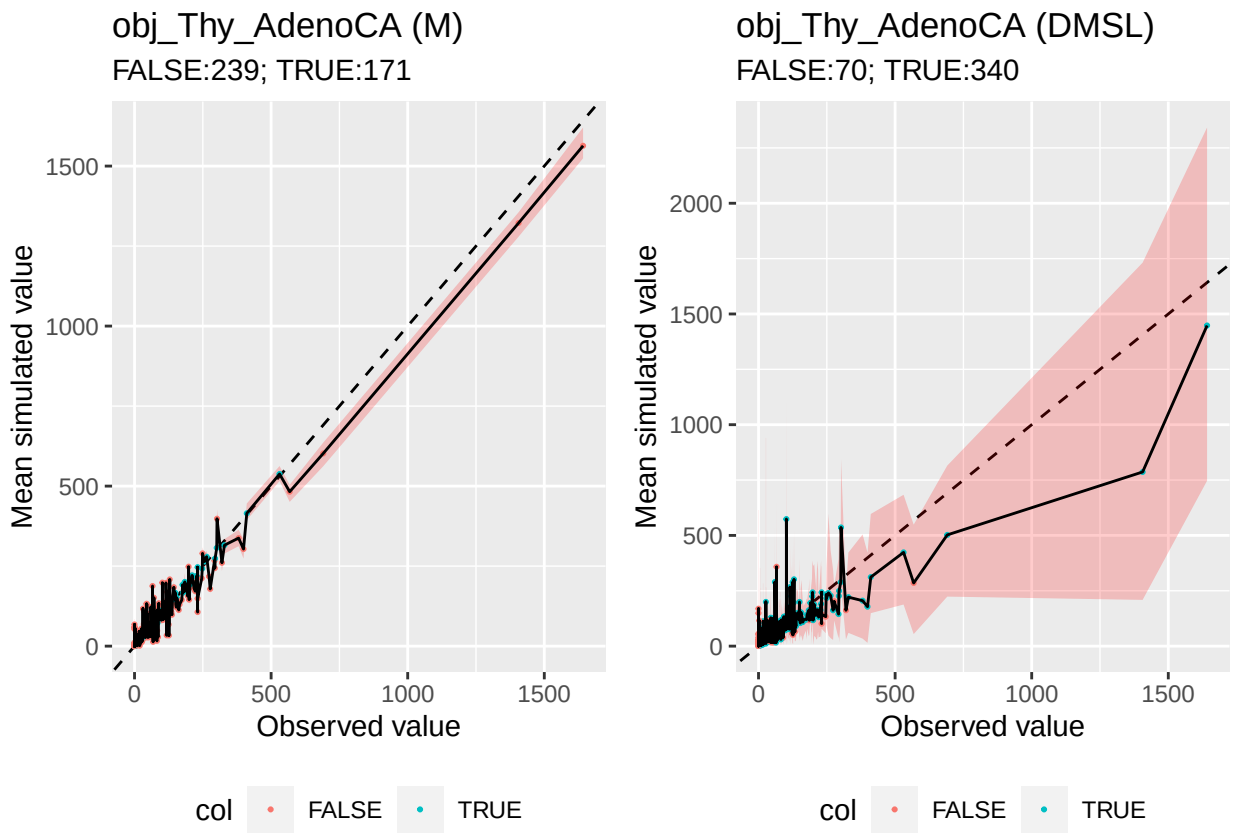
```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```



Ranked plot for coverage

```
ct <- "Thy-AdenoCA"
integer_overdispersion_param_DMSL <- 1
obj_Thy_AdenoCA_nonexo <- give_subset_sigs_TMBobj(obj_Thy_AdenoCA, sigs_to_remove = nonexogenous$V1)
obj_Thy_AdenoCA_nonexo_sorted <- sort_columns_TMB(give_subset_sigs_TMBobj(obj_Thy_AdenoCA, sigs_to_remove
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = sor
                  data_object = obj_Thy_AdenoCA_nonexo_sorted,
                  print_plot = F, nreps = 20, model = "M")), function(i){
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Thy_AdenoCA_nonexo_sorted,
                  loglog = F, title = 'obj_Thy_AdenoCA (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = diagRE_DMSL_nor
                  data_object = obj_Thy_AdenoCA_nonexo,
                  print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                    lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                           rank_number=1:length(j)) )})[[1]],
                  data_object = obj_Thy_AdenoCA_nonexo,
```

```
          loglog = F, title = 'obj_Thy_AdenoCA (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

```
obj_Thy_AdenoCA_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

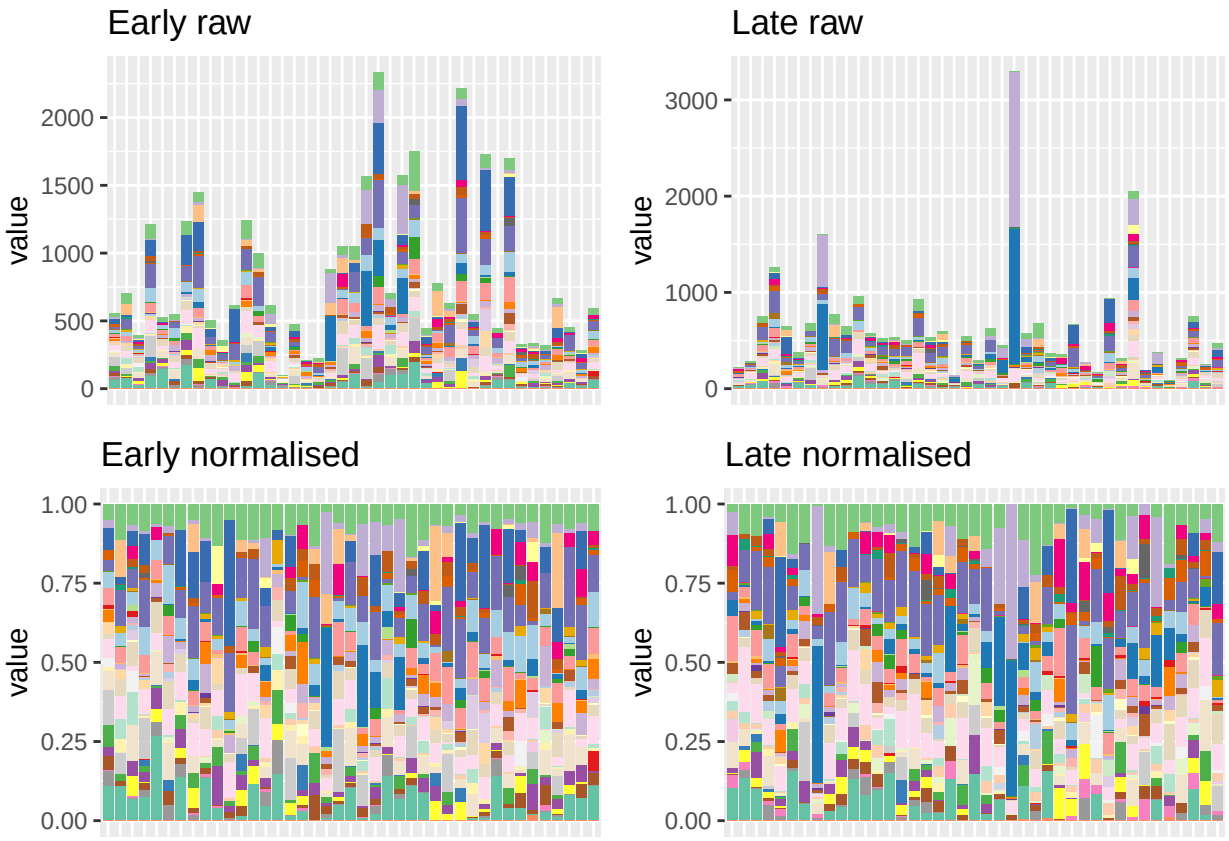
```
## [1] 41
```

```
give_barplot_from_obj(obj = obj_Thy_AdenoCA_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 41
## Creating plot... it might take some time if the data are large. Number of samples: 41
## Creating plot... it might take some time if the data are large. Number of samples: 41
## Creating plot... it might take some time if the data are large. Number of samples: 41
```

```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```

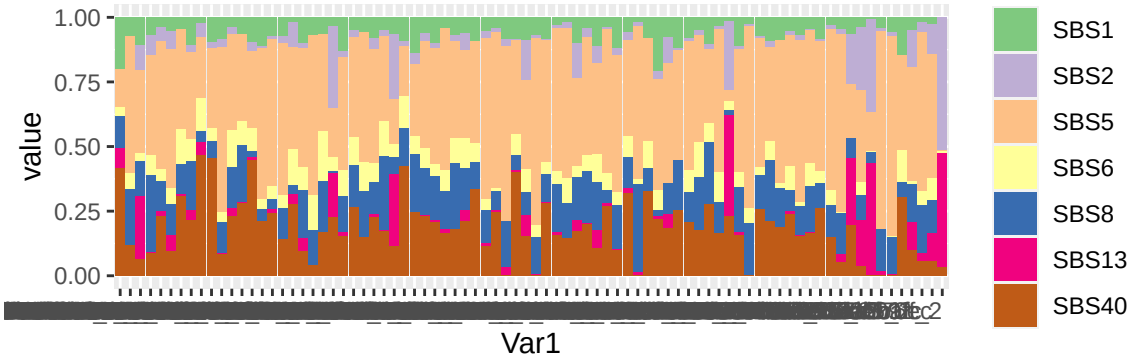
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Thy_AdenoCA$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Thy_AdenoCA$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 82
```

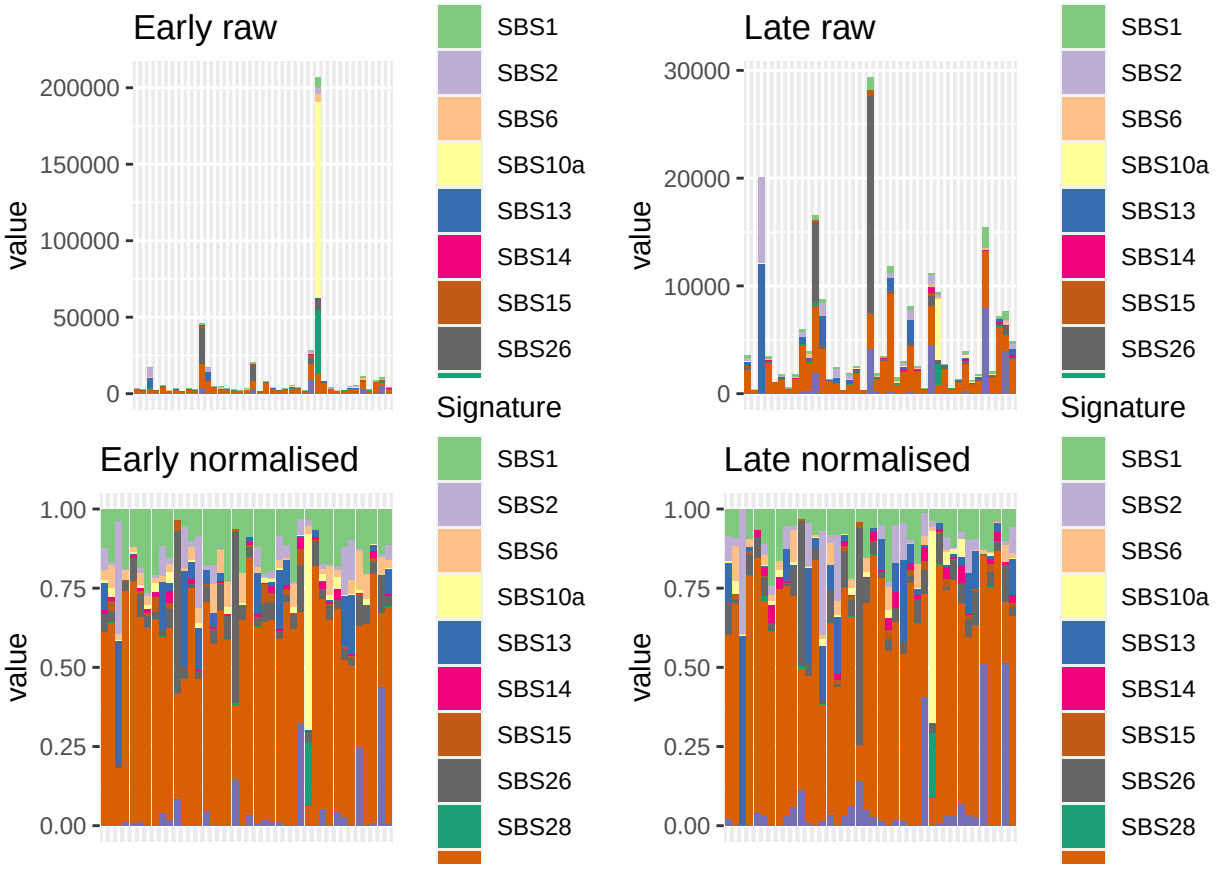


Uterus-AdenoCA

Barplot and general statistics

```
## [1] 40
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 40
## Creating plot... it might take some time if the data are large. Number of samples: 40
## Creating plot... it might take some time if the data are large. Number of samples: 40
## Creating plot... it might take some time if the data are large. Number of samples: 40
```



The number of samples and signatures is:

```
## [1] 82  7
```

The signatures are:

```
## [1] "SBS1"  "SBS2"  "SBS5"  "SBS6"  "SBS8"  "SBS13" "SBS40"
```

Convergence table

These are the results for the convergence of models fits. Almost everything has converged.

```
##             value                                L2                   L1
## 1  Uterus-AdenoCA hessian_nonpositivedefinite_bool              diagRE_M
## 2  Uterus-AdenoCA hessian_nonpositivedefinite_bool              fullRE_M
## 3  Uterus-AdenoCA hessian_nonpositivedefinite_bool            diagRE_DMDL
## 4  Uterus-AdenoCA                          Timeout          fullRE_halfDM
```

```
## 5  Uterus-AdenoCA hessian_nonpositivedefinite_bool             fullRE_DMDL
## 6  Uterus-AdenoCA    hessian_positivedefinite_bool             diagRE_DMSL
## 7  Uterus-AdenoCA    hessian_positivedefinite_bool           sparseRE_DMSL
## 8  Uterus-AdenoCA                          Timeout             fullRE_DMSL
## 9  Uterus-AdenoCA hessian_nonpositivedefinite_bool        fullRE_DMSL_SBS1
## 10 Uterus-AdenoCA    hessian_positivedefinite_bool         fullRE_M_nonexo
## 11 Uterus-AdenoCA    hessian_positivedefinite_bool      diagRE_DMSL_nonexo
## 12 Uterus-AdenoCA    hessian_positivedefinite_bool    sparseRE_DMSL_nonexo
## 13 Uterus-AdenoCA                          Timeout      fullRE_DMSL_nonexo
## 14 Uterus-AdenoCA hessian_nonpositivedefinite_bool      fullRE_DMDL_nonexo
## 15 Uterus-AdenoCA    hessian_positivedefinite_bool fullRE_DMDL_sortednonexo
```

Re-running of fitting

Using fullRE_M_nonexo to fit fullRE_DMSL_nonexo.

If we use the values of the fullRE M exo as initial values for the fullRE DMSL exo doesn't converge:

```
## [1] FALSE
```

Potentially problematic signatures

We explore whether there are problematic signatures:

```
colSums(obj_Uterus_AdenoCA$Y == 0)/nrow(obj_Uterus_AdenoCA$Y)
```

```
##       SBS1       SBS2       SBS5       SBS6       SBS8      SBS13      SBS40
## 0.01219512 0.12195122 0.01219512 0.06097561 0.01219512 0.35365854 0.07317073
```

```
colSums(obj_Uterus_AdenoCA$Y)/sum(obj_Uterus_AdenoCA$Y)
```

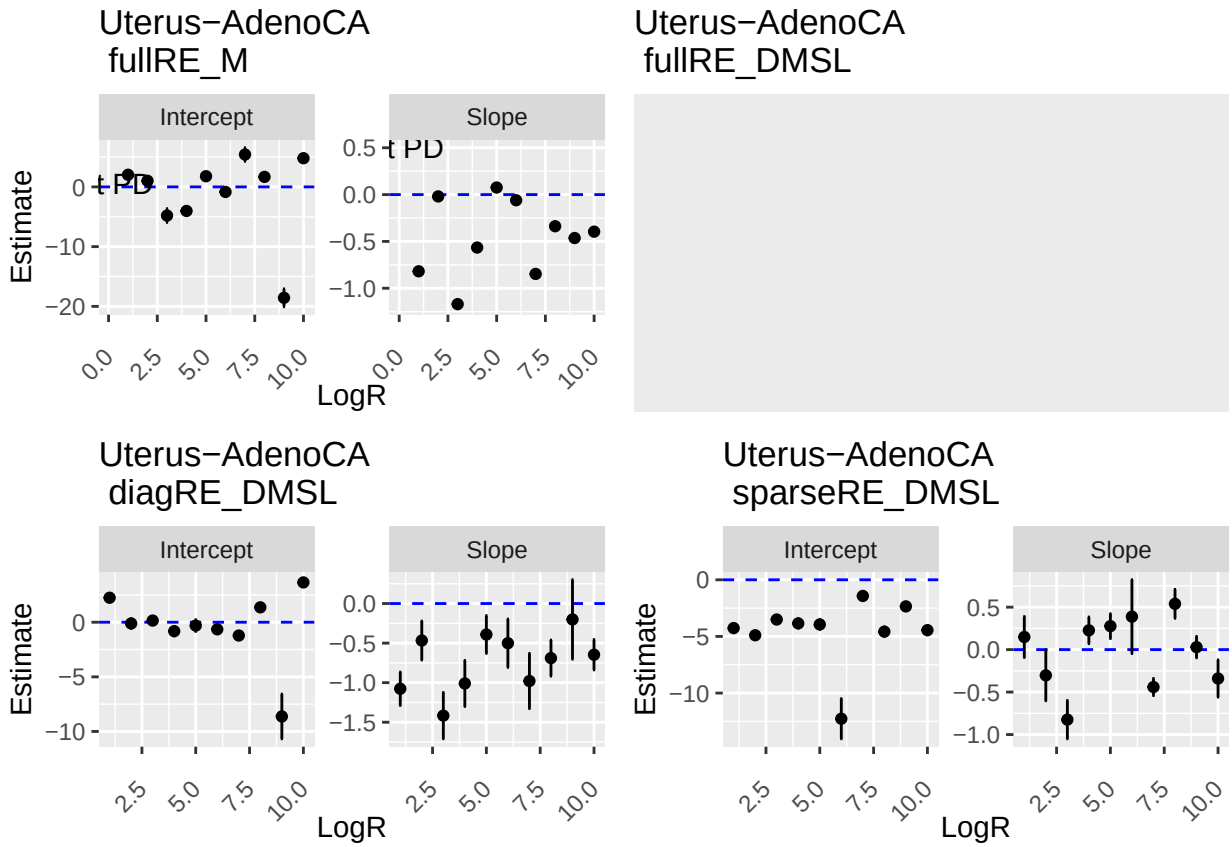
```
##       SBS1       SBS2       SBS5       SBS6       SBS8      SBS13      SBS40
## 0.06120959 0.08303459 0.44489809 0.05581557 0.12930691 0.07239594 0.15333931
```

Betas

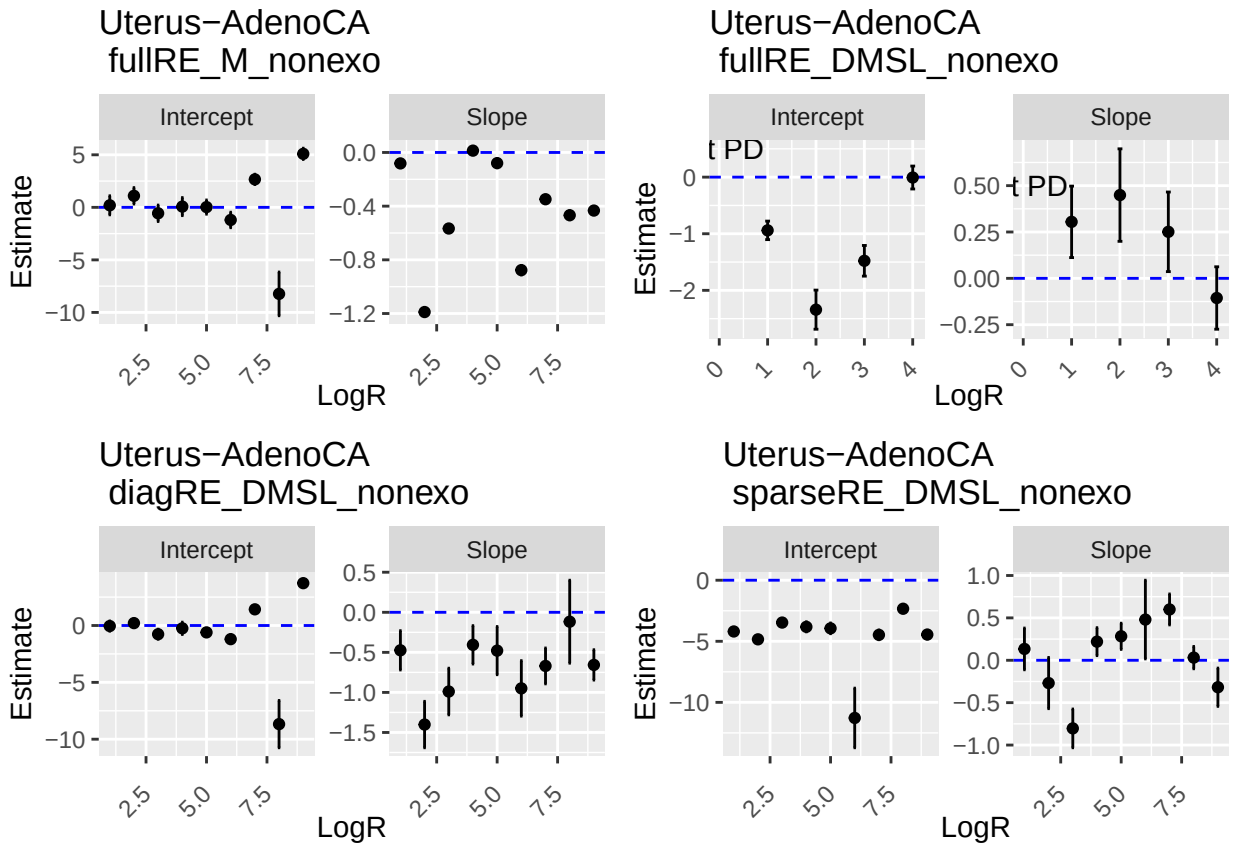
```
ct <- "Uterus-AdenoCA"

grid.arrange(plot_betas(fullRE_M[[ct]])+ggtitle(paste0(ct, '\n fullRE_M')),
plot_betas(fullRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n fullRE_DMSL')),
plot_betas(diagRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL')),
plot_betas(sparseRE_DMSL[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL')), nrow=2)
```

```
## Warning in sqrt(diag(object$cov.fixed)): NaNs produced
```

```
## Warning in sqrt(as.numeric(object$diag.cov.random)): NaNs produced
```



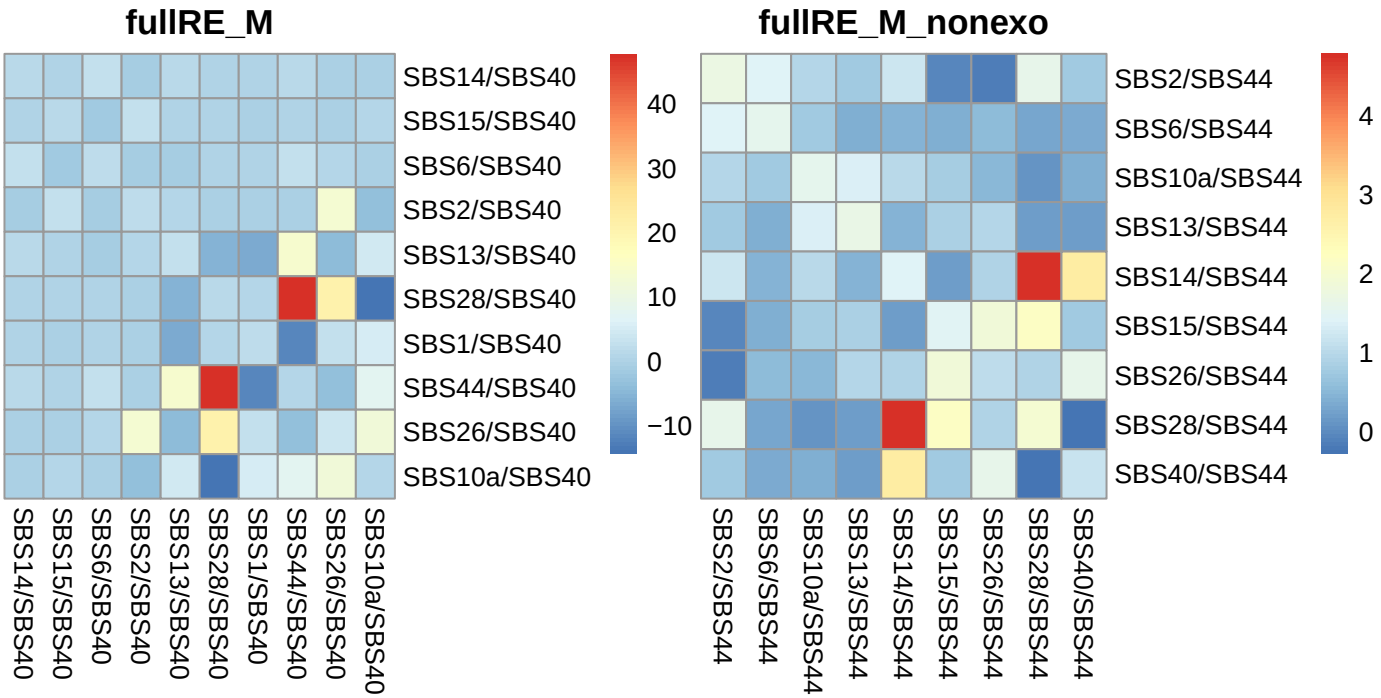

```
grid.arrange(
  plot_betas(fullRE_M_nonexo[[ct]])+ggtitle(paste0(ct, '\n fullRE_M_nonexo')),
  plot_betas(sortedDM_UterusAdenoCA)+ggtitle(paste0(ct, '\n fullRE_DMSL_nonexo')),
plot_betas(diagRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n diagRE_DMSL_nonexo')),
plot_betas(sparseRE_DMSL_nonexo[[ct]])+ggtitle(paste0(ct, '\n sparseRE_DMSL_nonexo')), nrow=2)
```




```
## Warning in select_slope_2(which(names(i$par.fixed) == "beta"), verbatim
## = verbatim): As per 27 August it seems clear that this version, and not
## <select_slope>, is correct

## Warning in if (is.na(idx_beta)) {: the condition has length > 1 and only the
## first element will be used

## Warning in wald_generalised(v = i$par.fixed[idx_beta], sigma =
## i$cov.fixed[idx_beta, : 20201218: sigma**(1/2) has now been replaced by (as we
## had before sometime in November) sigma
```

We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of 1.4837739×10^{-4}.

Covariance matrices



Simulation under inferred data

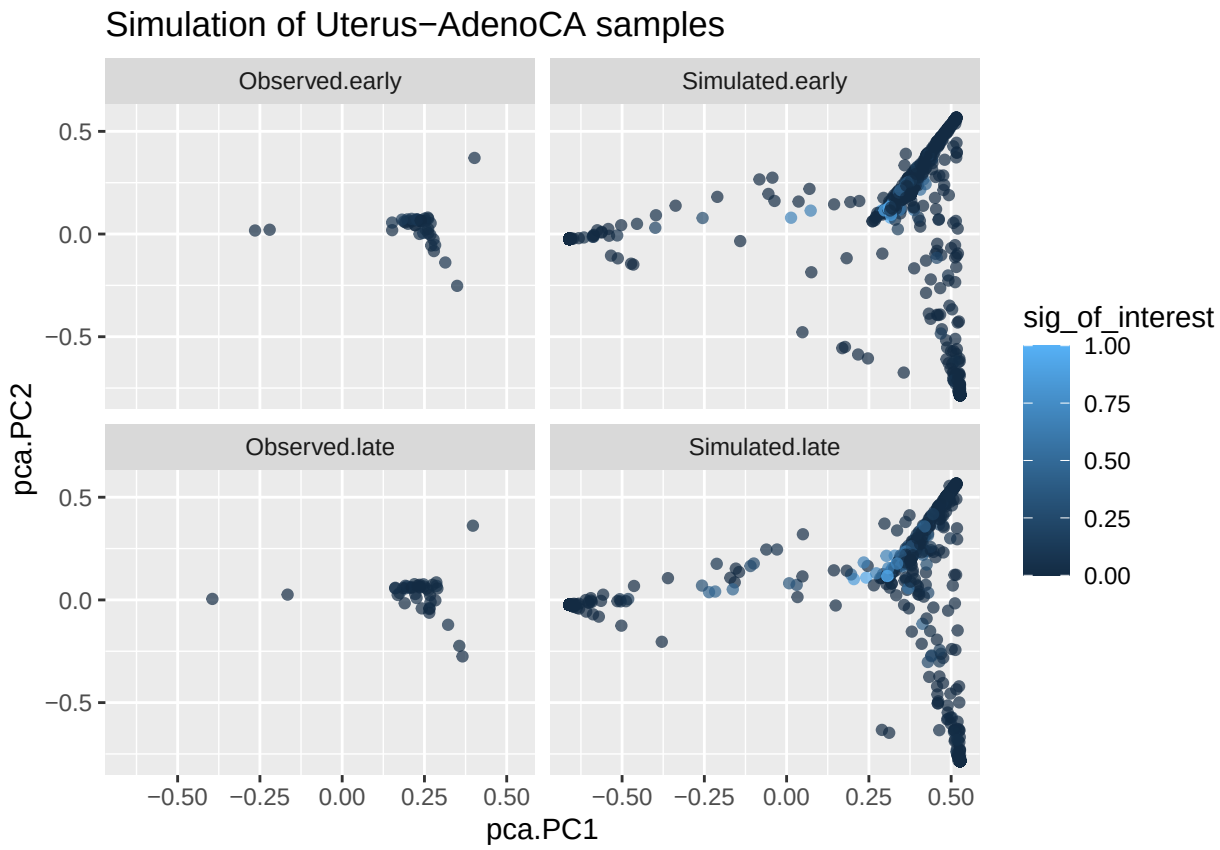
```
## [1] 40
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```

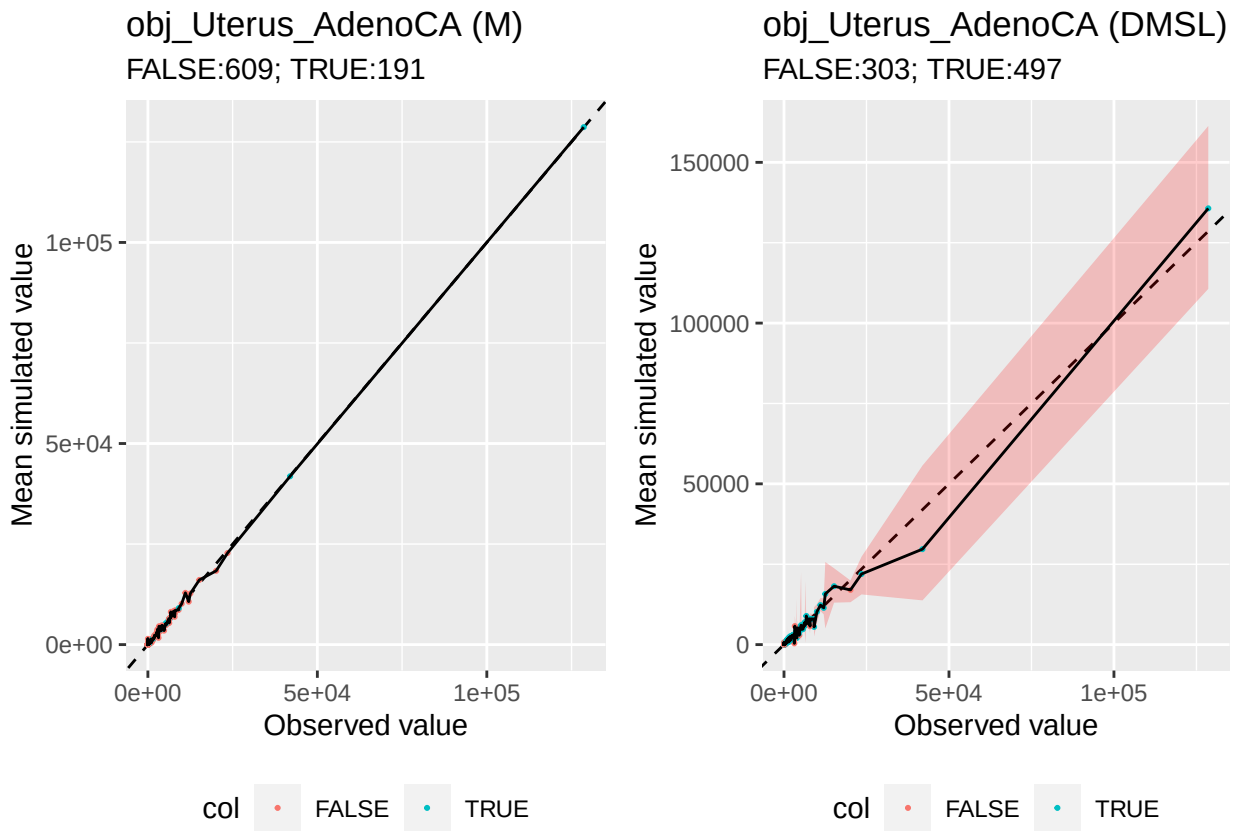
```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i - 1) * arg_d + :
## number of items to replace is not a multiple of replacement length
```

```
## Warning in .sigma[unlist(sapply(1:(arg_d - 1), function(i) (i) + ((i):(arg_d - :
## number of items to replace is not a multiple of replacement length
```



Ranked plot for coverage

```
ct <- "Uterus-AdenoCA"
integer_overdispersion_param_DMSL <- 1
obj_Uterus_AdenoCA_nonexo <- give_subset_sigs_TMBobj(obj_Uterus_AdenoCA, sigs_to_remove = nonexogenous$V1
obj_Uterus_AdenoCA_nonexo_sorted <- sort_columns_TMB(give_subset_sigs_TMBobj(obj_Uterus_AdenoCA, sigs_to_
grid.arrange(give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = ful
                data_object = obj_Uterus_AdenoCA_nonexo_sorted,
                print_plot = F, nreps = 20, model = "M")), function(i){
                  lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                         rank_number=1:length(j)) )})[[1]],
                data_object = obj_Uterus_AdenoCA_nonexo,
                loglog = F, title = 'obj_Uterus_AdenoCA (M)'),
 give_interval_plots_2(df_rank = lapply(list(give_ranked_plot_simulation(tmb_fit_object = diagRE_DMSL_nor
                data_object = obj_Uterus_AdenoCA_nonexo_sorted,
                print_plot = F, nreps = 20, model = "DMSL", integer_overdispersion_param = integer_overd
                  lapply(i, function(j) cbind.data.frame(sorted_value=as.vector(j),
                                                         rank_number=1:length(j)) )})[[1]],
                data_object = obj_Uterus_AdenoCA_nonexo,
           loglog = F, title = 'obj_Uterus_AdenoCA (DMSL)'), ncol=2)
```



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

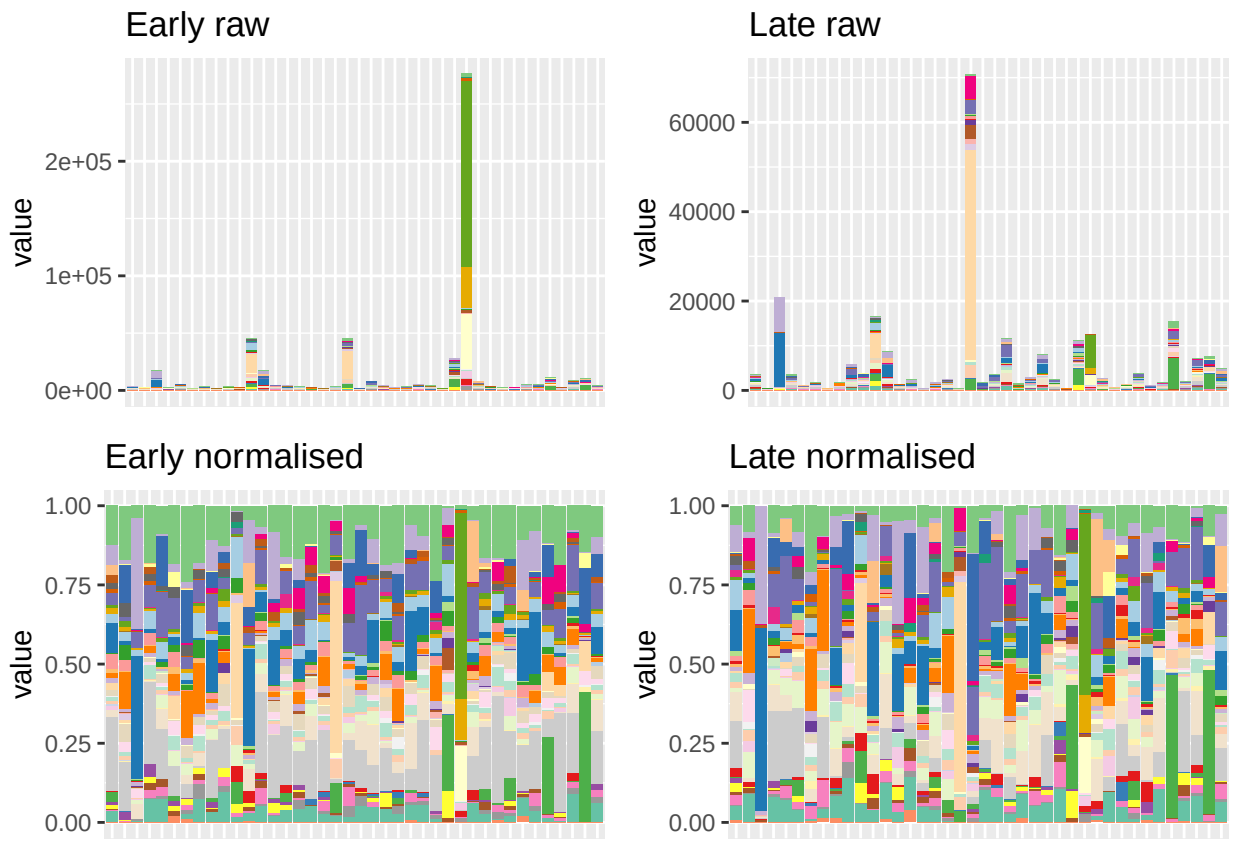
```
obj_Uterus_AdenoCA_mutSigExtractor <- load_PCAWG(ct = ct, typedata = "signaturesmutSigExtractor",
                                    path_to_data = "../../data/")
```

```
## [1] 40
```

```
give_barplot_from_obj(obj = obj_Uterus_AdenoCA_mutSigExtractor, legend_on = FALSE)
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 40
## Creating plot... it might take some time if the data are large. Number of samples: 40
## Creating plot... it might take some time if the data are large. Number of samples: 40
## Creating plot... it might take some time if the data are large. Number of samples: 40
```

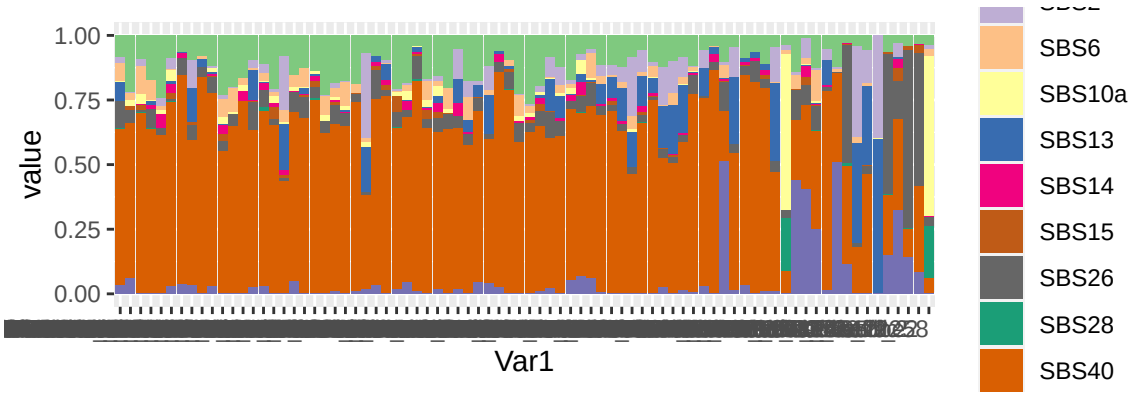
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```



Exposures sorted by increasing number of mutations: there is a trend of hypermutated samples being very chaotic.

```
createBarplot(normalise_rw(non_duplicated_rows(obj_Uterus_AdenoCA$Y)),
              order_labels = names(sort(rowSums(non_duplicated_rows(obj_Uterus_AdenoCA$Y)),
                                        decreasing = F)))
```

```
## Creating plot... it might take some time if the data are large. Number of samples: 80
```



All p-values for non-exogenous signatures

% latex table generated in R 4.0.3 by xtable 1.8-4 package % Tue Jun 1 20:41:50 2021

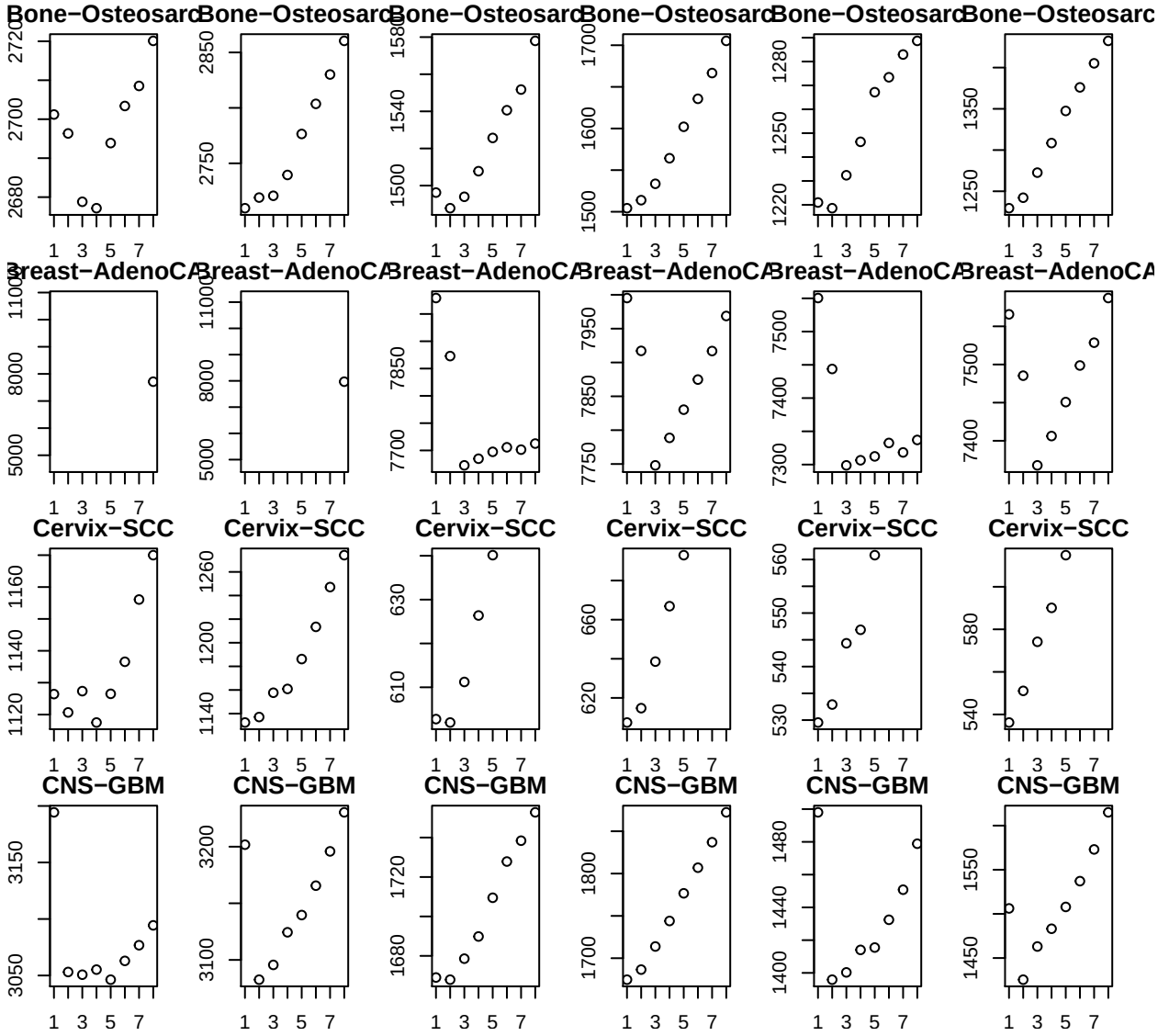
	ct	pvalue	model
1	Bone-Osteosarc	0.00	diagRE_DMSL_nonexo
2	Breast-AdenoCA	0.00	diagRE_DMSL_nonexo
3	Cervix-SCC	0.00	fullRE_DMSL_nonexo
4	CNS-Oligo	0.52	fullRE_DMSL_nonexo

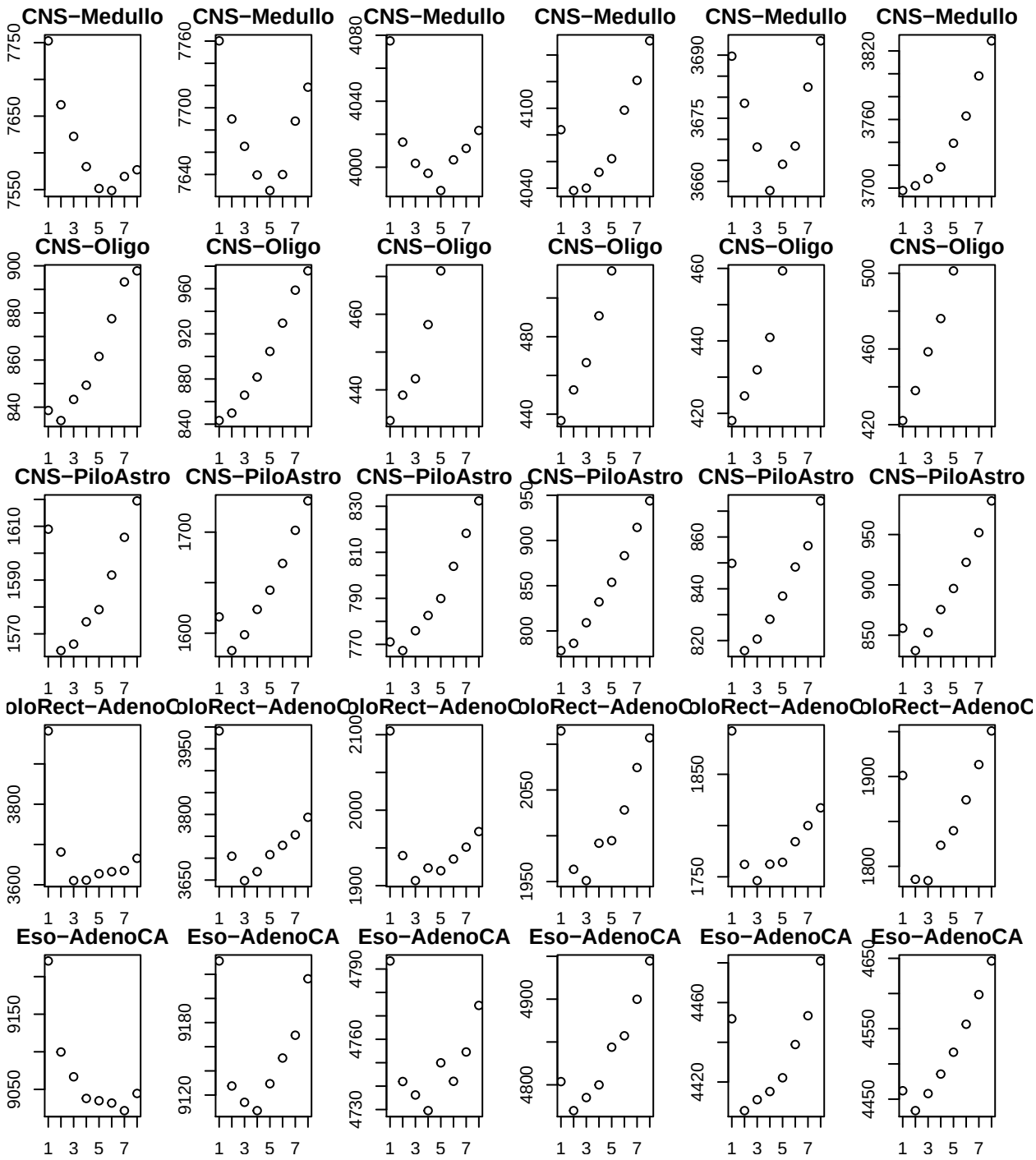
Dirichlet-Multinomial Mixtures

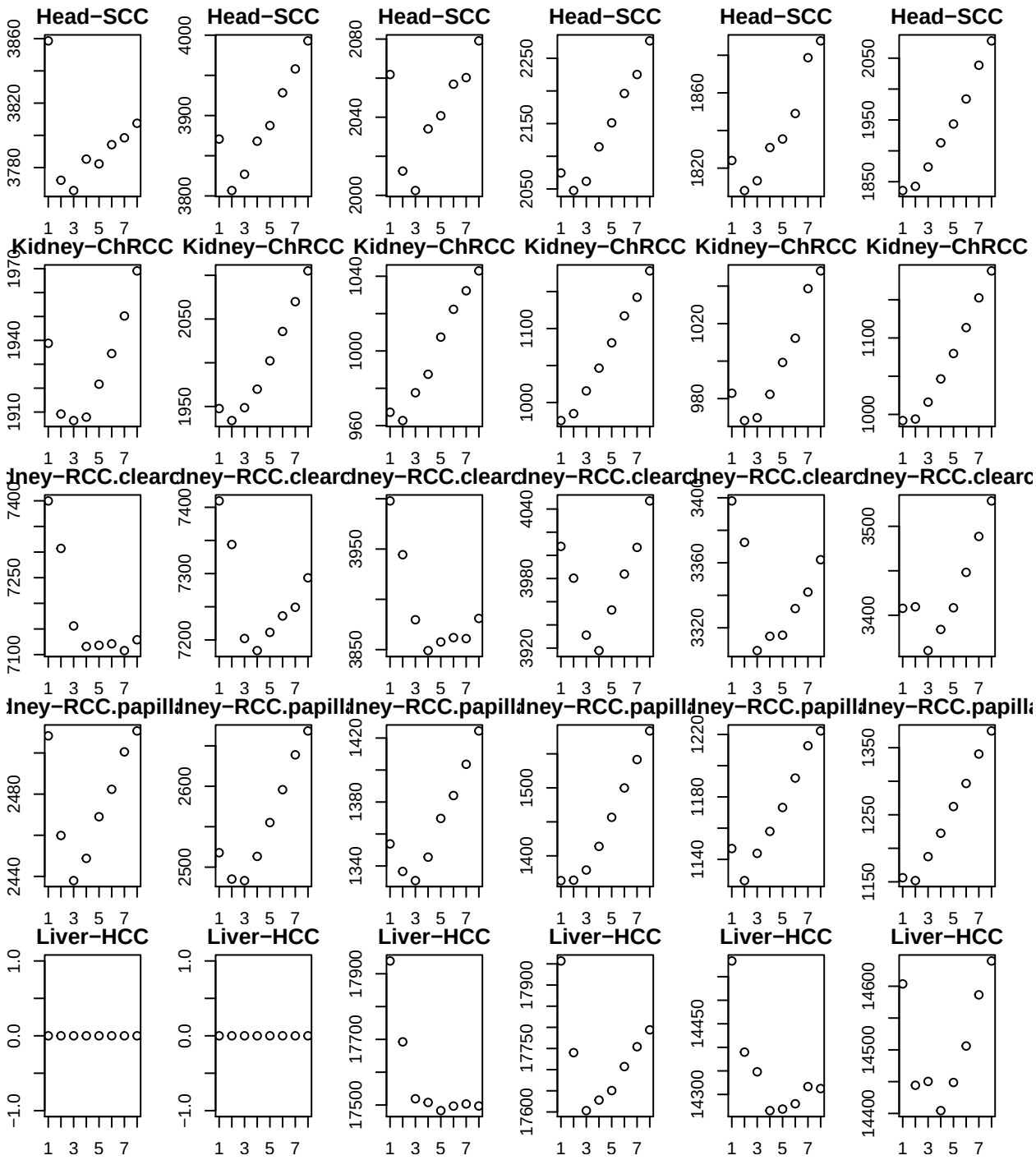
We run the software `MicrobeDMMv1.0` to determine whether we are facing DMM mixtures or not.

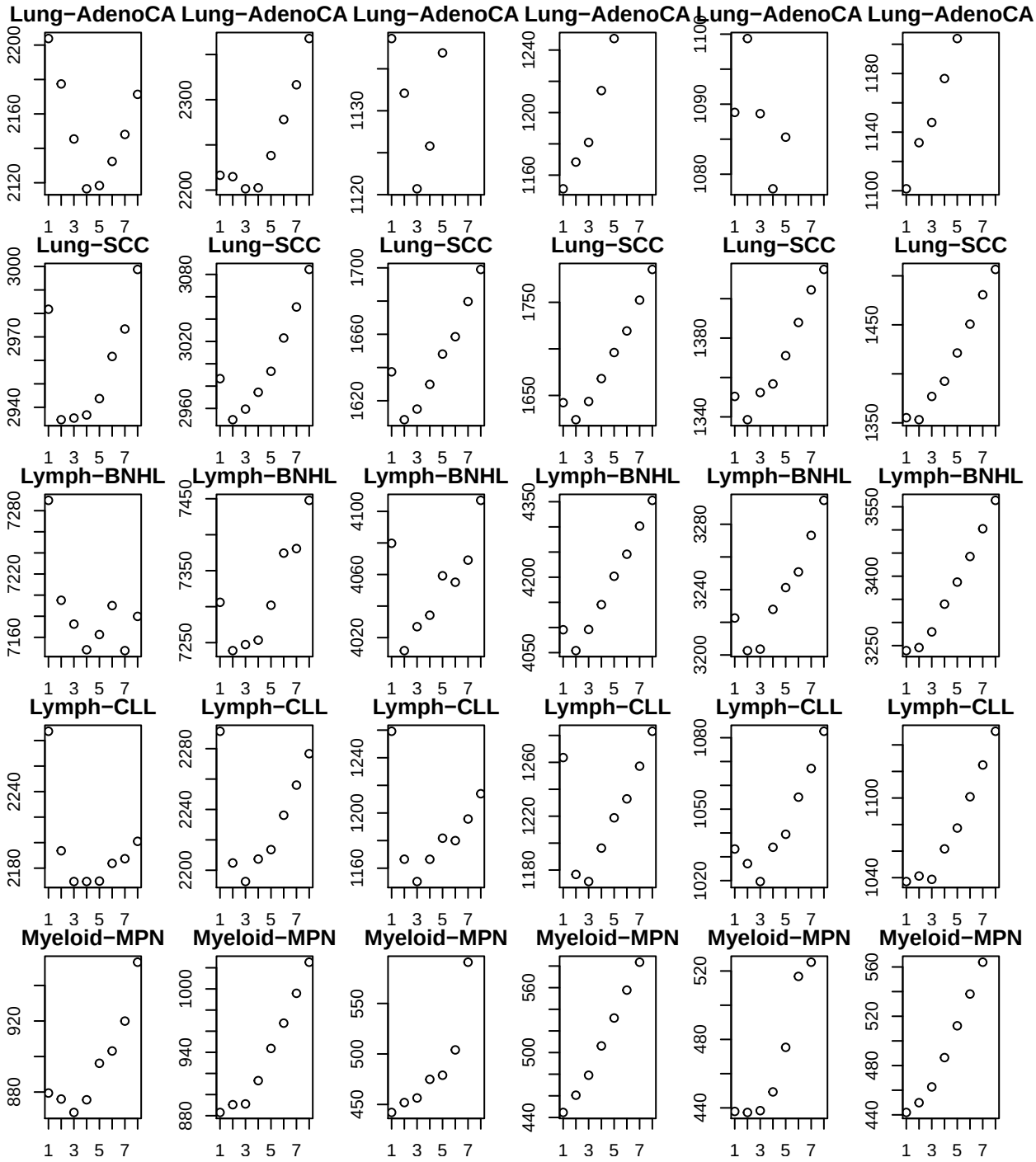
We save the files in two ways: all of the samples - early or not - together, and separately.

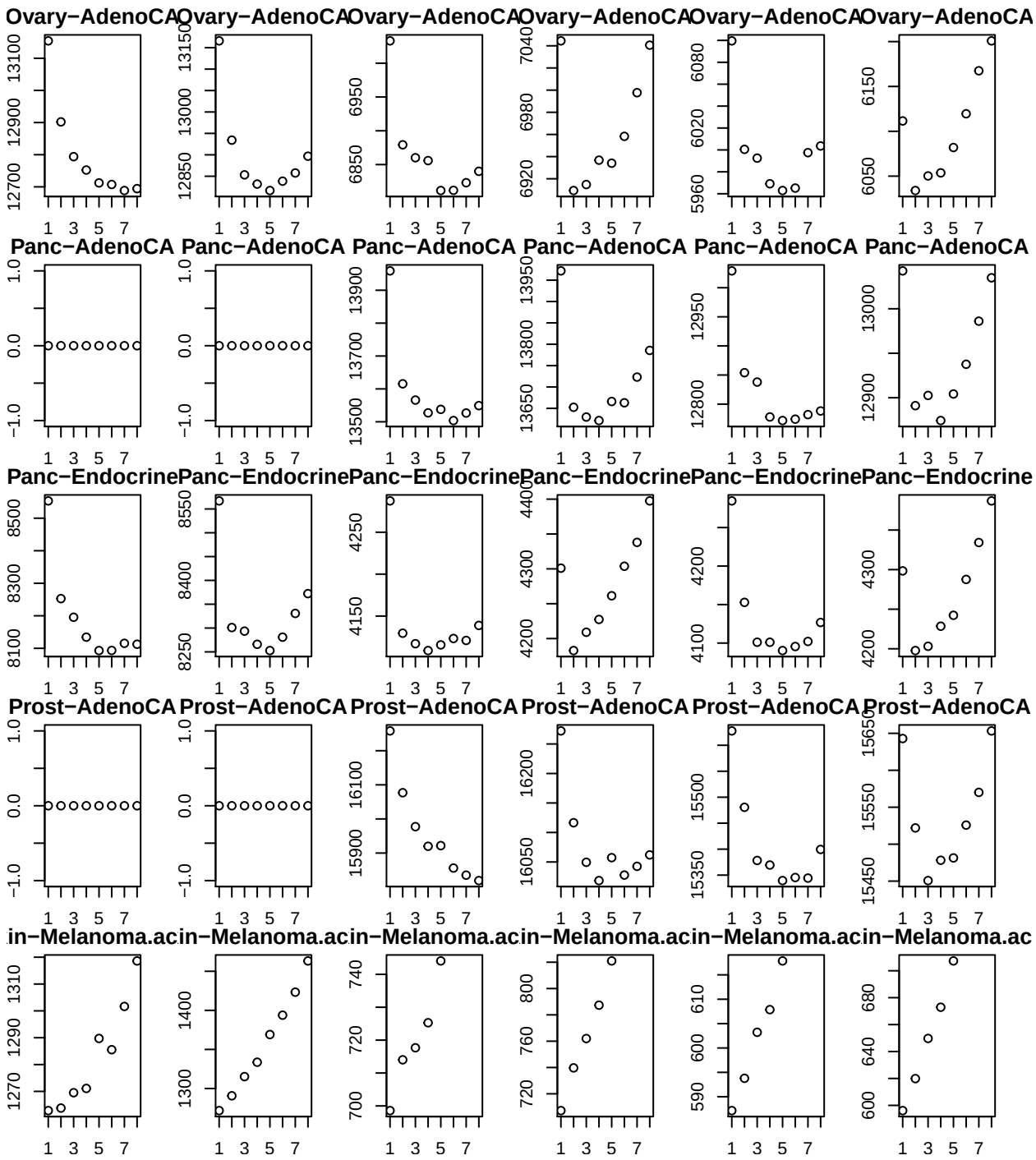
In some cases DMM says that there is an error with the input file - in this case the AIC or BIC is not plotted. If all of them are missing, all BIC and AIC are set to zero.

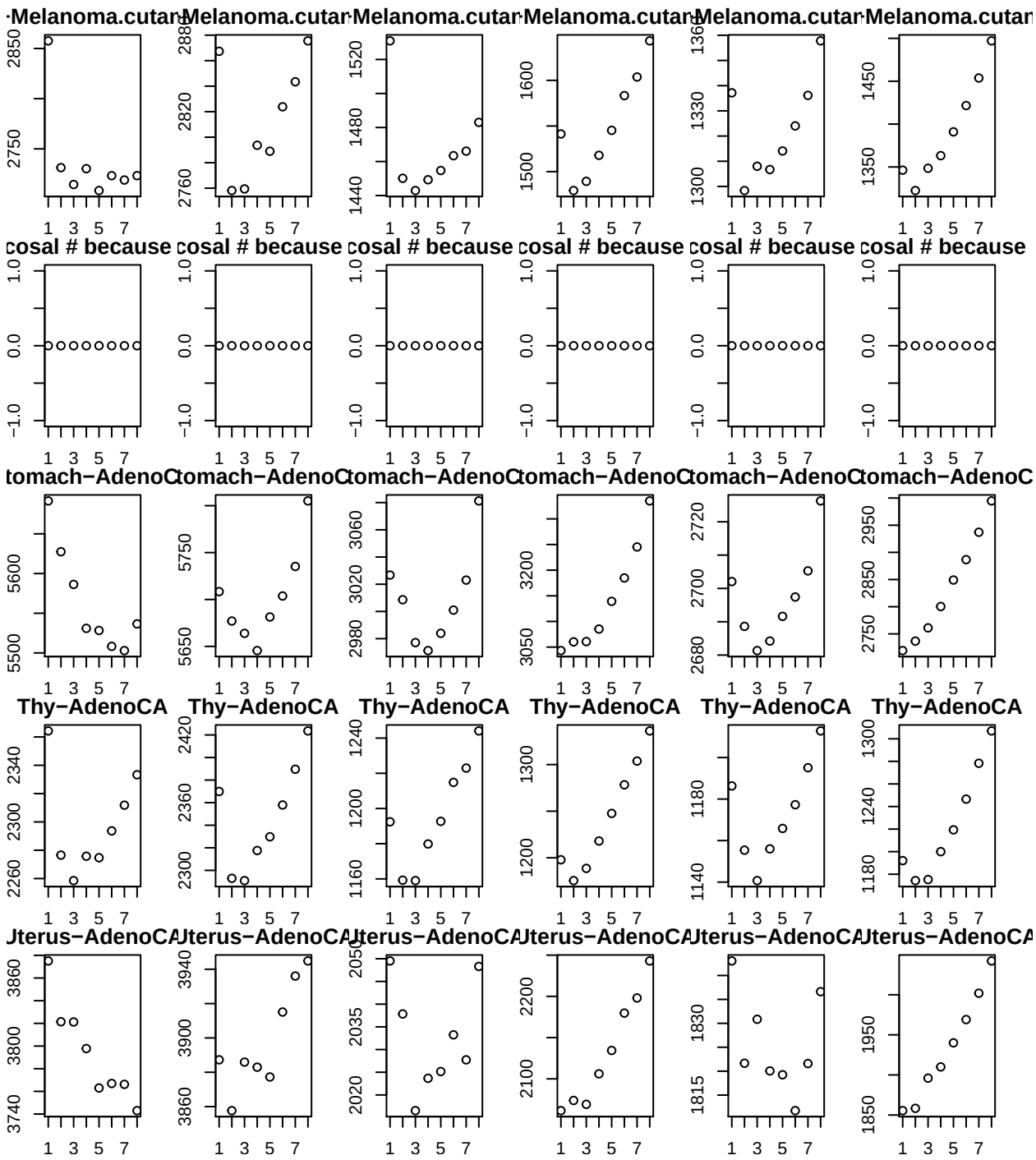



CNS−Medullo
CNS−Medullo
CNS−Medullo
CNS−Medullo
CNS−Medullo
CNS−Medullo
CNS−Oligo
CNS−Oligo
CNS−Oligo
CNS−Oligo
CNS−Oligo
CNS−Oligo
CNS−PiloAstro
CNS−PiloAstro
CNS−PiloAstro
CNS−PiloAstro
CNS−PiloAstro
CNS−PiloAstro
oloRect−AdenoC
oloRect−AdenoC
oloRect−AdenoC
oloRect−AdenoC
oloRect−AdenoC
oloRect−AdenoC
Eso−AdenoCA
Eso−AdenoCA
Eso−AdenoCA
Eso−AdenoCA
Eso−AdenoCA
Eso−AdenoCA


Head−SCC
Kidney−ChRCC
Liver−HCC


Lung−AdenoCA
Lung−SCC
Lymph−BNHL
Lymph−CLL
Myeloid−MPN


Ovary−AdenoCA
Ovary−AdenoCA
Ovary−AdenoCA
Ovary−AdenoCA
Ovary−AdenoCA
Ovary−AdenoCA
Panc−AdenoCA
Panc−AdenoCA
Panc−AdenoCA
Panc−AdenoCA
Panc−AdenoCA
Panc−AdenoCA
Panc−Endocrine
Panc−Endocrine
Panc−Endocrine
Panc−Endocrine
Panc−Endocrine
Panc−Endocrine
Prost−AdenoCA
Prost−AdenoCA
Prost−AdenoCA
Prost−AdenoCA
Prost−AdenoCA
Prost−AdenoCA
in−Melanoma.ac
in−Melanoma.ac
in−Melanoma.ac
in−Melanoma.ac
in−Melanoma.ac
in−Melanoma.ac


·Melanoma.cutan
cosal # because
tomach−AdenoC
Thy−AdenoCA
Jterus−AdenoCA

Comparison of signature exposures with QP and mutsigextractor

```
signature_mutsigextractor_roo2 <- sapply(fles_roo[grepl('_signaturesmutSigExtractor_', fles_roo)], readRD
roo_obj2 <- roo_obj
names(signature_mutsigextractor_roo2) <- gsub("_signaturesmutSigExtractor_ROO.RDS", "", basename(names(si
names(roo_obj2) <- gsub("_signatures_ROO.RDS", "", basename(names(roo_obj2)))
```

```
par(mfrow=c(2,3))
for(i in names(roo_obj2)){
  try({

  sig1 <- roo_obj2[[i]]
  sig2 <- signature_mutsigextractor_roo2[[i]]

  sig1 <- do.call('rbind', sig1@count_matrices_active)
  sig2 <- do.call('rbind', sig2@count_matrices_all)

  sig2 <- as.vector(sig2[,match(colnames(sig1), colnames(sig2))])
  sig1 <- as.vector(sig1)
  plot(sig1, sig2)
  })
}
```

```
## Error in do.call("rbind", sig2@count_matrices_all) :
##   trying to get slot "count_matrices_all" from an object of a basic class ("NULL") with no slots
```

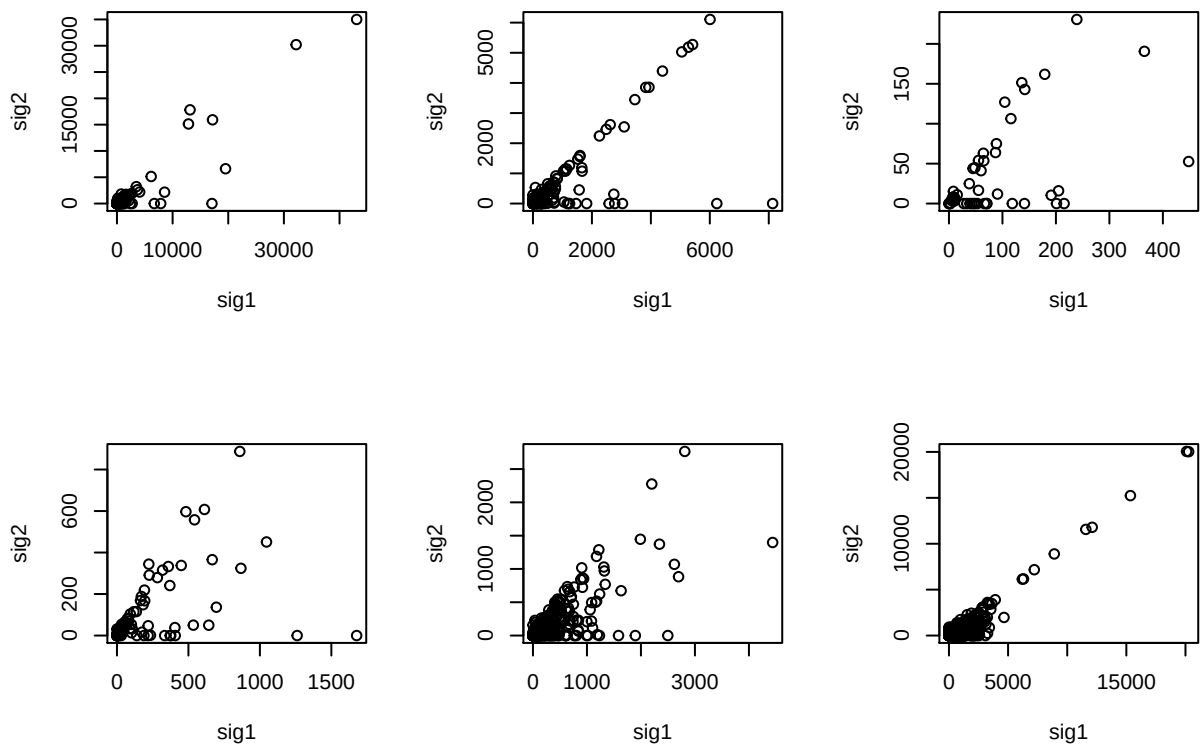
```
## Error in do.call("rbind", sig2@count_matrices_all) :
##   trying to get slot "count_matrices_all" from an object of a basic class ("NULL") with no slots
```

```
## Warning in min(x): no non-missing arguments to min; returning Inf
```

```
## Warning in max(x): no non-missing arguments to max; returning -Inf
```

```
## Warning in min(x): no non-missing arguments to min; returning Inf
```

```
## Warning in max(x): no non-missing arguments to max; returning -Inf
```




```
## Error in plot.window(...) : need finite 'xlim' values
```

```
## Error in xy.coords(x, y, xlabel, ylabel, log) :
##   'x' and 'y' lengths differ
```

```
## Error in do.call("rbind", sig1@count_matrices_active) :
##   trying to get slot "count_matrices_active" from an object of a basic class ("logical") with no slots
## Error in do.call("rbind", sig2@count_matrices_all) :
##   trying to get slot "count_matrices_all" from an object of a basic class ("NULL") with no slots
```

```
cbind.data.frame(pvals_fullRE_M=pvals_fullRE_M,
                 pvals_diagRE_DM=pvals_diagRE_DM,
                 pvals_DM=pvals_DM,
                 pvals_DMnonexo=pvals_DMnonexo)
```

```
##                         pvals_fullRE_M pvals_diagRE_DM     pvals_DM
## Bone-Osteosarc            0.000000e+00    2.847099e-08 1.283415e-08
## Breast-AdenoCA            0.000000e+00    2.366485e-35 3.192087e-34
## Cervix-SCC               1.269057e-204    1.109283e-01 1.172648e-01
## CNS-GBM                   0.000000e+00    9.413763e-09 3.147710e-02
## CNS-Medullo              2.636002e-129    1.751080e-02 1.621432e-02
## CNS-Oligo                2.055546e-155    3.429210e-02 3.147710e-02
## CNS-PiloAstro             8.624590e-48    3.429210e-02 3.352191e-02
## ColoRect-AdenoCA          0.000000e+00    6.922344e-23 2.607337e-22
## Eso-AdenoCA               0.000000e+00    1.959292e-19 1.616523e-20
## Head-SCC                  0.000000e+00    1.812725e-04 6.168366e-05
## Kidney-ChRCC              0.000000e+00    3.298283e-06 2.968403e-06
```

```
## Kidney-RCC.clearcell      0.000000e+00    1.236684e-24 6.365567e-25
## Kidney-RCC.papillary      0.000000e+00    5.703174e-18 2.271530e-18
## Liver-HCC                 0.000000e+00    2.452590e-65 6.112670e-66
## Lung-AdenoCA              0.000000e+00    1.352595e-02 4.666292e-05
## Lung-SCC                  0.000000e+00    1.523581e-20 1.688513e-22
## Lymph-BNHL                0.000000e+00    4.795960e-12 2.058732e-13
## Lymph-CLL                 0.000000e+00    1.534926e-19 3.305201e-21
## Myeloid-MPN              4.472448e-113    9.320422e-08 4.518344e-08
## Ovary-AdenoCA             0.000000e+00    1.150681e-21 7.691981e-27
## Panc-AdenoCA              0.000000e+00    2.826716e-72 2.622351e-77
## Panc-Endocrine            0.000000e+00    2.784969e-18 8.995411e-20
## Prost-AdenoCA             0.000000e+00    1.603706e-88 3.647368e-91
## Skin-Melanoma.acral      5.621465e-210    1.802106e-01 1.475018e-01
## Skin-Melanoma.cutaneous   0.000000e+00    8.452268e-20 3.079994e-22
## Stomach-AdenoCA           0.000000e+00    9.504291e-04 1.166767e-05
## Thy-AdenoCA              6.170318e-310    2.707976e-02 1.621432e-02
## Uterus-AdenoCA            0.000000e+00    3.298283e-06 1.091244e-07
##                         pvals_DMnonexo
## Bone-Osteosarc                      NA
## Breast-AdenoCA            3.347067e-11
## Cervix-SCC                1.023813e-02
## CNS-GBM                   8.425463e-04
## CNS-Medullo               4.674452e-01
## CNS-Oligo                           NA
## CNS-PiloAstro             6.382416e-01
## ColoRect-AdenoCA          4.799950e-15
## Eso-AdenoCA               2.352755e-19
## Head-SCC                  1.221425e-03
## Kidney-ChRCC              6.382416e-01
## Kidney-RCC.clearcell      7.826378e-20
## Kidney-RCC.papillary      3.446472e-06
## Liver-HCC                 7.946301e-50
## Lung-AdenoCA              1.023813e-02
## Lung-SCC                  1.669362e-01
## Lymph-BNHL                1.412634e-05
## Lymph-CLL                           NA
## Myeloid-MPN                         NA
## Ovary-AdenoCA             4.790258e-20
## Panc-AdenoCA              1.789201e-44
## Panc-Endocrine            5.008201e-08
## Prost-AdenoCA             3.131201e-61
## Skin-Melanoma.acral                 NA
## Skin-Melanoma.cutaneous             NA
## Stomach-AdenoCA           7.963662e-02
## Thy-AdenoCA               4.674452e-01
## Uterus-AdenoCA            8.425463e-04
```