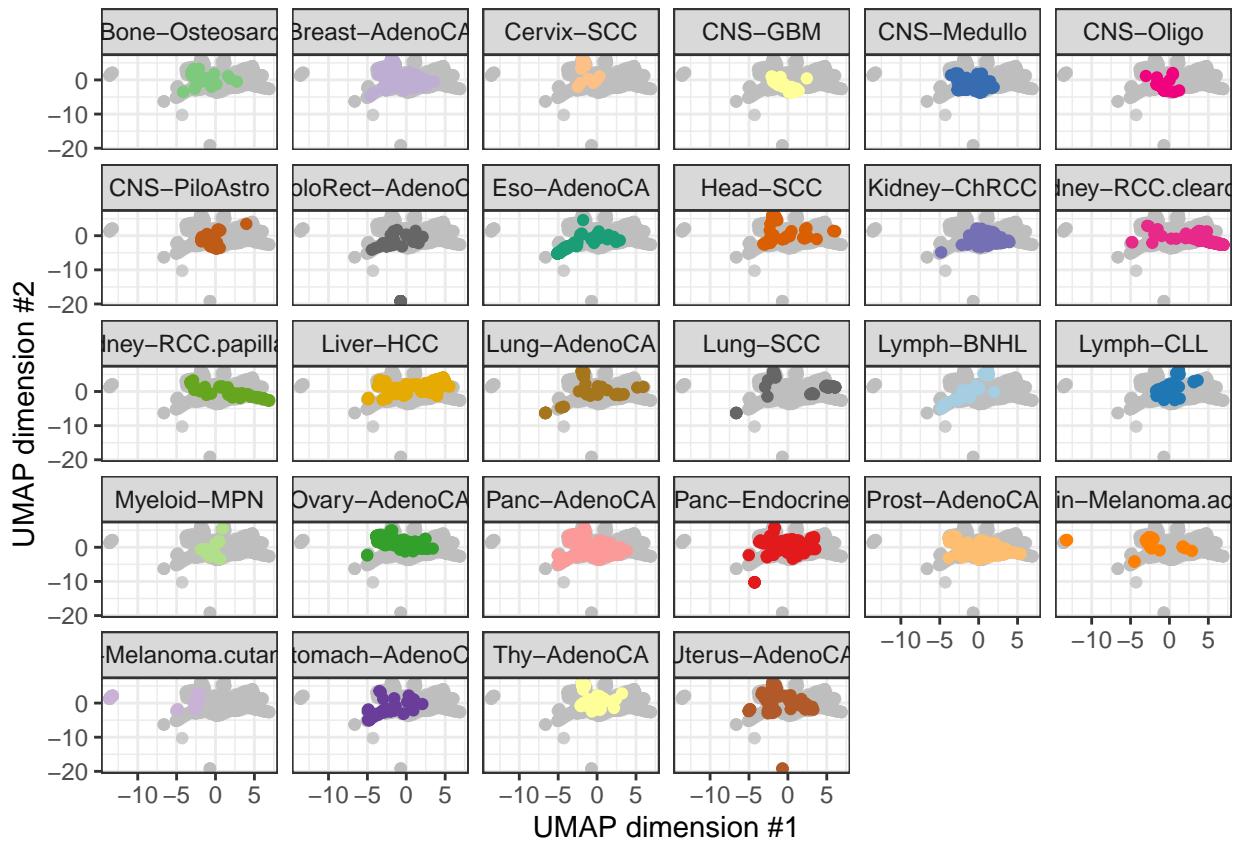


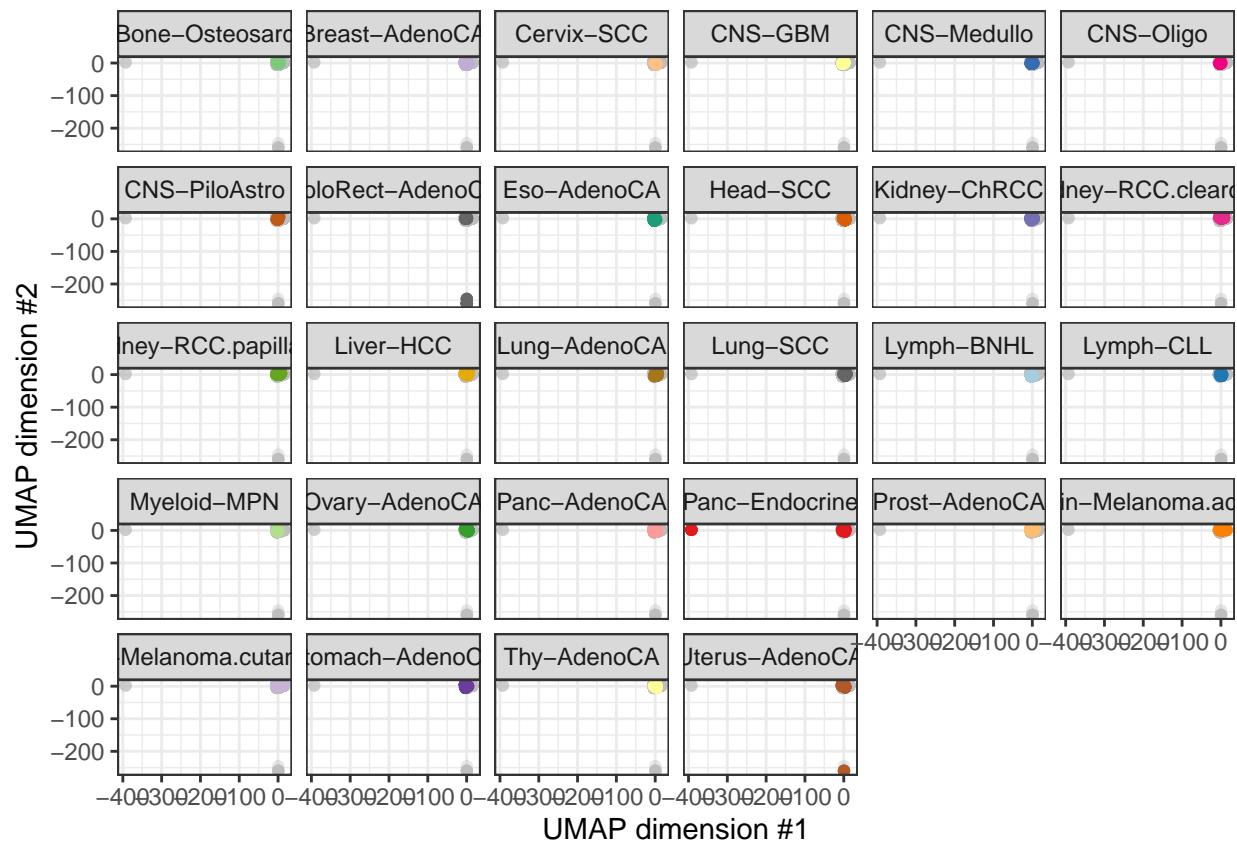
Summary of TMB runs

Lena Morrill

24/05/2021

```
## Loading required package: coda
## Loading required package: MASS
## Warning in .recacheSubclasses(def@class$Name, 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"
```





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 | fullRE_nonexo_DM_ | Not sorted | find_subset_signatures.R |
| diagREDMsinglelambda | diagRE_DMSL_ | Not sorted | find_subset_signatures.R |

```
## [1] 27
## [1] 27
## [1] 27
## [1] 136
## [1] 136
## [1] 136
## [1] 16
## [1] 16
## [1] 16
## [1] 34
## [1] 34
## [1] 34
## [1] 106
## [1] 106
## [1] 106
## [1] 15
## [1] 15
## [1] 15
## [1] 42
## [1] 42
## [1] 42
## [1] 37
## [1] 37
## [1] 65
## [1] 65
## [1] 65
## [1] 32
```

```
## [1] 32
## [1] 32
## [1] 38
## [1] 38
## [1] 38
## [1] 86
## [1] 86
## [1] 86
## [1] 30
## [1] 30
## [1] 30
## [1] 207
## [1] 207
## [1] 207
## [1] 17
## [1] 17
## [1] 17
## [1] 34
## [1] 34
## [1] 34
## [1] 51
## [1] 51
## [1] 51
## [1] 53
## [1] 53
## [1] 53
## [1] 19
## [1] 19
## [1] 19
## [1] 97
## [1] 97
## [1] 97
## [1] 193
## [1] 193
## [1] 193
## [1] 70
## [1] 70
## [1] 70
## [1] 208
## [1] 208
## [1] 208
## [1] 15
## [1] 15
## [1] 15
## [1] 30
## [1] 30
## [1] 30
## [1] 30
## [1] 30
## [1] 30
## [1] 41
```

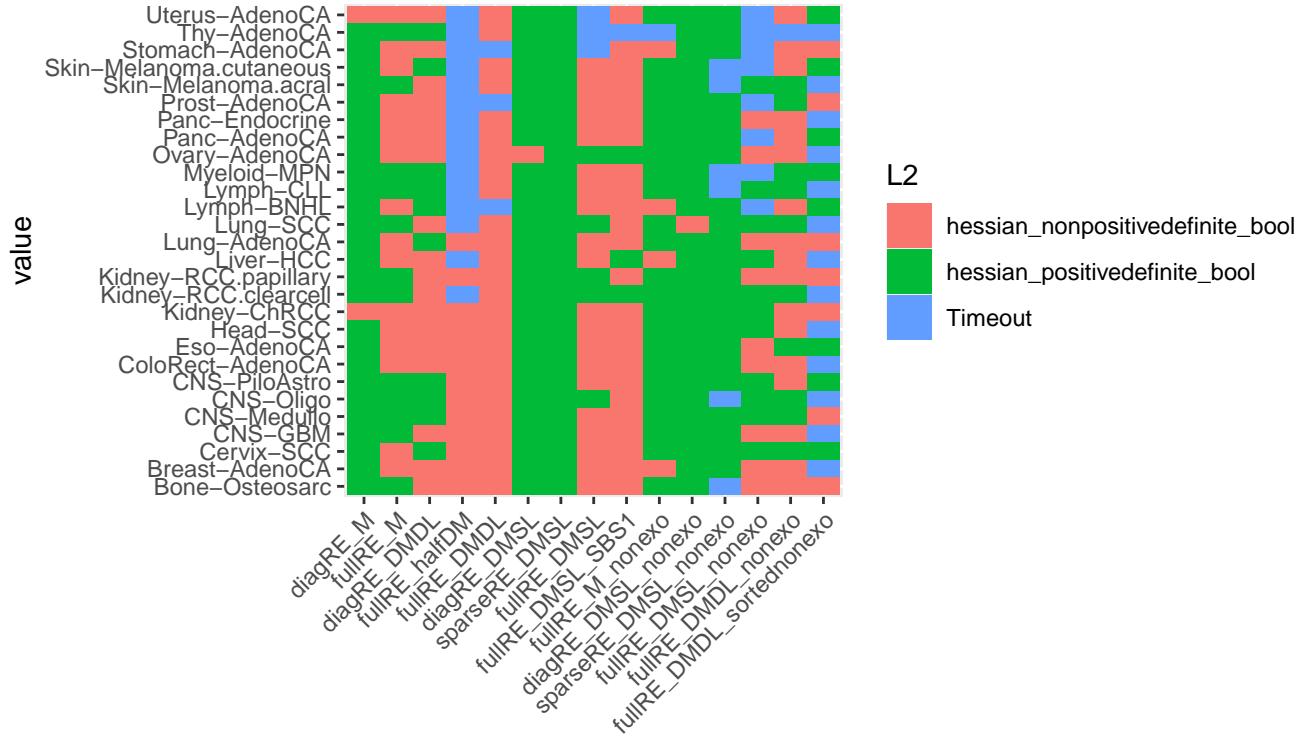
```

## [1] 41
## [1] 41
## [1] 40
## [1] 40
## [1] 40

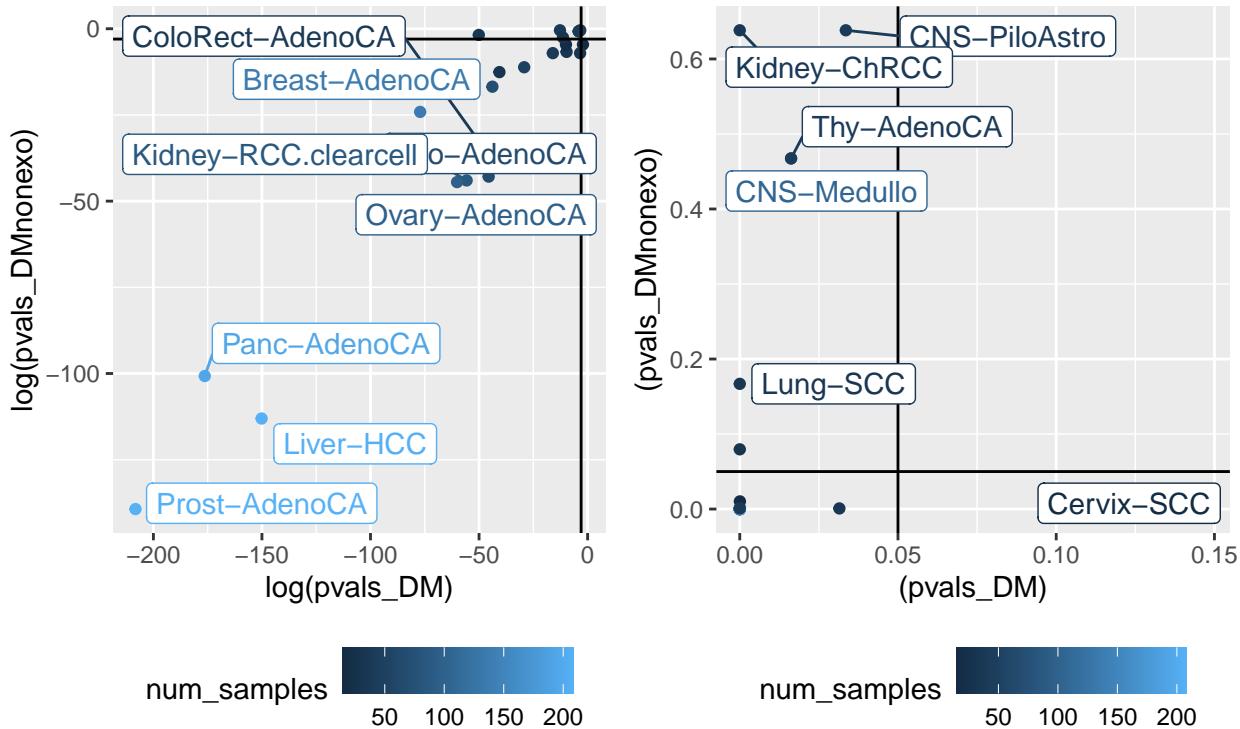
```

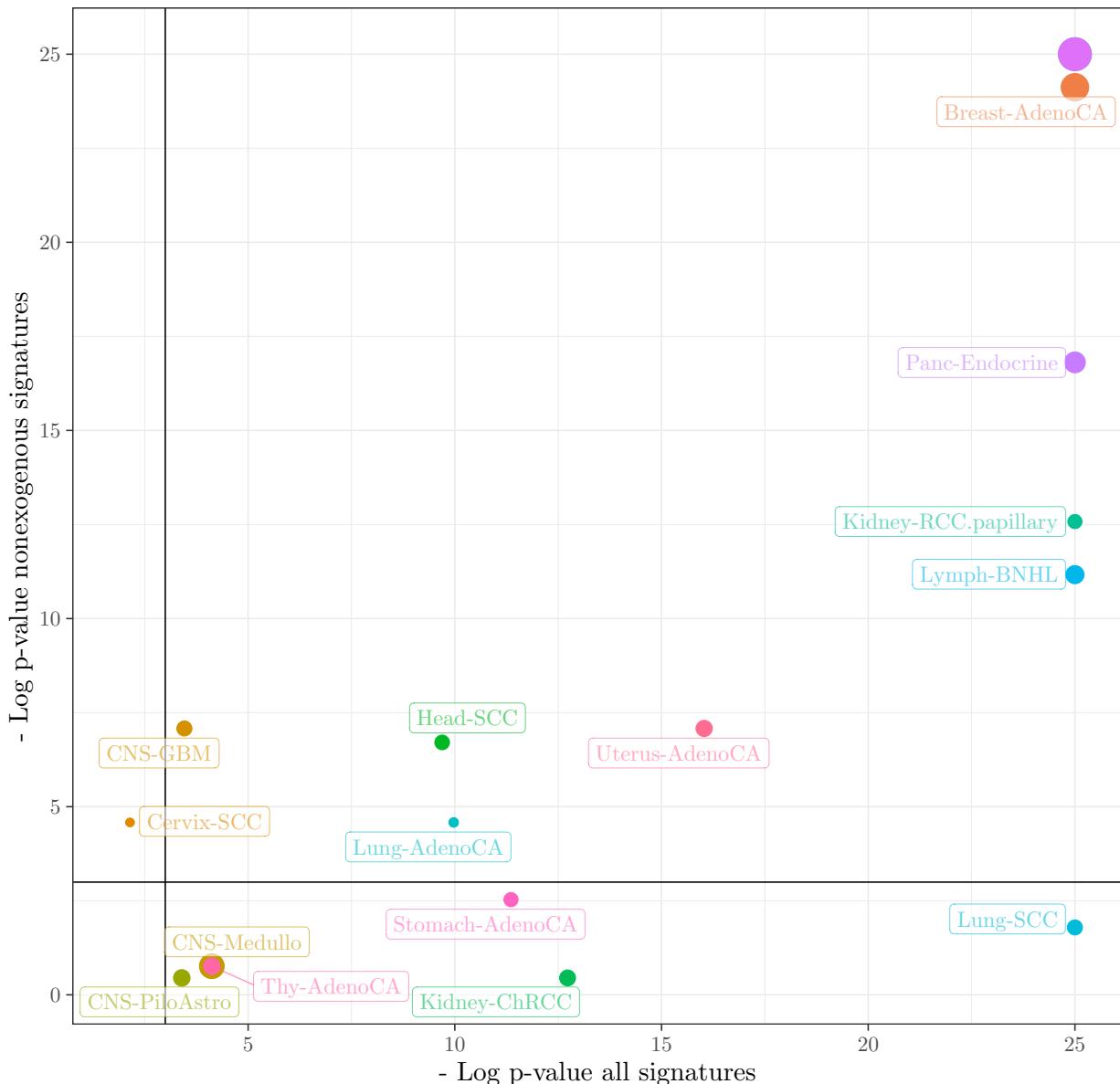
General results of all models

Check the results of all of the models



P-values for all cancer types



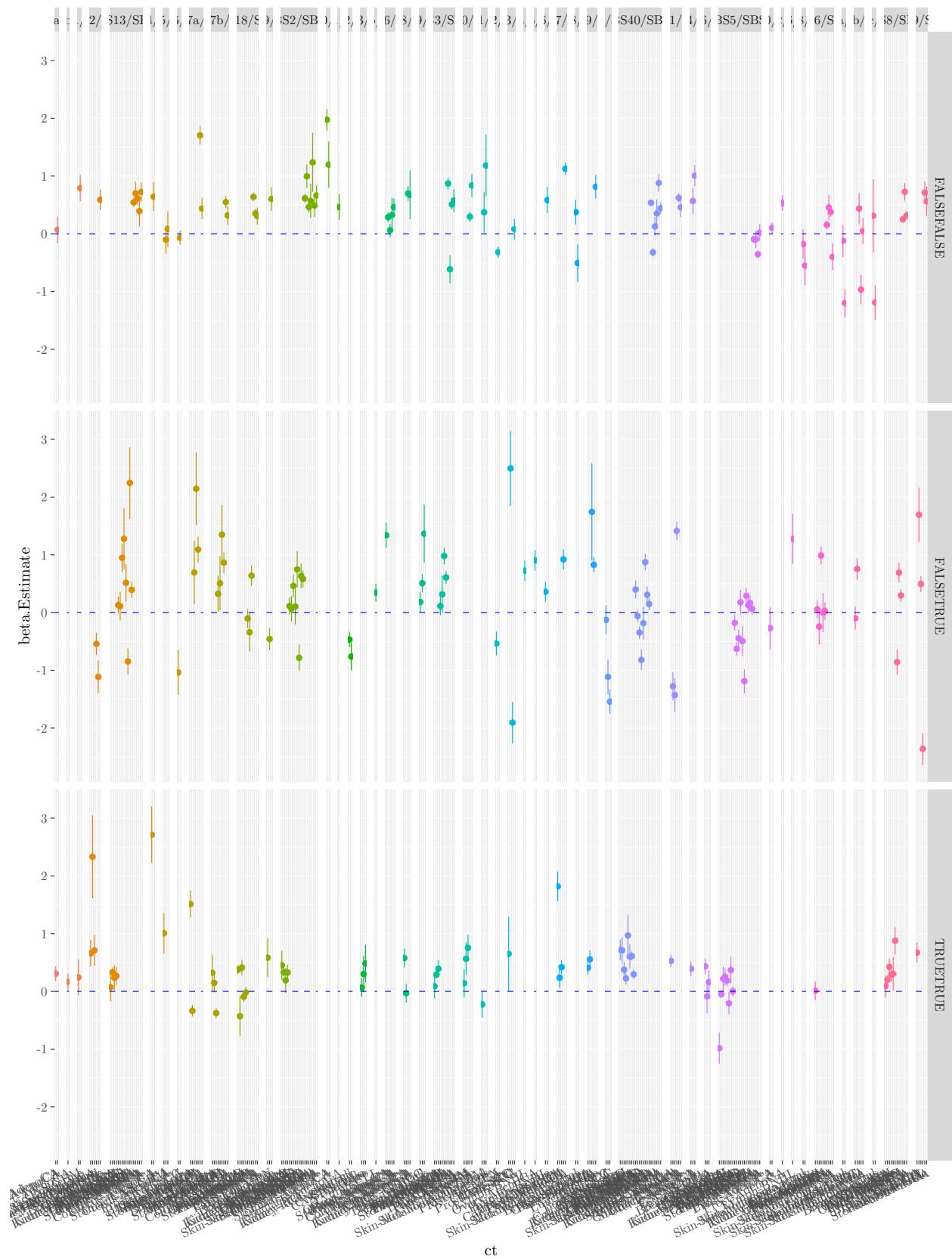


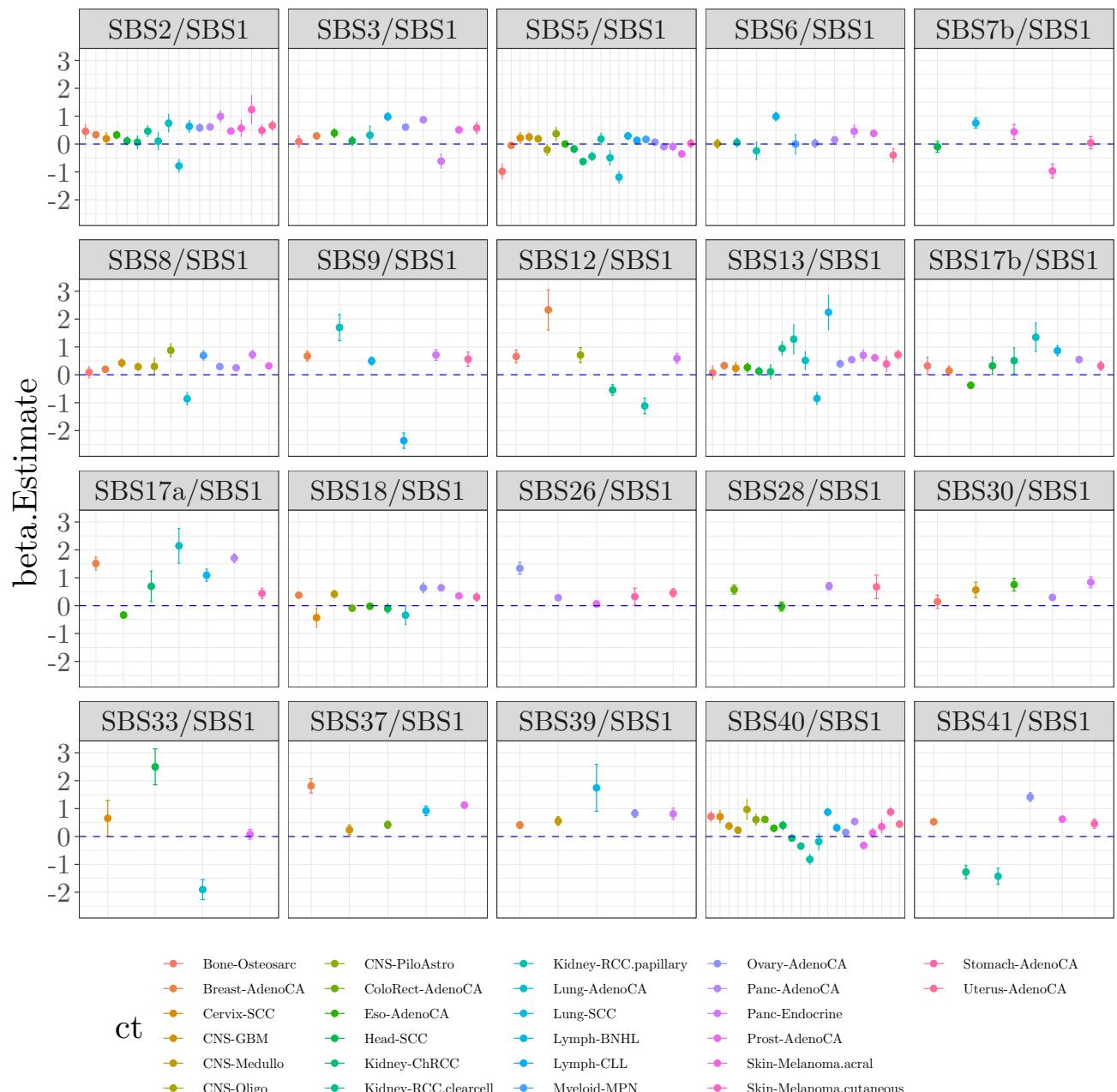
| | | | | |
|----|----------------|----------------------|---------------|-------------------------|
| ct | Bone-Osteosarc | ColoRect-AdenoCA | Lung-AdenoCA | Panc-Endocrine |
| | Breast-AdenoCA | Eso-AdenoCA | Lung-SCC | Prost-AdenoCA |
| | Cervix-SCC | Head-SCC | Lymph-BNHL | Skin-Melanoma.acral |
| | 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 |

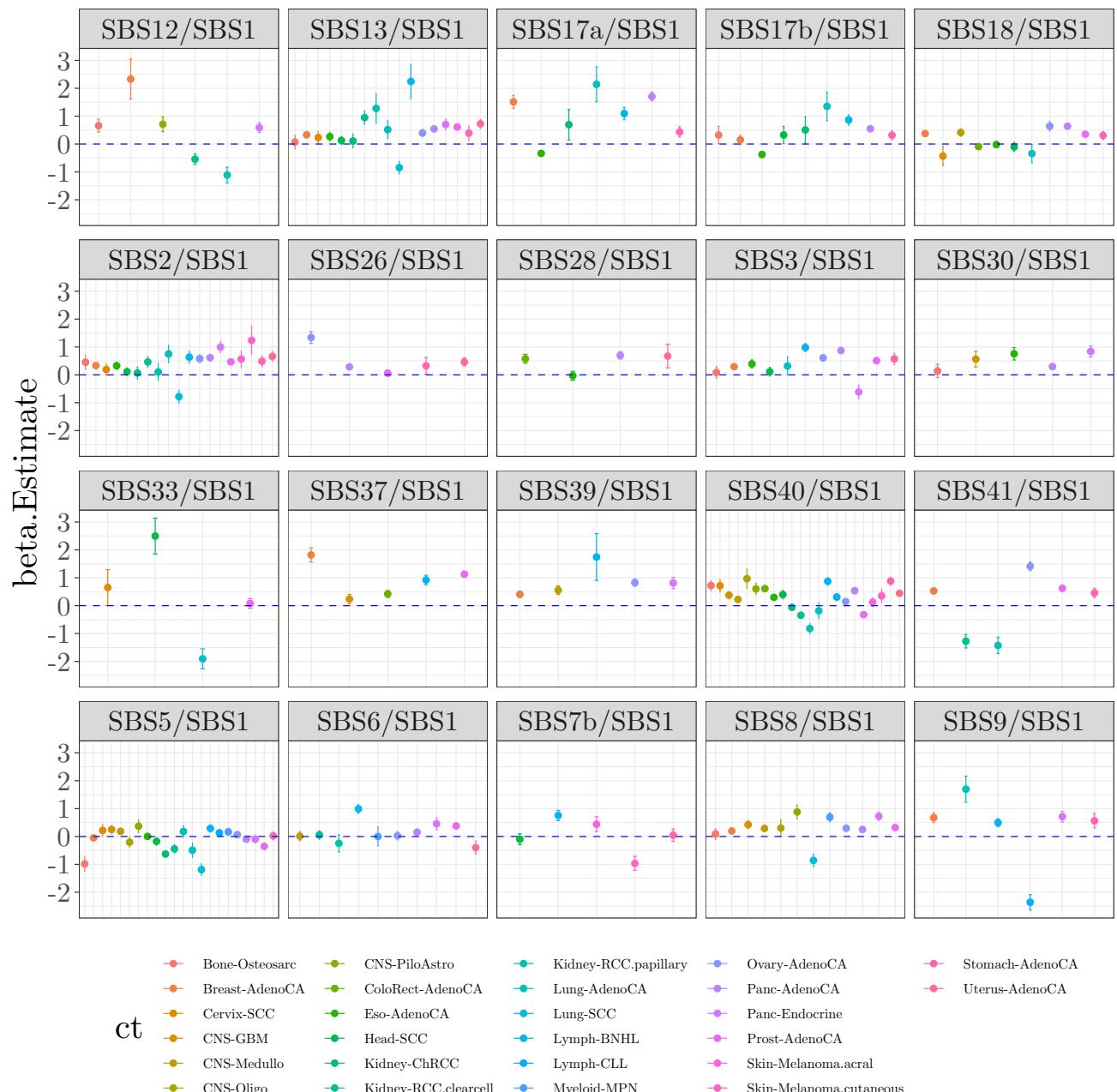
All betas with SBS1 as baseline

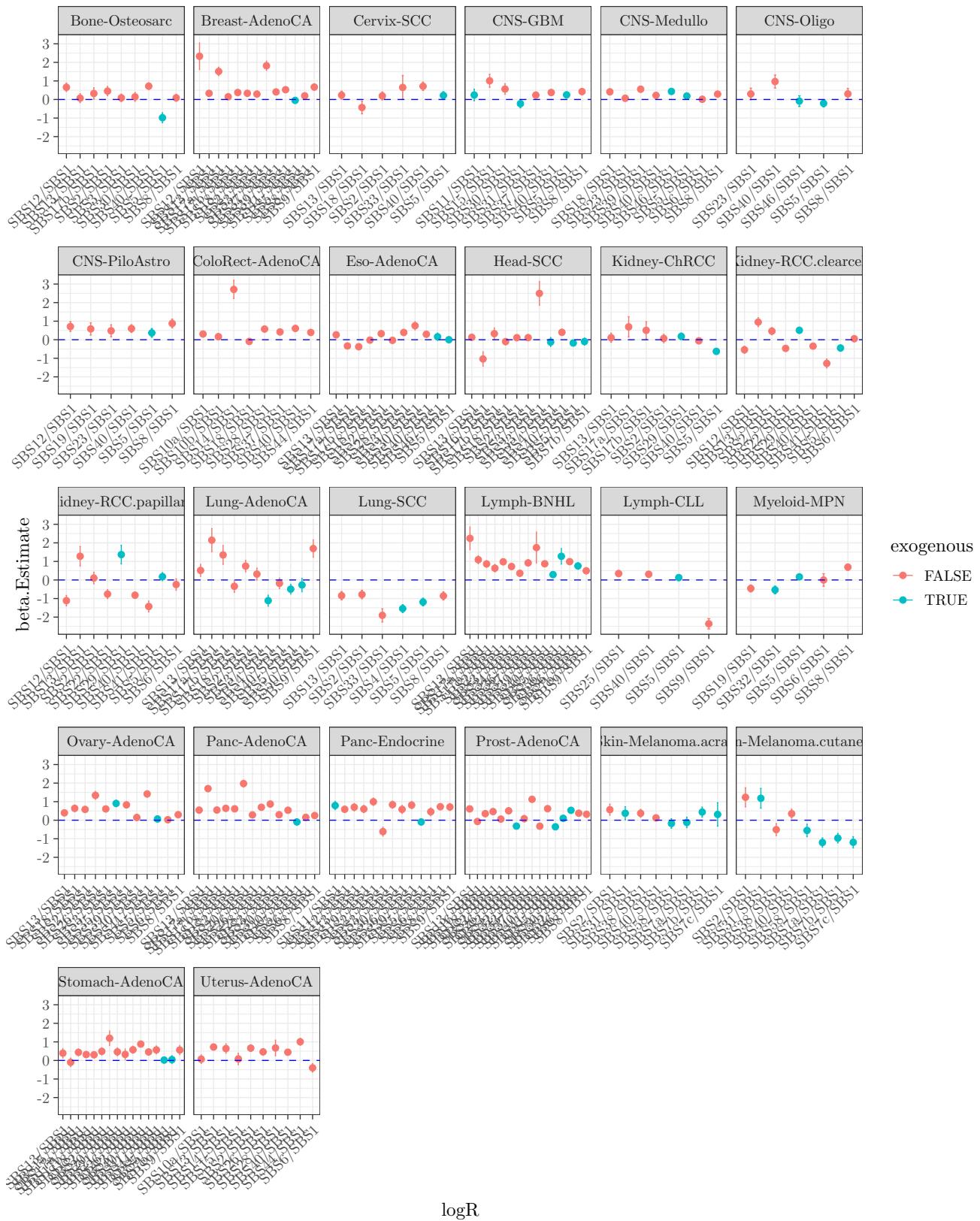
```
##  
## FALSEFALSE FALSETRUE TRUETRUE
```

85 89 74





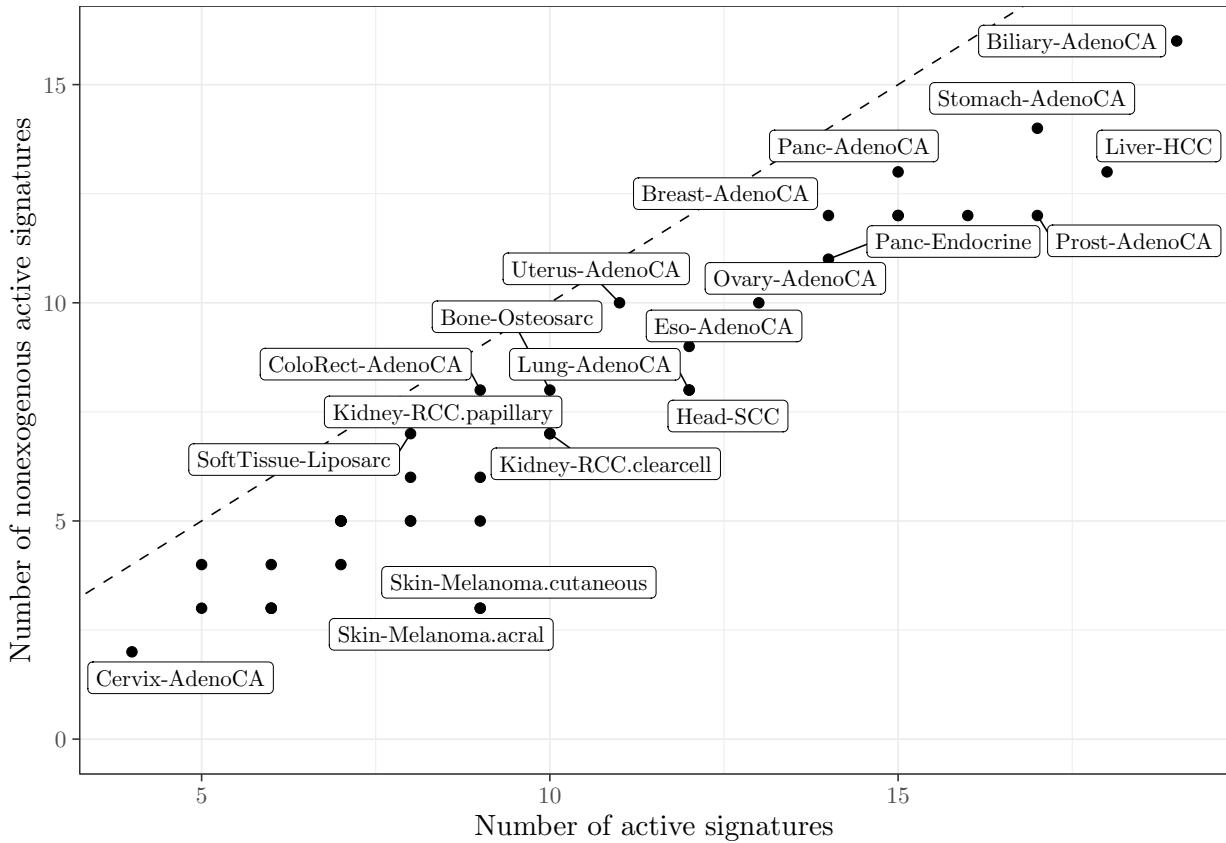




logR

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
```

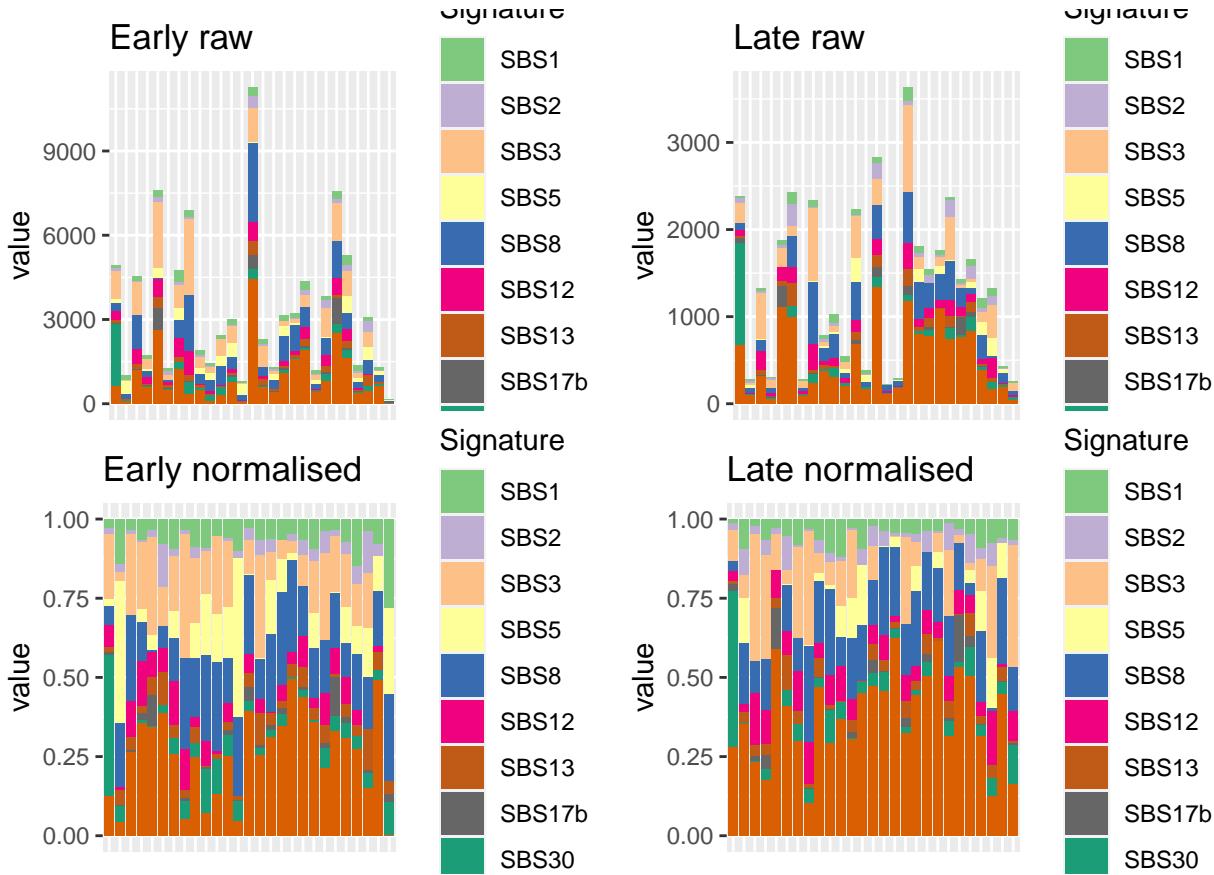


Analysis per cancer type

Bone osteosarcoma

Barplot and general statistics

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



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)
```

```

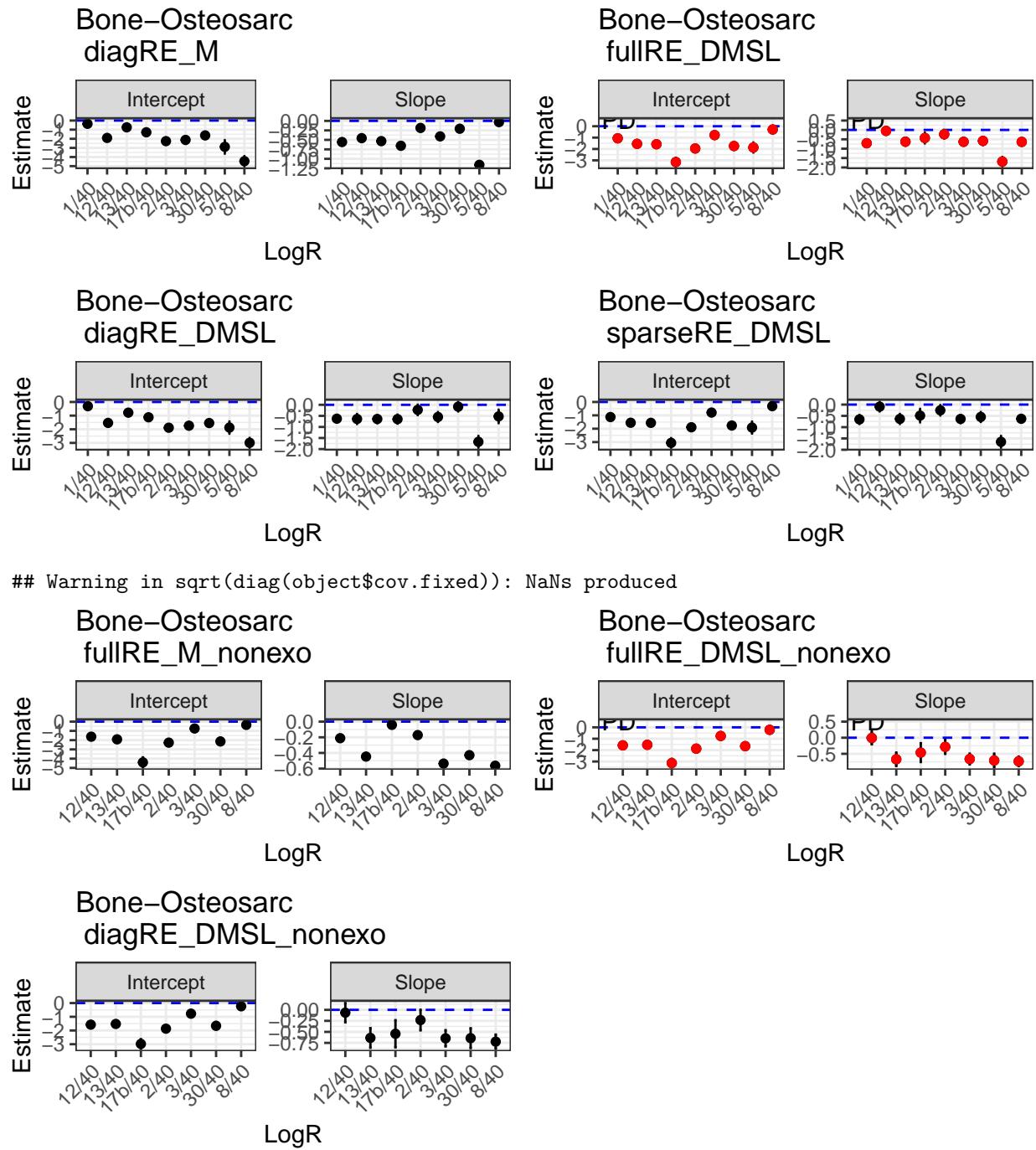
##      SBS1      SBS2      SBS3      SBS5      SBS8      SBS12     SBS13
## 0.05099661 0.03376971 0.17876022 0.05053018 0.17164713 0.07538325 0.04159022
##      SBS17b     SBS30     SBS40
## 0.02866227 0.06128922 0.30737119

```

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 overall has an exposure of only 6.1%
- SBS5 is 0 in 37% of cases and has an overall exposure of 5.1%

Betas



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

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

Note that sortedDM did not converge.

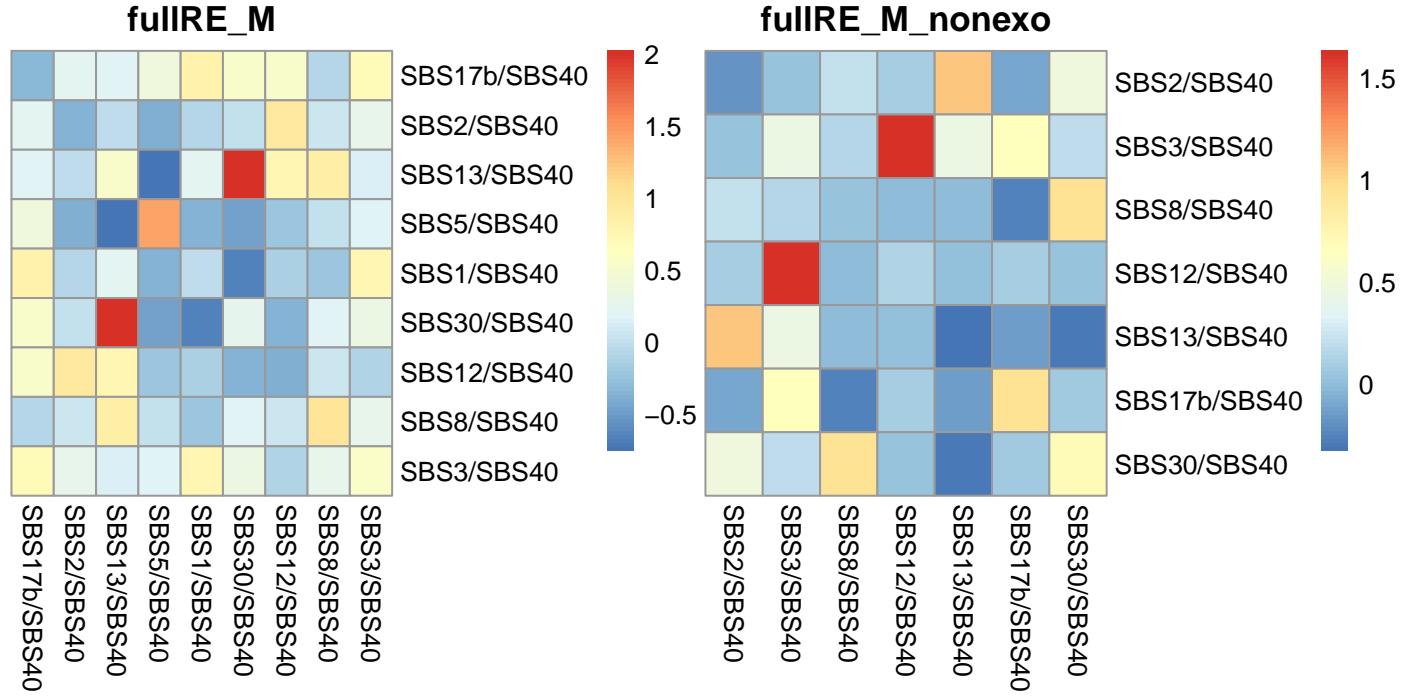
Nevertheless, both versions of fullRE M – both of which converged and use the same baseline – give very different covariances matrices.

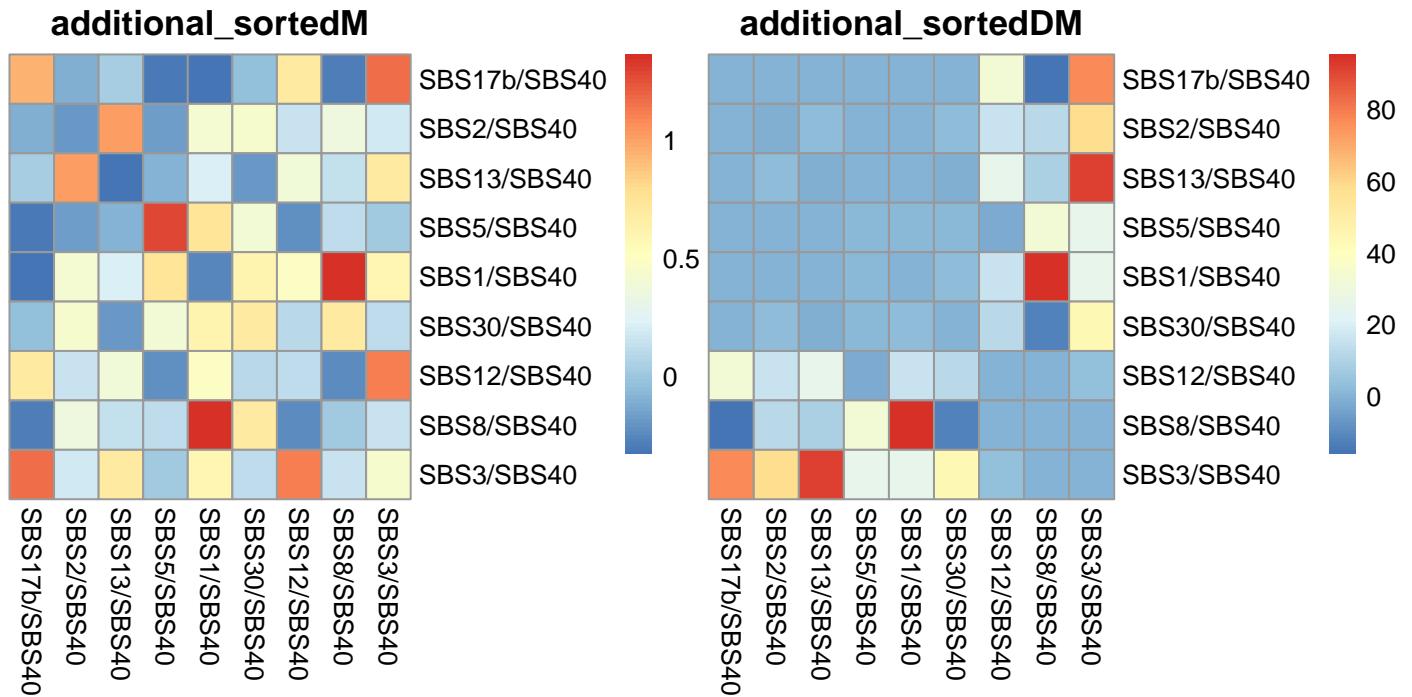
```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```



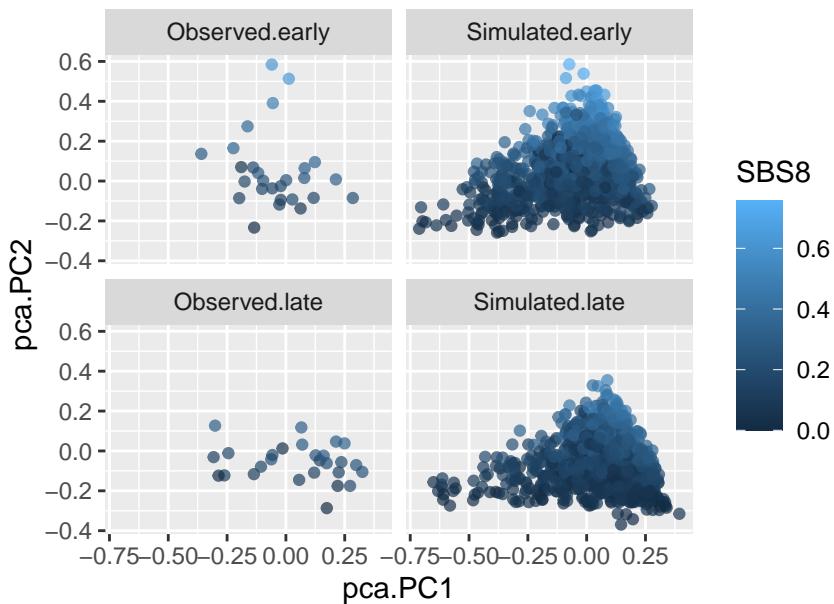


Simulation under inferred data

Simulating with diagRE DMSL nonexo.

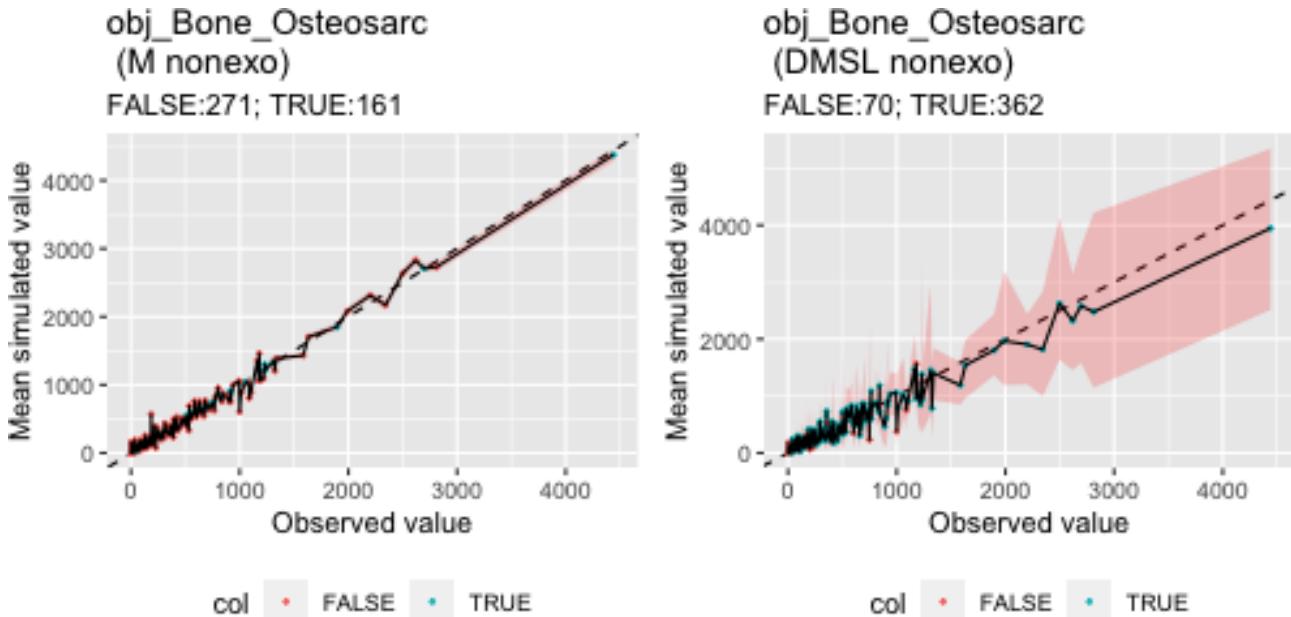
```
## [1] 27
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

Simulation of Bone osteosarcoma samples



Ranked plot for coverage

Note that fullRE DMSL nonexo has not converged!

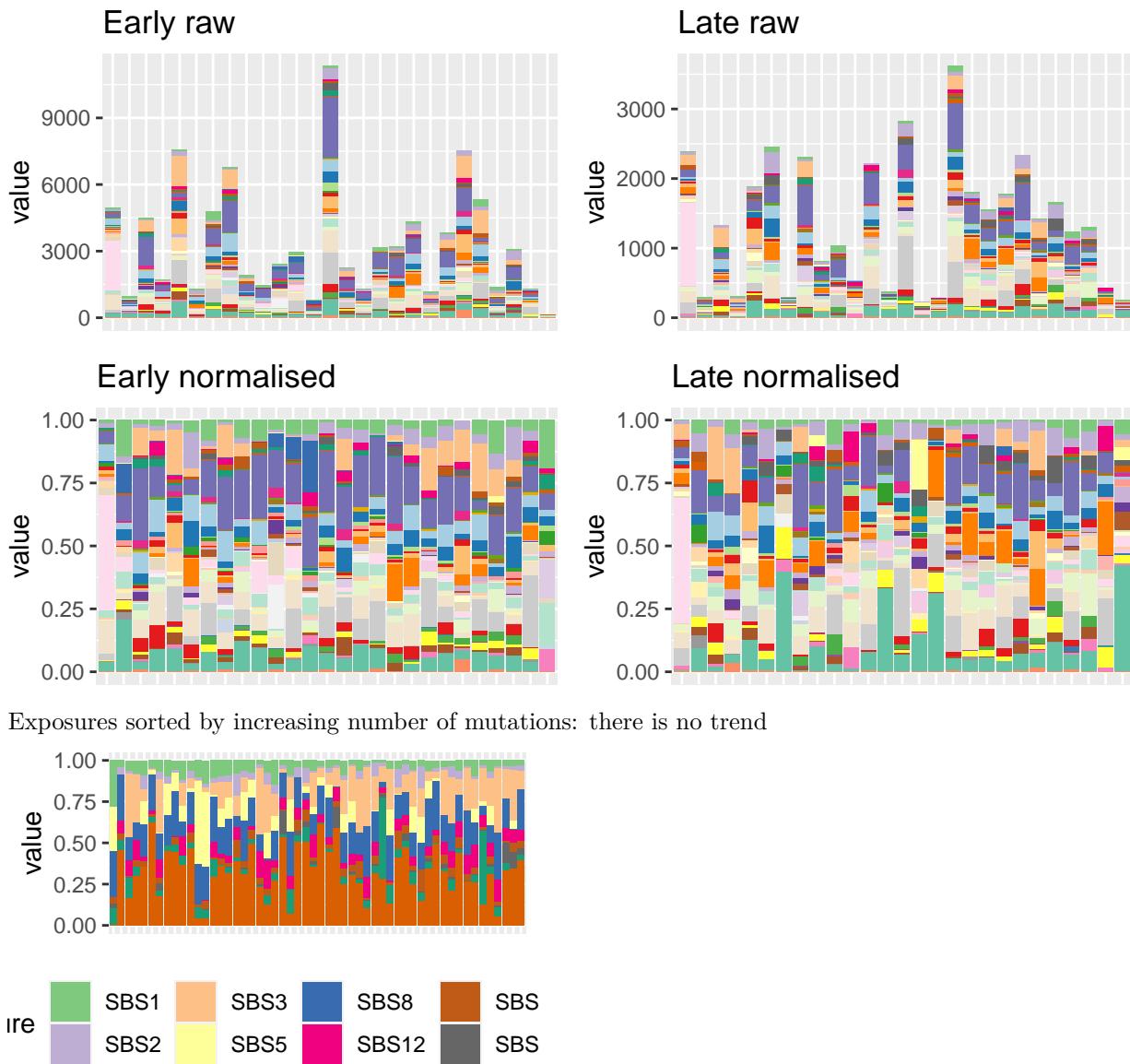


73/359=20% of values are not included in the confidence interval of the DMSL.

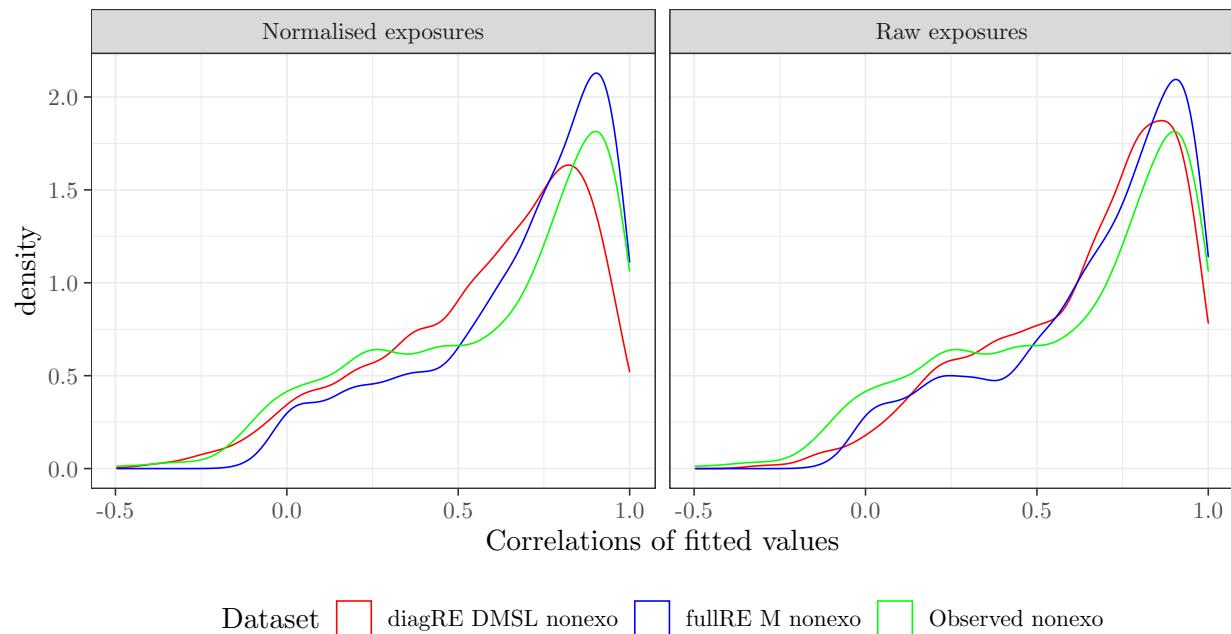
Signatures from mutSigExtractor

The signatures from mutSigExtractor are a bit more chaotic:

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



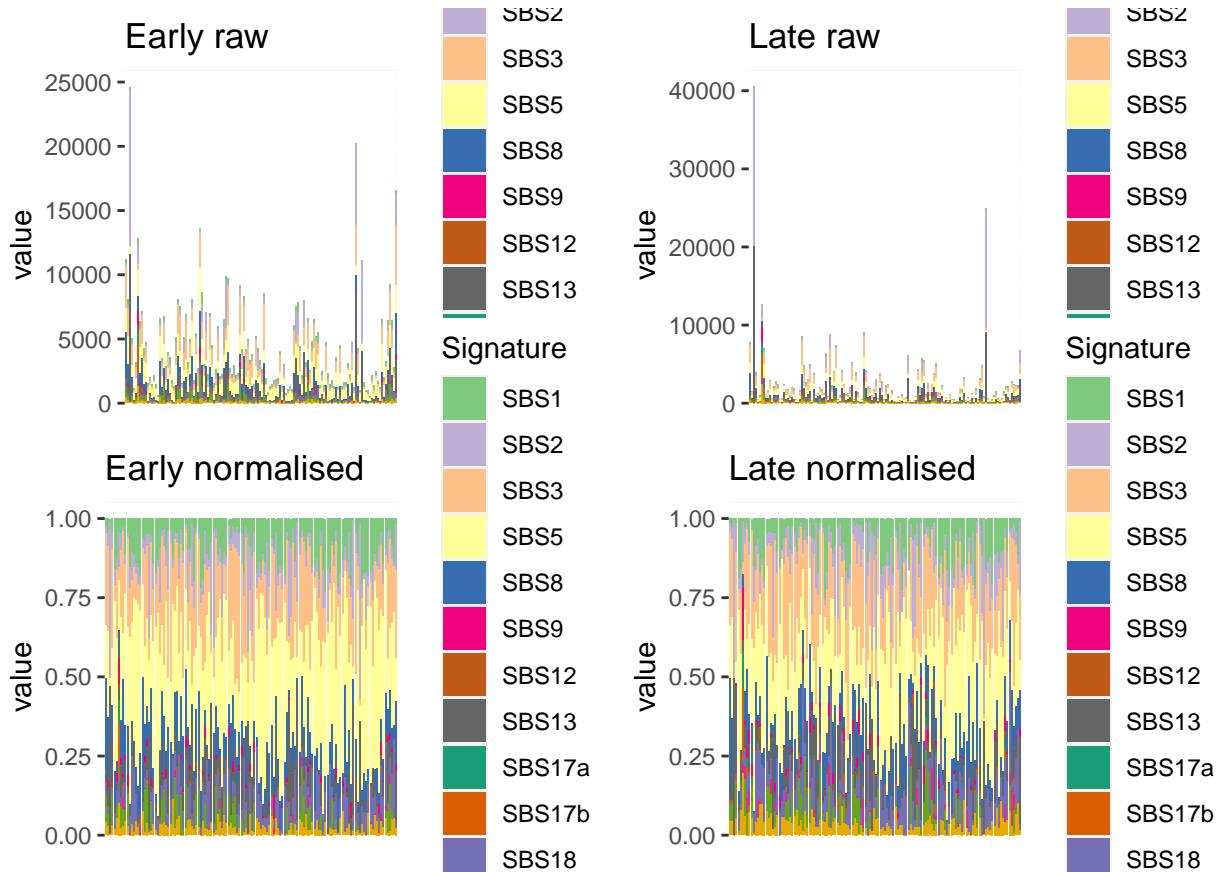
Correlations of signatures



Breast-AdenoCA

Barplot and general statistics

```
## [1] 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 see 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
```

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)
```

```

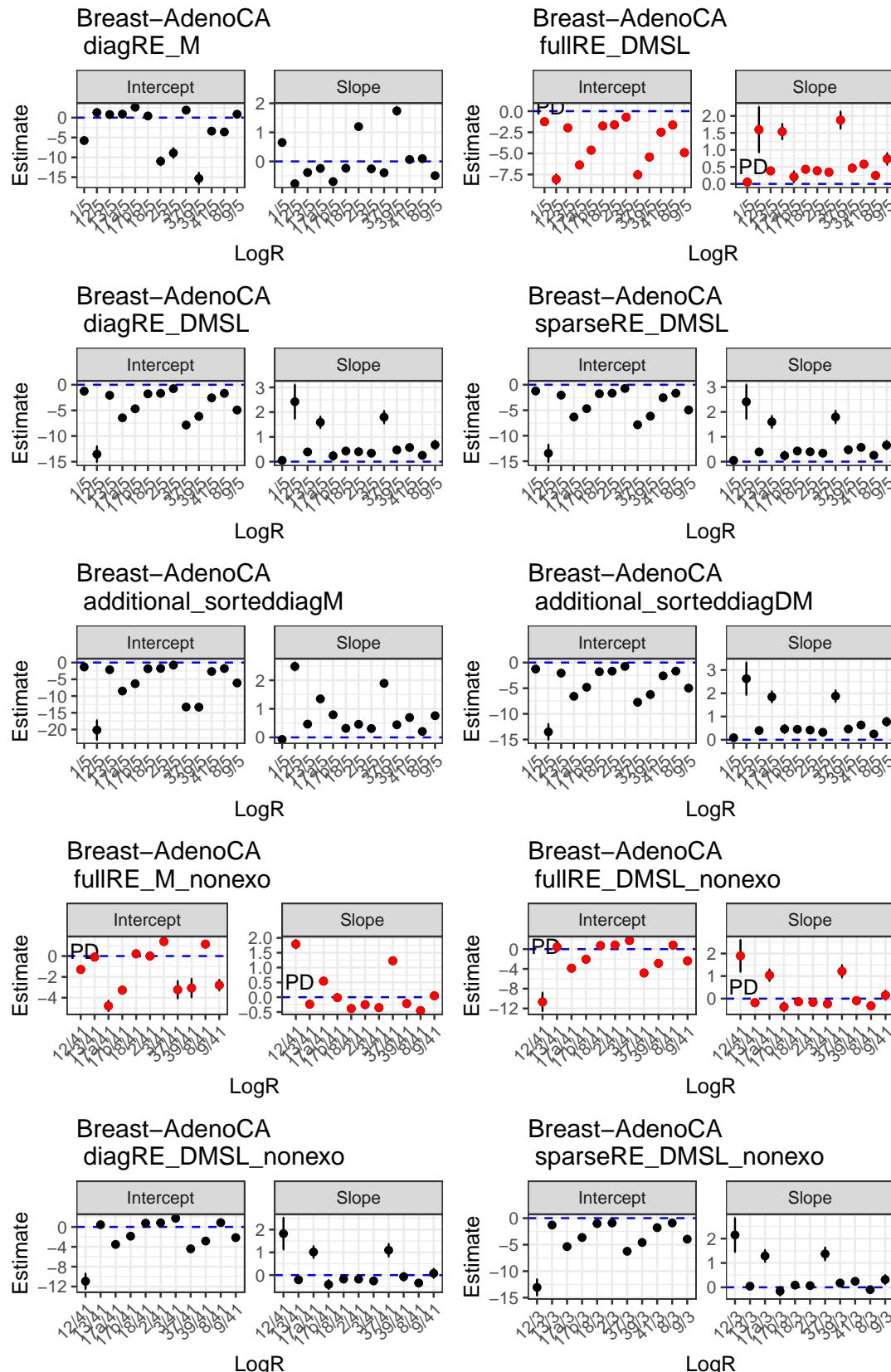
##      SBS1      SBS2      SBS3      SBS5      SBS8      SBS9
## 0.0553410311 0.1376261991 0.1993274971 0.2185906789 0.0969490005 0.0132833987
##      SBS12     SBS13     SBS17a     SBS17b     SBS18     SBS37
## 0.0003532317 0.1360853961 0.0036266519 0.0081714966 0.0531199688 0.0057240307
##      SBS39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

```

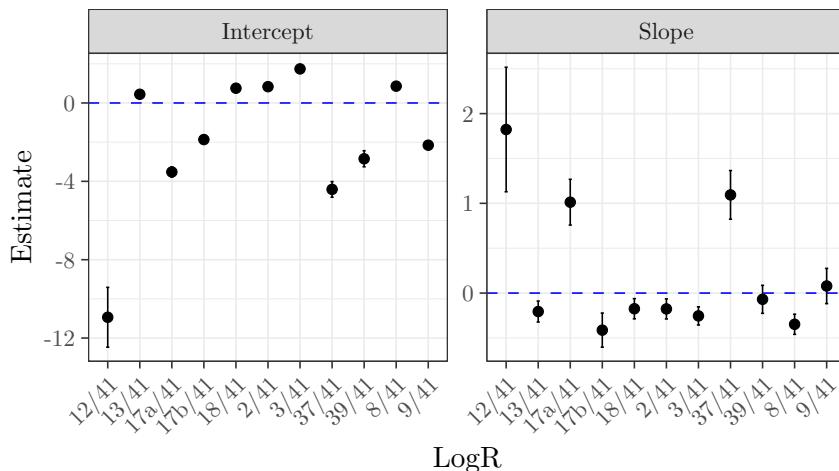
E.g.

- 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



Breast-AdenoCA
Breast adenocarcinoma
diagRE DMSL non-exogenous

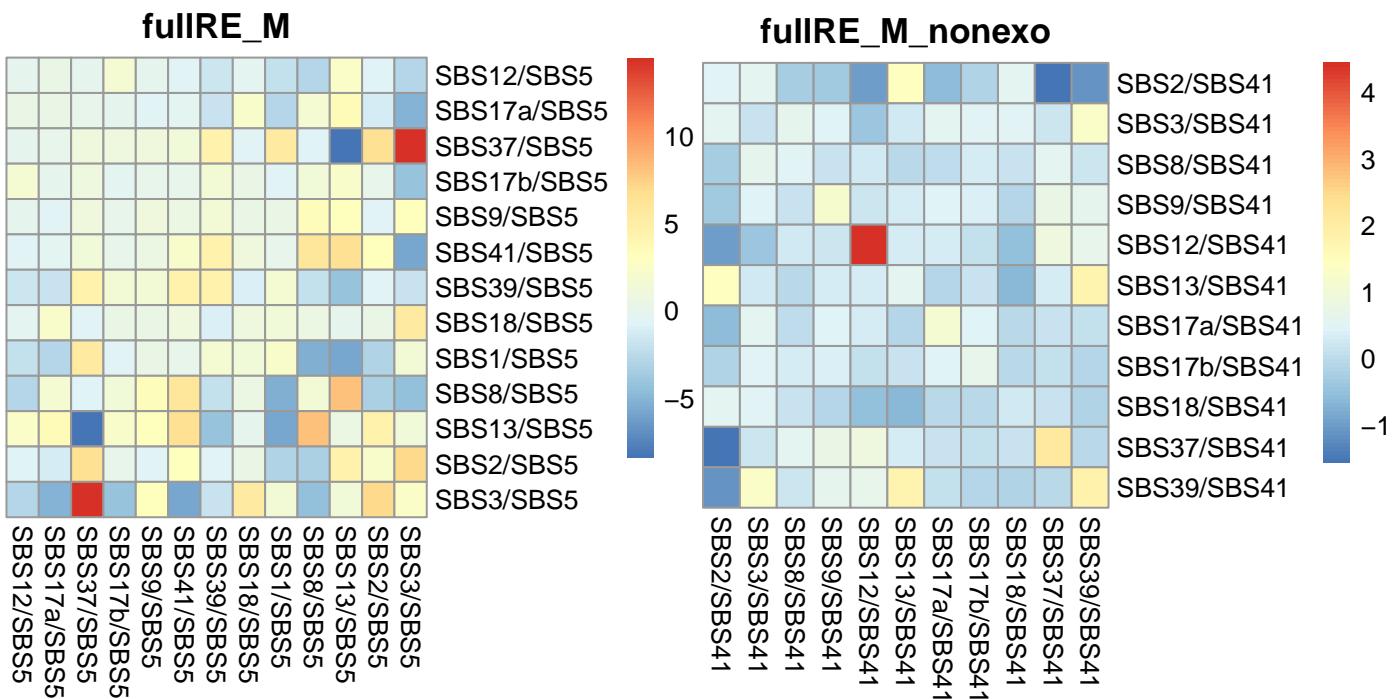


We use the results from the diagonal single lambda DM to test for differential abundance, giving a p-value of 7.748574×10^{-12} .

Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]])$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]])$par.fixed, : This function had been incorrect until now (30 july 2021)
```

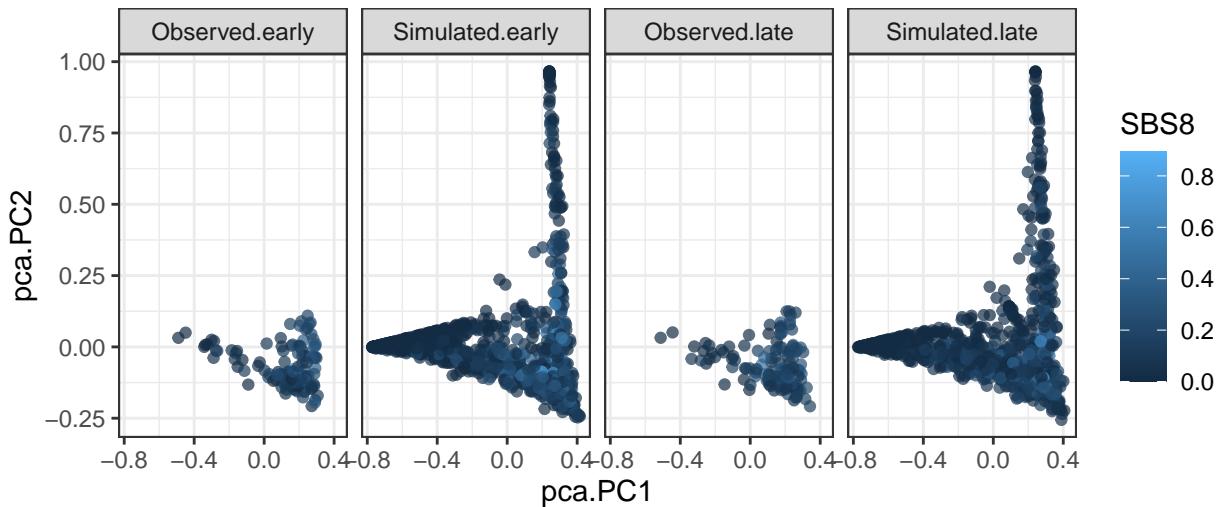


Simulation under inferred data

Sorting the object as we are using sparseRE_DM.

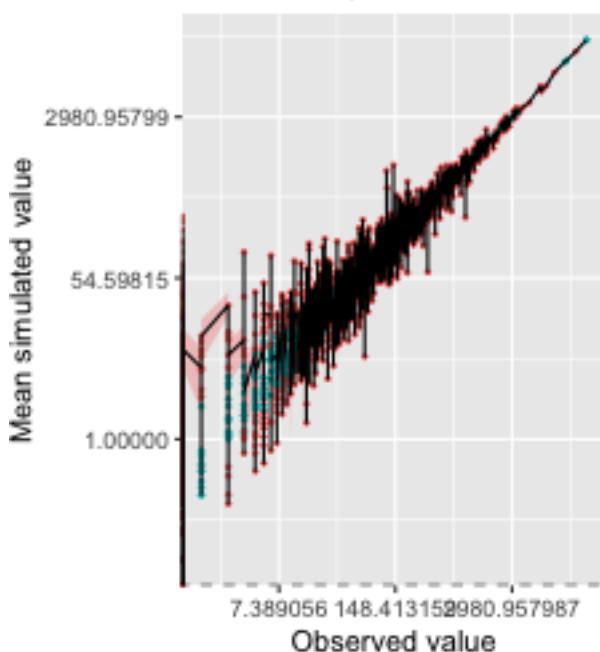
```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :  
## This function had been incorrect until now (30 july 2021)  
  
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :  
## This function had been incorrect until now (30 july 2021)  
  
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):  
## sigma is numerically not positive semidefinite
```

Simulation of Breast Adenocarcinoma samples

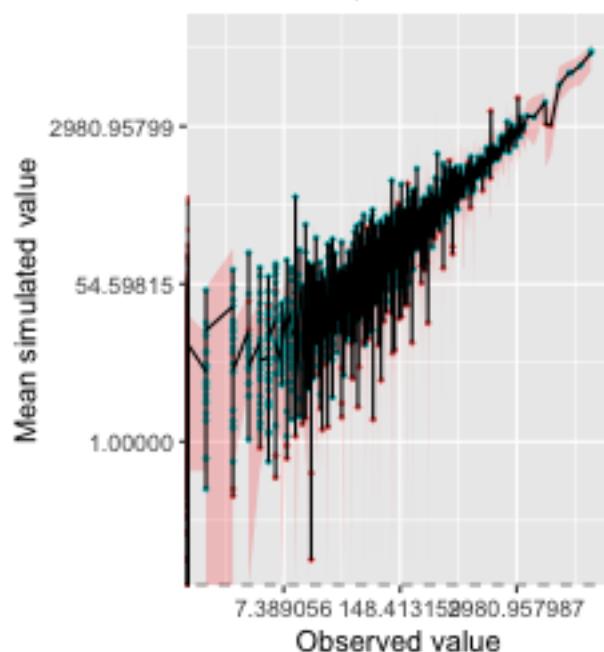


Ranked plot for coverage

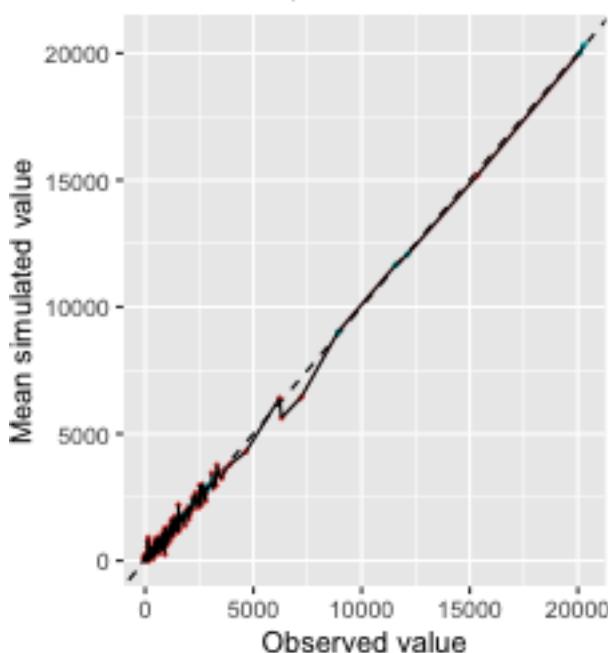
Breast_AdenoCA_nonexo (I)
FALSE:2396; TRUE:868



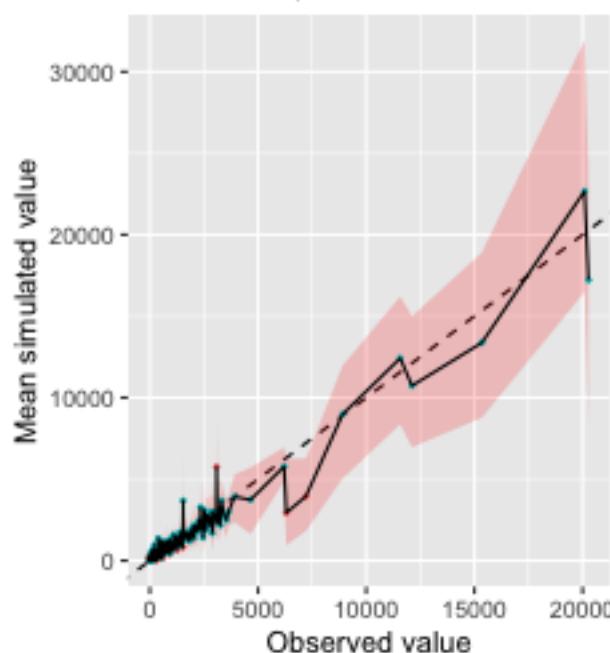
Breast_AdenoCA_nonexo (L)
FALSE:1347; TRUE:1917



col ● FALSE ● TRUE
Breast_AdenoCA_nonexo (M)
FALSE:2417; TRUE:847



col ● FALSE ● TRUE
Breast_AdenoCA_nonexo (DMS)
FALSE:1337; TRUE:1927



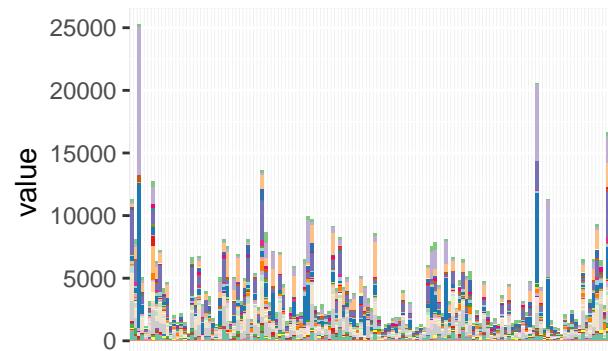
col ● FALSE ● TRUE

col ● FALSE ● TRUE

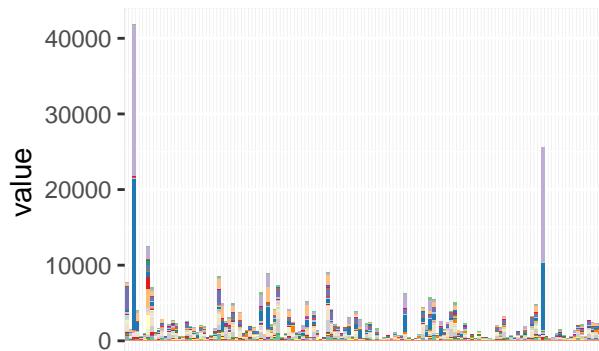
Signatures from mutSigExtractor

[1] 136

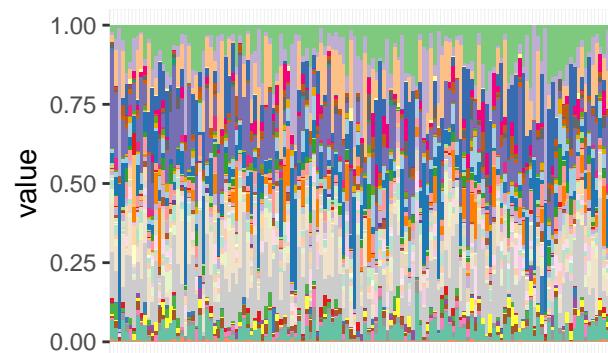
Early raw



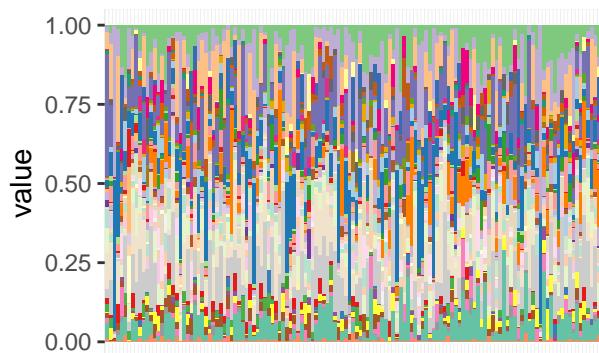
Late raw



Early normalised



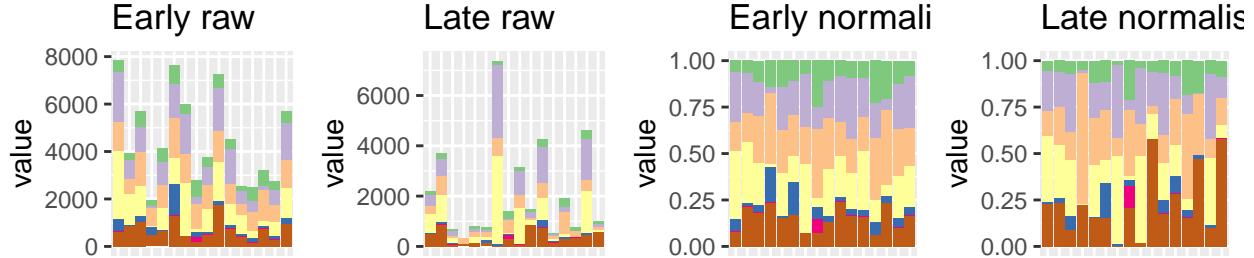
Late normalised



Cervix-SCC

Barplot and general statistics

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



The number of samples and signatures is:

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

The signatures are:

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

Convergence table

| | 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%.

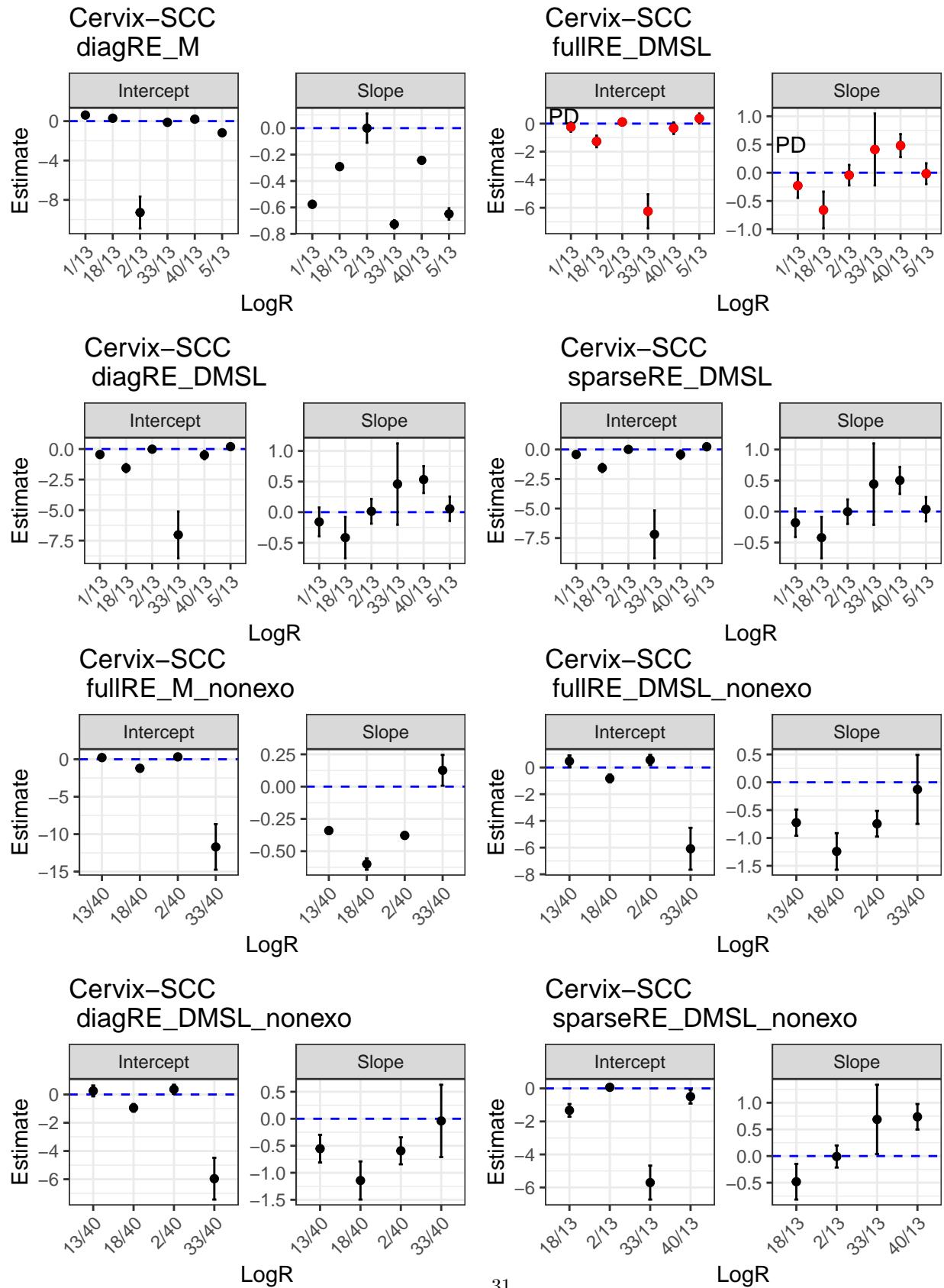
```
colSums(obj_Cervix_SCC$Y == 0)/nrow(obj_Cervix_SCC$Y)
```

```
##      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

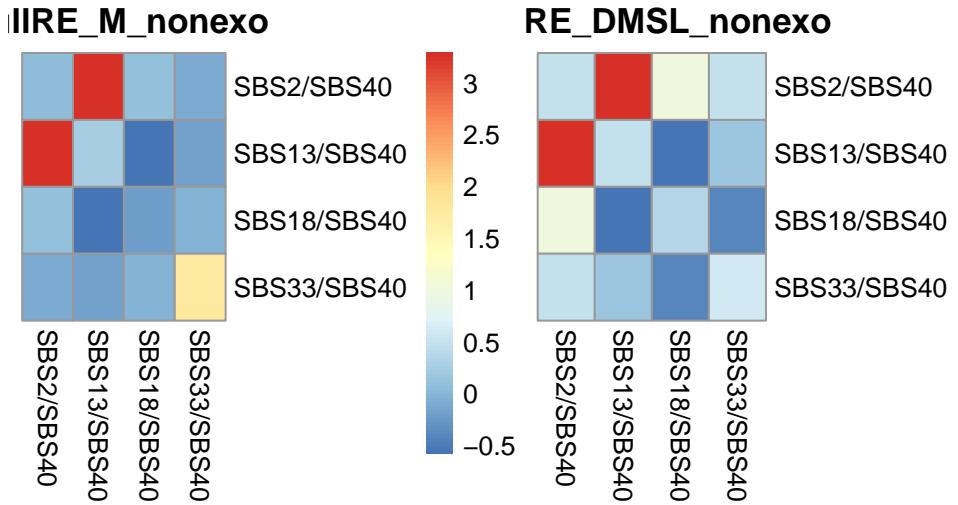


We use the results from the fullRE single lambda DM to test for differential abundance, giving a p-value of 3.8923434×10^{-5} .

Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```



Simulation under inferred data

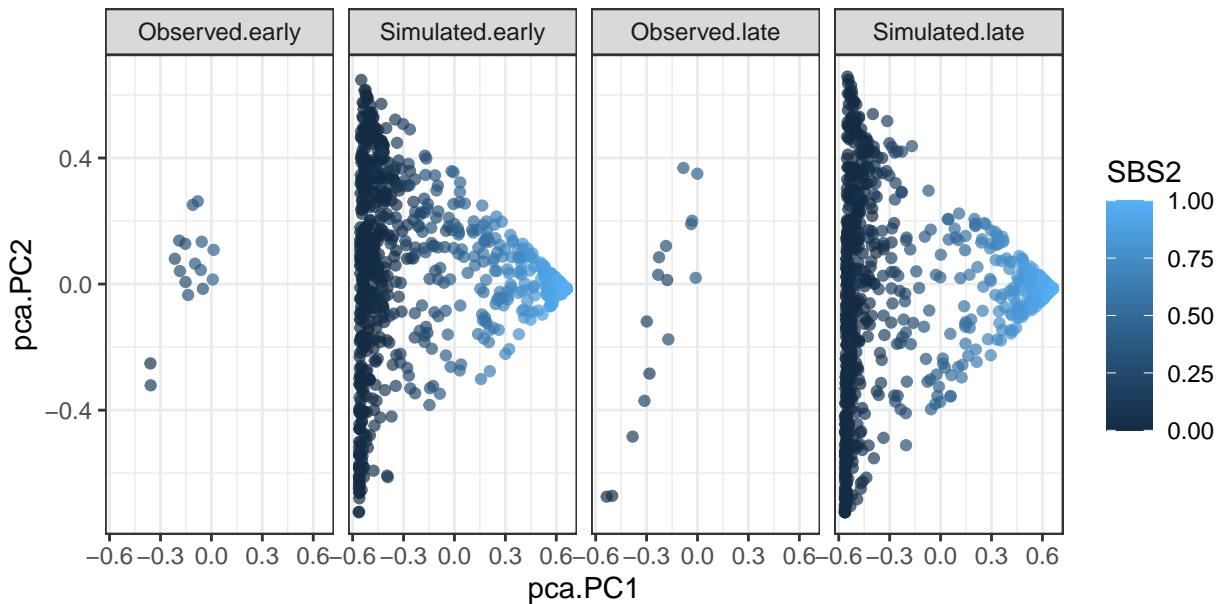
We are using the sorted version of the exposures, as we are using sparseRE DMSL.

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)

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

Simulation of Cervix SCC samples



Comparison of the estimated covariance matrix and the closest positive semidefinite matrix.

```
ct <- "Cervix-SCC"

dmin1_Cervix_SCC_cov_mat_sparse <- length(python_like_select_name(sparseRE_DMSL_nonexo[[ct]]$par.fixed, "dmin1"))
cov_vec_Cervix_SCC_cov_mat_sparse = rep(0, (dmin1_Cervix_SCC_cov_mat_sparse*2-dmin1_Cervix_SCC_cov_mat_sparse))
cov_vec_Cervix_SCC_cov_mat_sparse[as.numeric(strsplit(subset_sigs_sparse_cov_idx_nonexo[subset_sigs_sparse], ",")[[1]])] = 1

cov_mat_Cervix_SCC <- fill_covariance_matrix(arg_d = dmin1_Cervix_SCC_cov_mat_sparse,
                                                arg_entries_var = exp(python_like_select_name(sparseRE_DMSL_nonexo[[ct]]$var, "var")),
                                                arg_entries_cov = cov_vec_Cervix_SCC_cov_mat_sparse)

cov_mat_Cervix_SCC

##          [,1]      [,2]      [,3]      [,4]
## [1,] 2.690655  1.554016  1.337713  0.0000000
## [2,] 1.554016  1.246623 103.048586  0.0000000
## [3,] 1.337713 103.048586   1.490150  0.0000000
## [4,] 0.000000  0.000000   0.000000  0.2029568

Matrix::nearPD(cov_mat_Cervix_SCC)

## $mat
## 4 x 4 Matrix of class "dpoMatrix"
##          [,1]      [,2]      [,3]      [,4]
## [1,] 2.690877  1.447736  1.443865  0.0000000
## [2,] 1.447736 52.148325 52.208484  0.0000000
## [3,] 1.443865 52.208484 52.268725  0.0000000
## [4,] 0.000000  0.000000   0.000000  0.2029568
##
## $eigenvalues
```

```

## [1] 1.044581e+02 2.649802e+00 2.029568e-01 1.044581e-06
##
## $corr
## [1] FALSE
##
## $normF
## [1] 101.6805
##
## $iterations
## [1] 2
##
## $rel.tol
## [1] 0
##
## $converged
## [1] TRUE
##
## attr(,"class")
## [1] "nearPD"

```

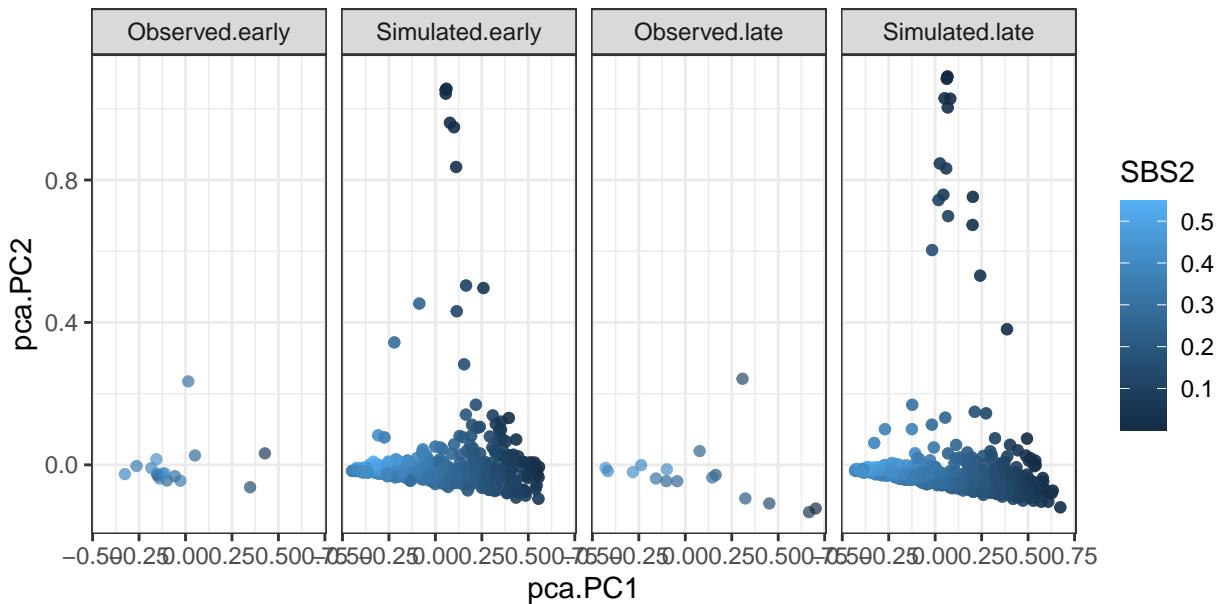
Now with fullRE M:

```

## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
## Warning in mvtnorm:::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite

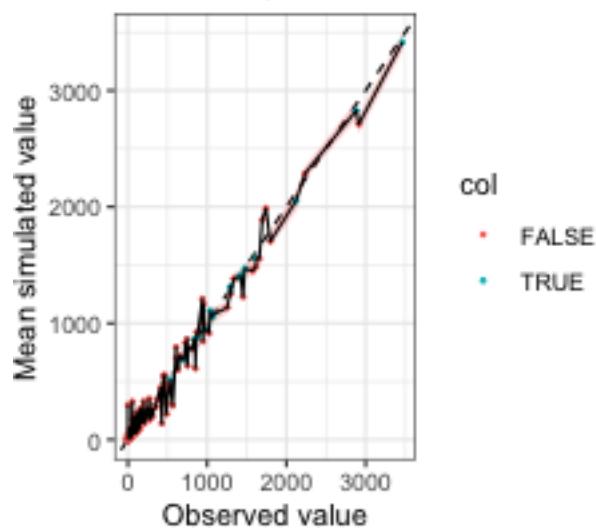
```

Simulation of Cervix SCC samples

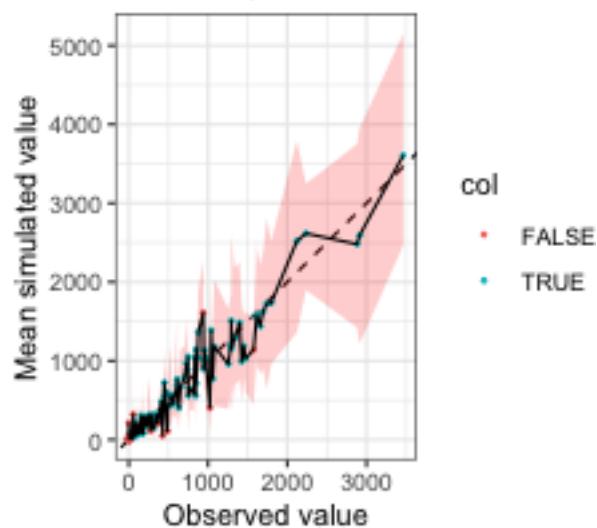


Ranked plot for coverage

obj_Cervix_SCC_nonexo
(fullRE M)
FALSE:122; TRUE:38

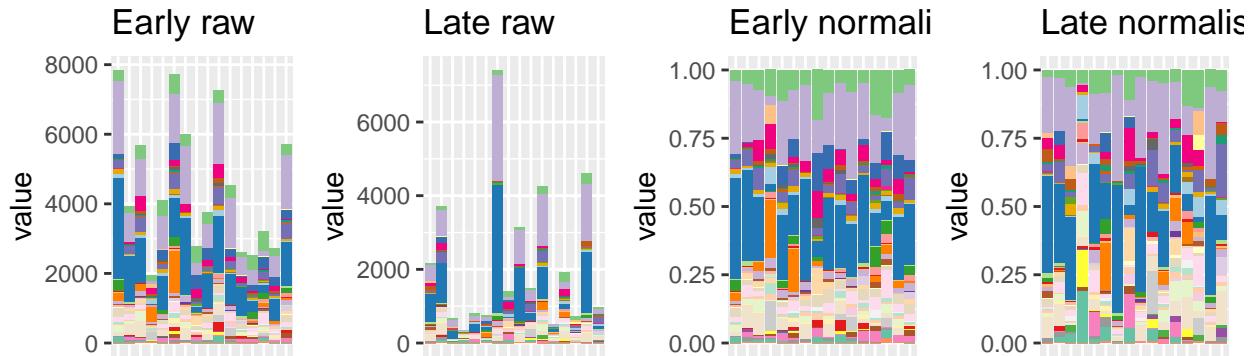


obj_Cervix_SCC_nonexo
(fullRE DMSL)
FALSE:44; TRUE:116



Signatures from mutSigExtractor

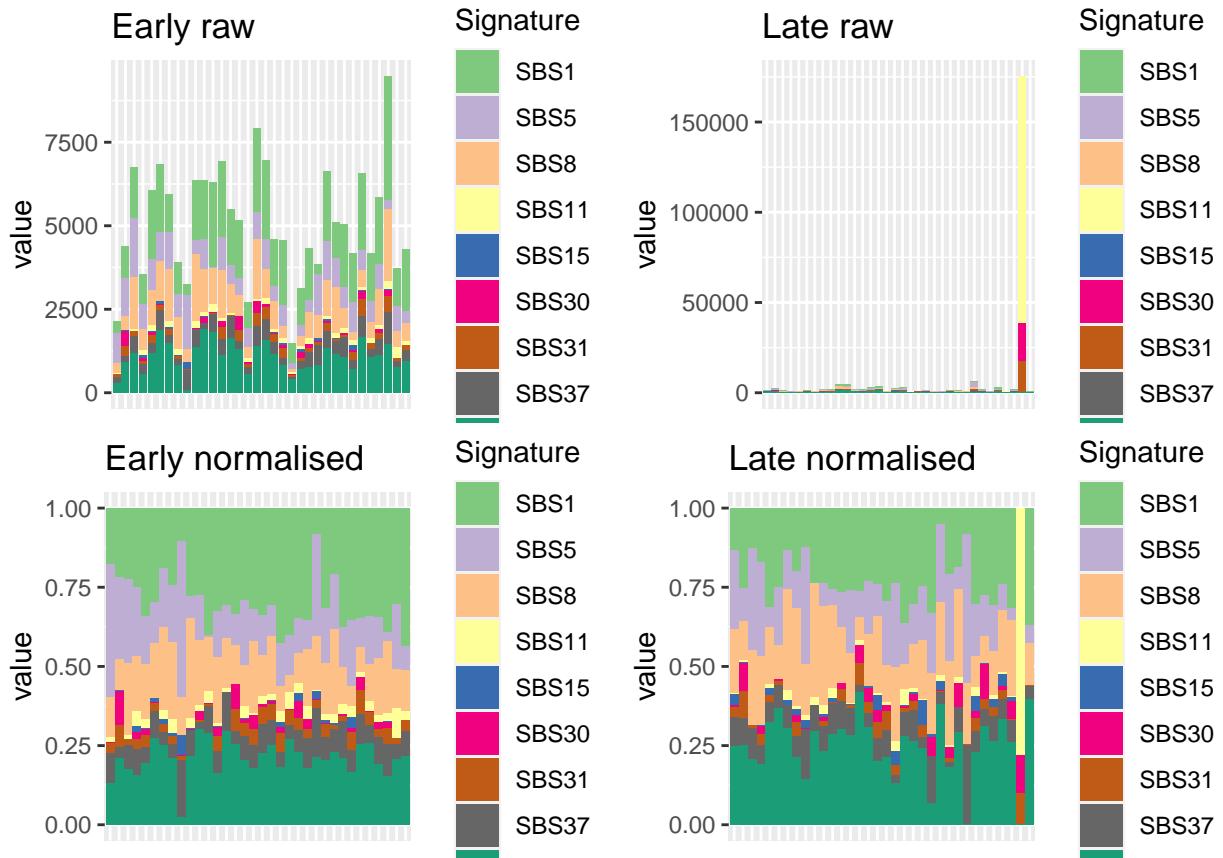
```
## [1] 16
```



CNS-GBM

Barplot and general statistics

```
## [1] 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.

| | 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
```

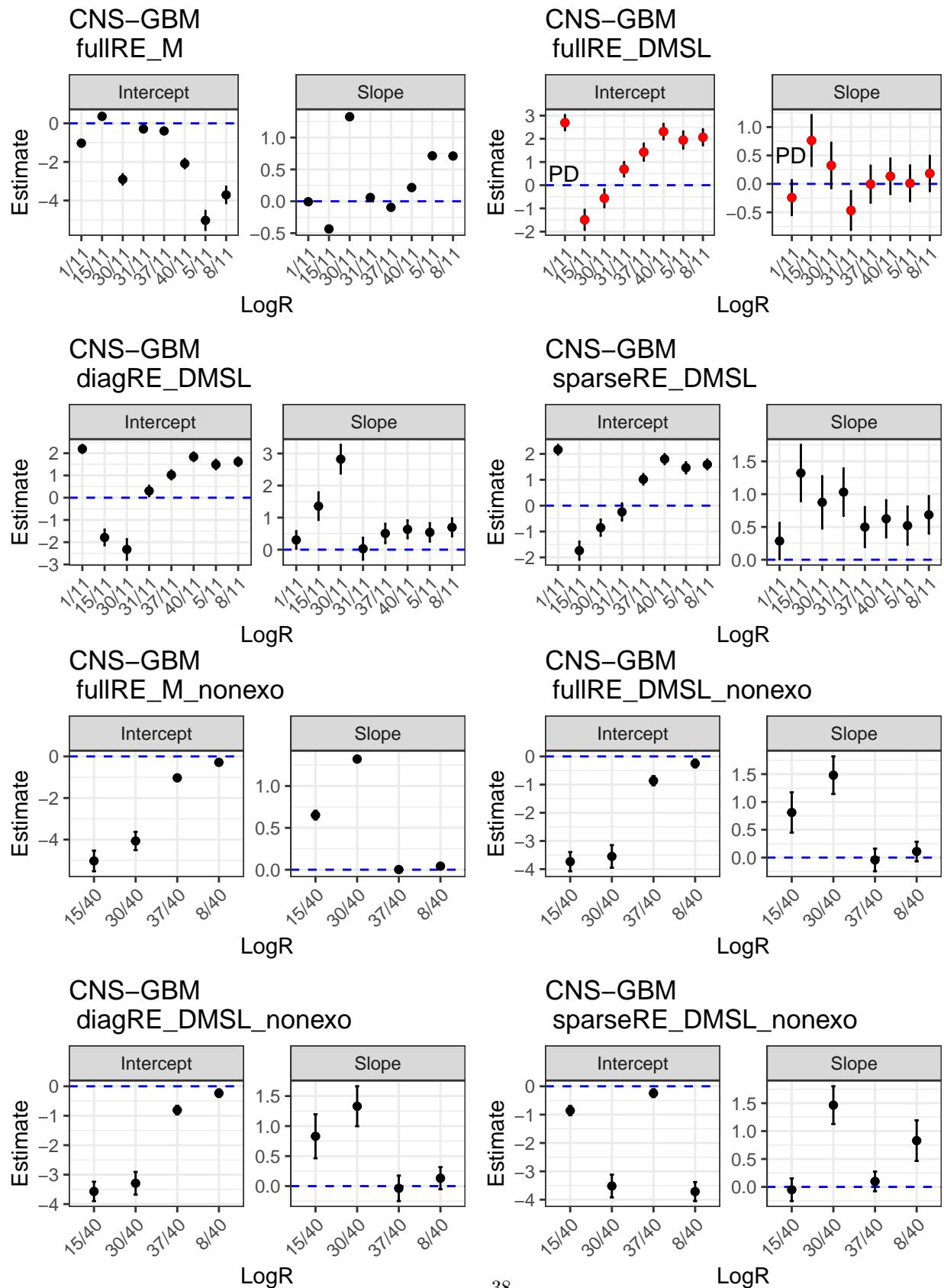
```
colSums(obj_CNS_GBM$Y)/sum(obj_CNS_GBM$Y)
```

```
##      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



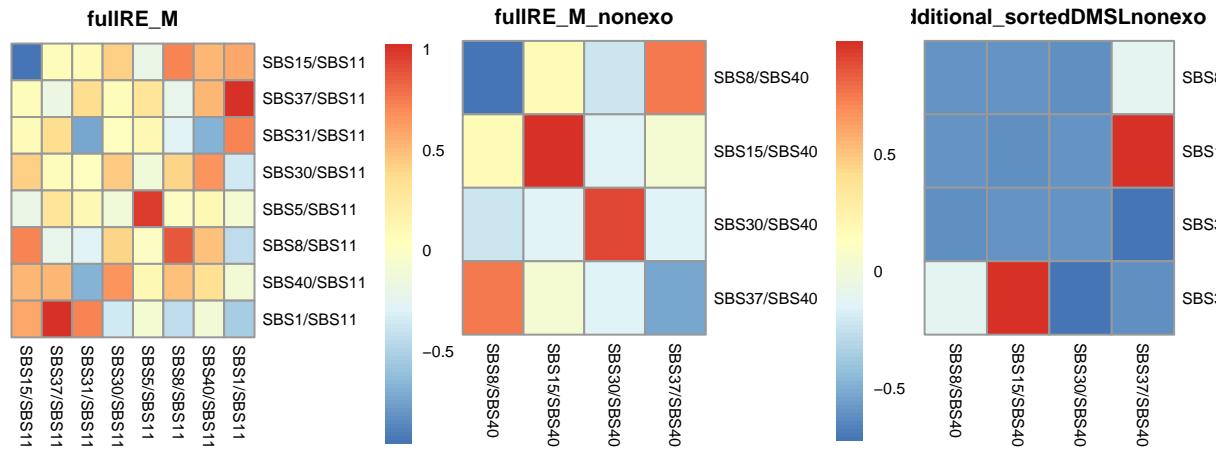
We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 6.6827492×10^{-5} .

Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```



Simulation under inferred data

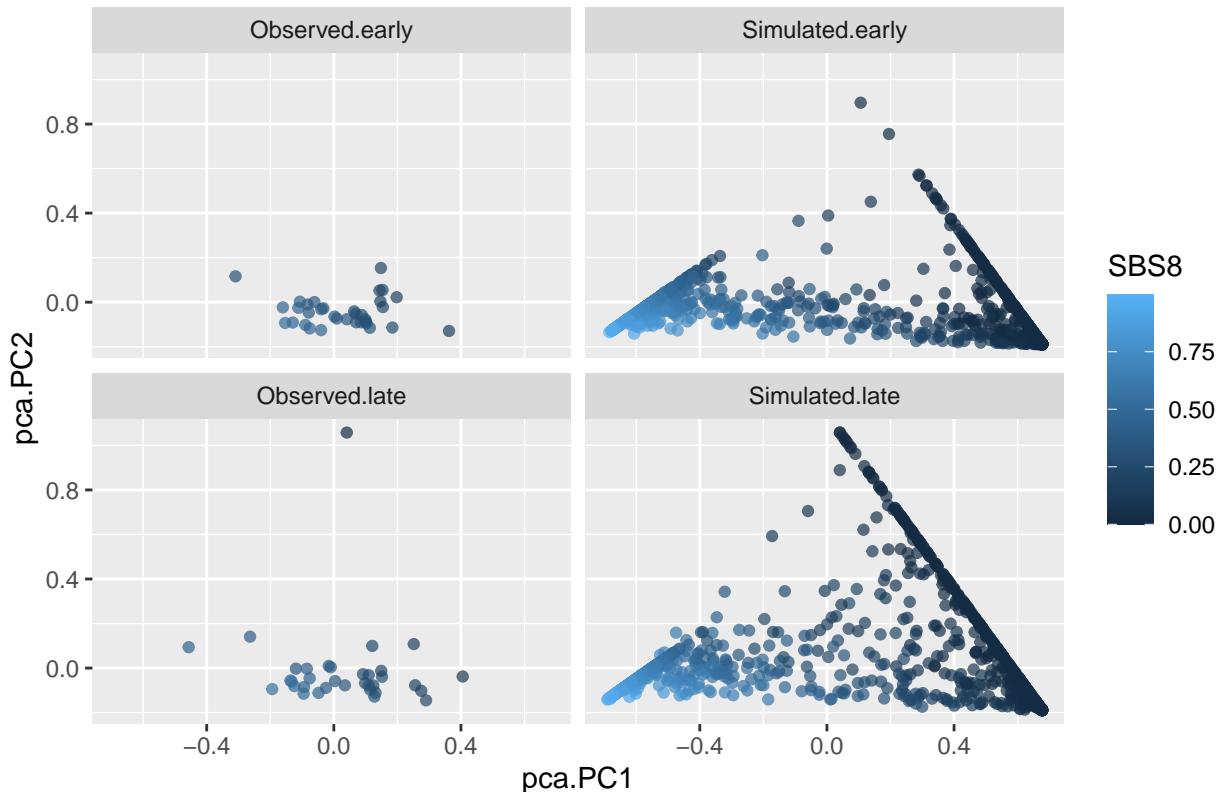
With fullRE DMSL:

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

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

Simulation of CNS–GBM samples



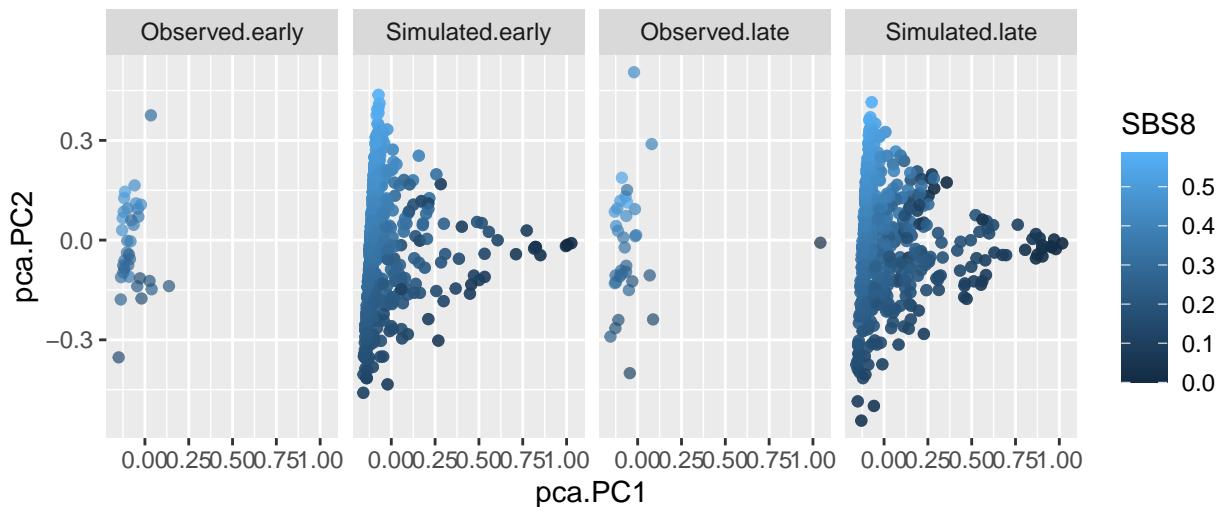
With fullRE M, this time the covariance matrix is positive semi-definite:

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)

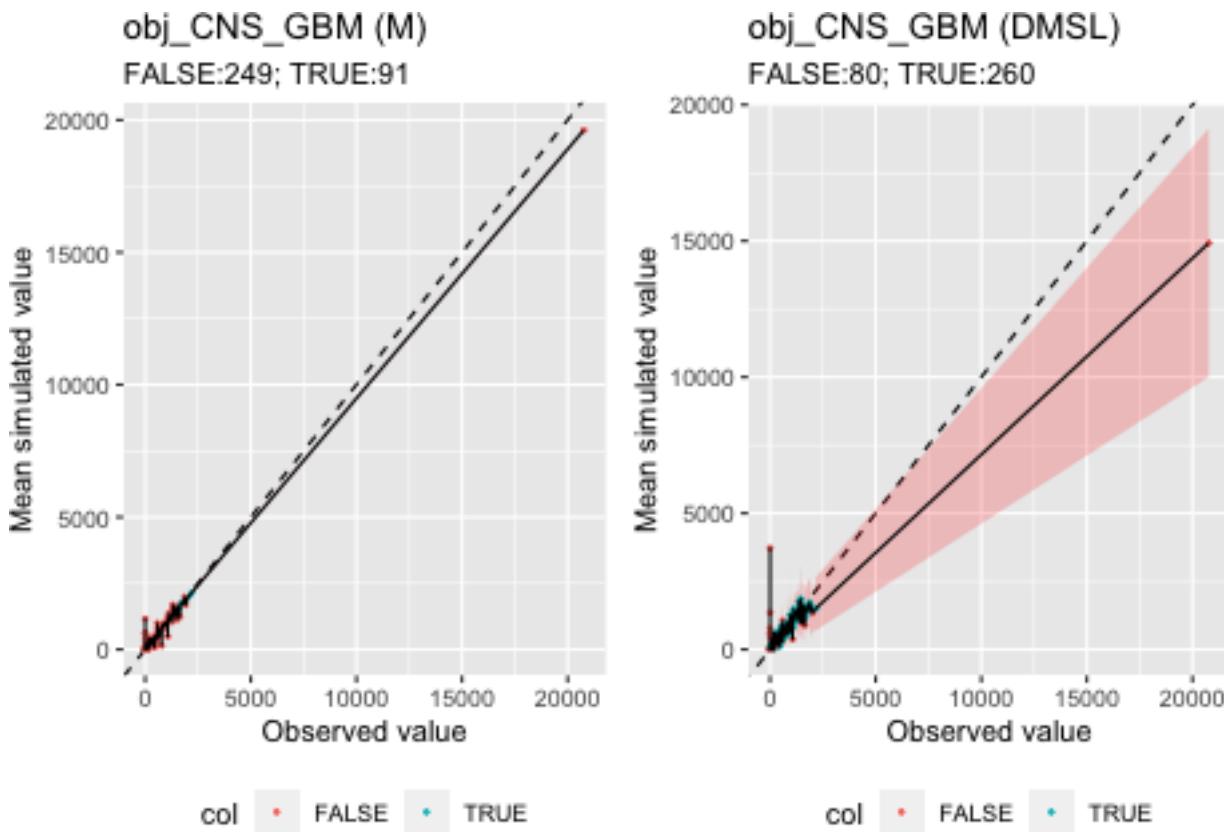
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)

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

Simulation of CNS–GBM samples (M)



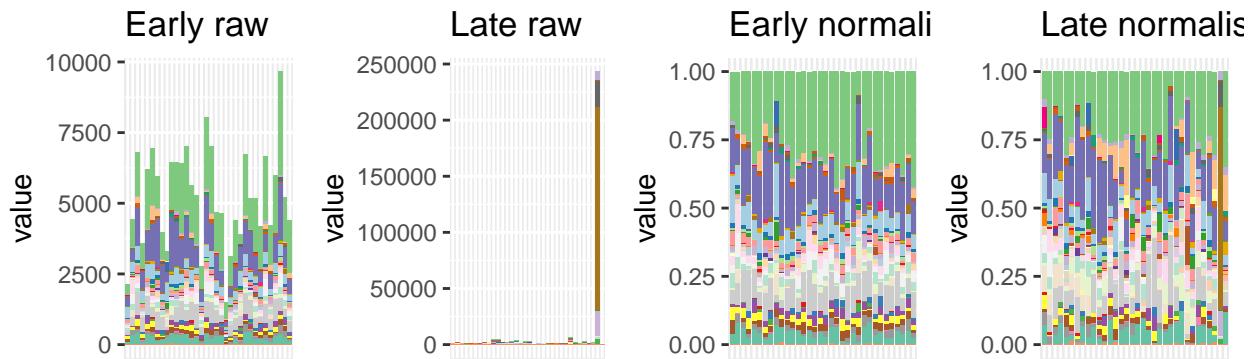
Ranked plot for coverage



Signatures from mutSigExtractor

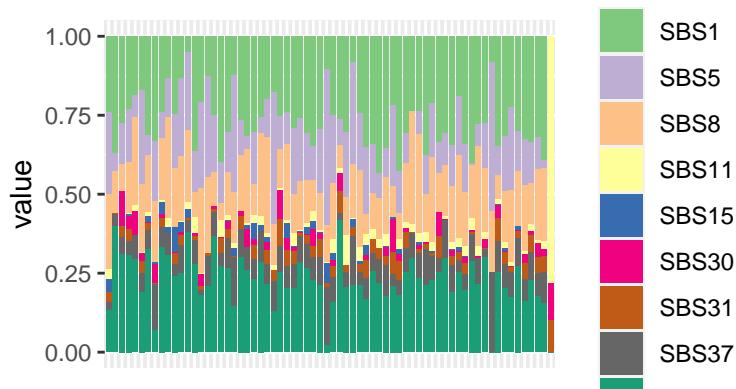
The signatures from mutSigExtractor are a bit more chaotic:

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



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: 68
```

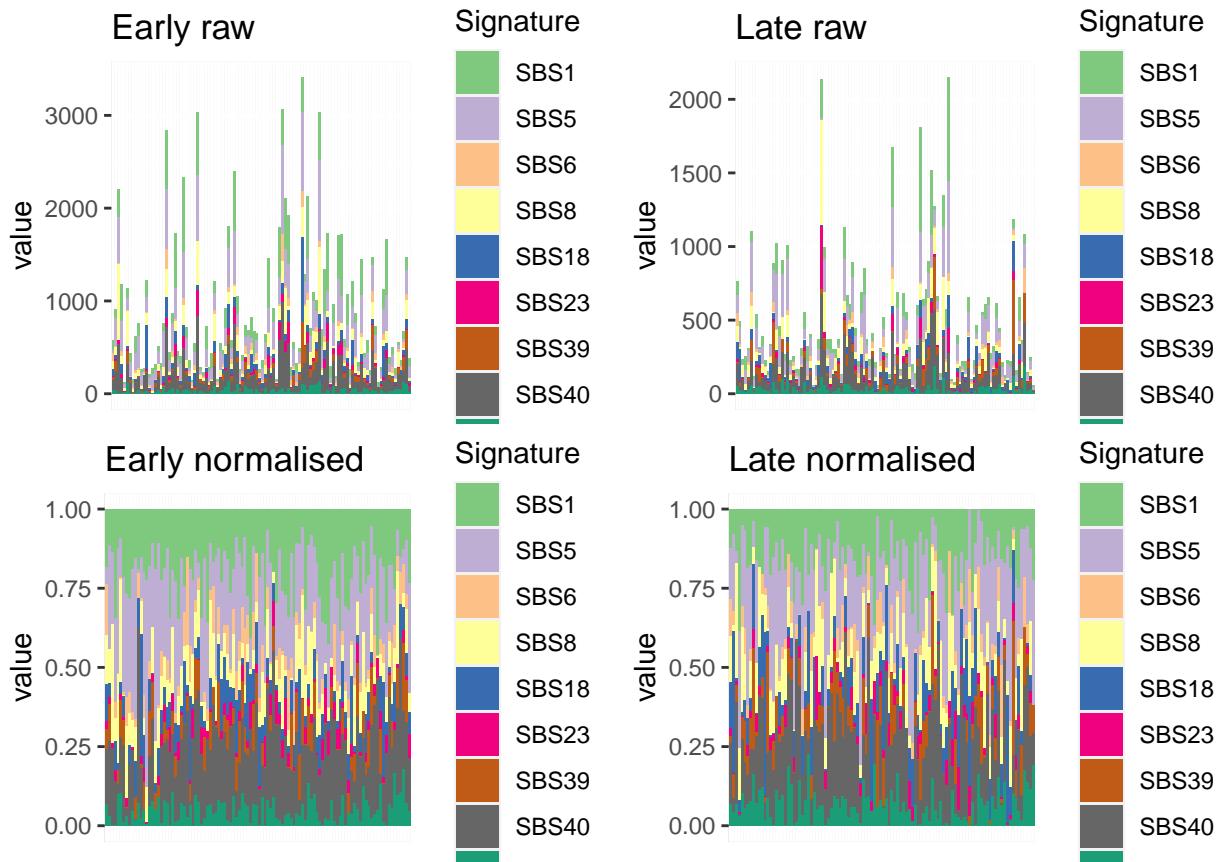


CNS-Medullo

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)
```

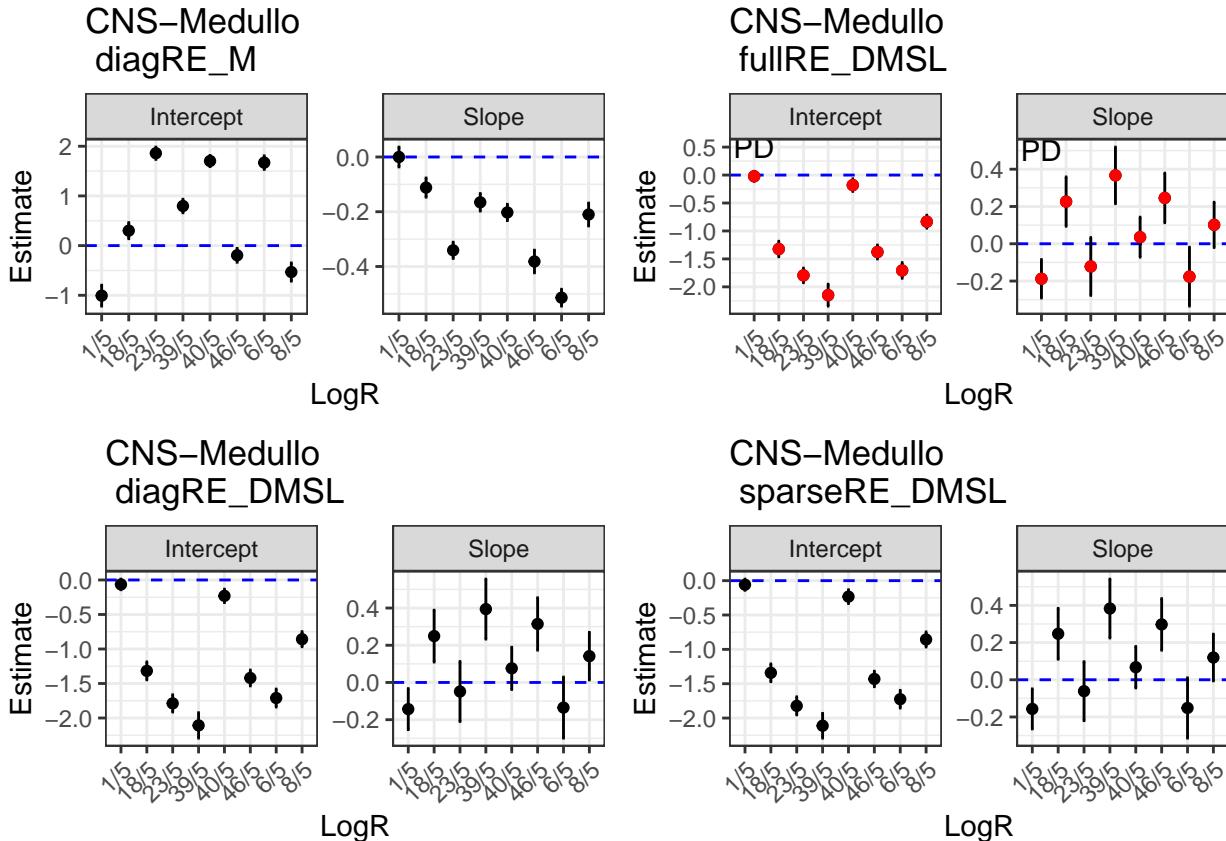
```

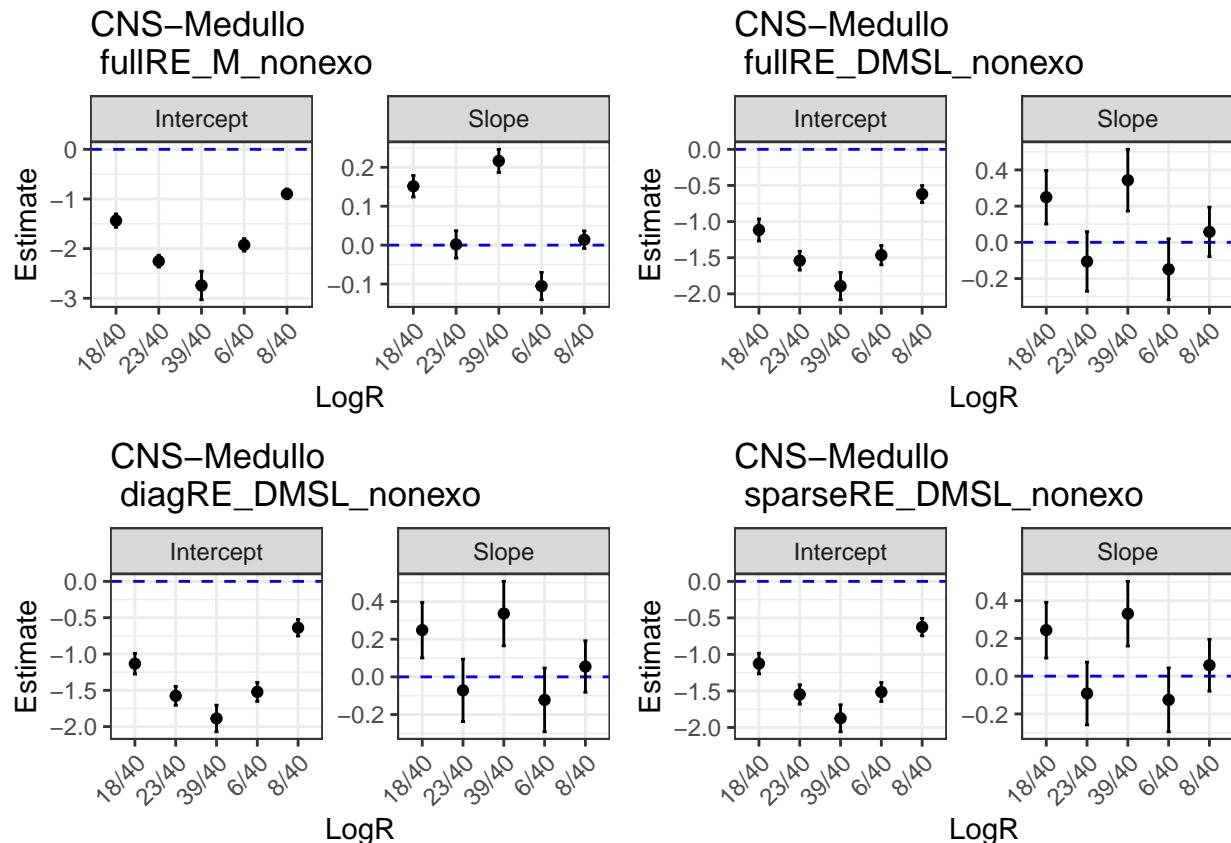
##      SBS1      SBS5      SBS6      SBS8      SBS18     SBS23     SBS39
## 0.19177483 0.22946904 0.03737123 0.11614418 0.07466844 0.03836035 0.05498025
##      SBS40     SBS46
## 0.21065558 0.04657610

```

Betas

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





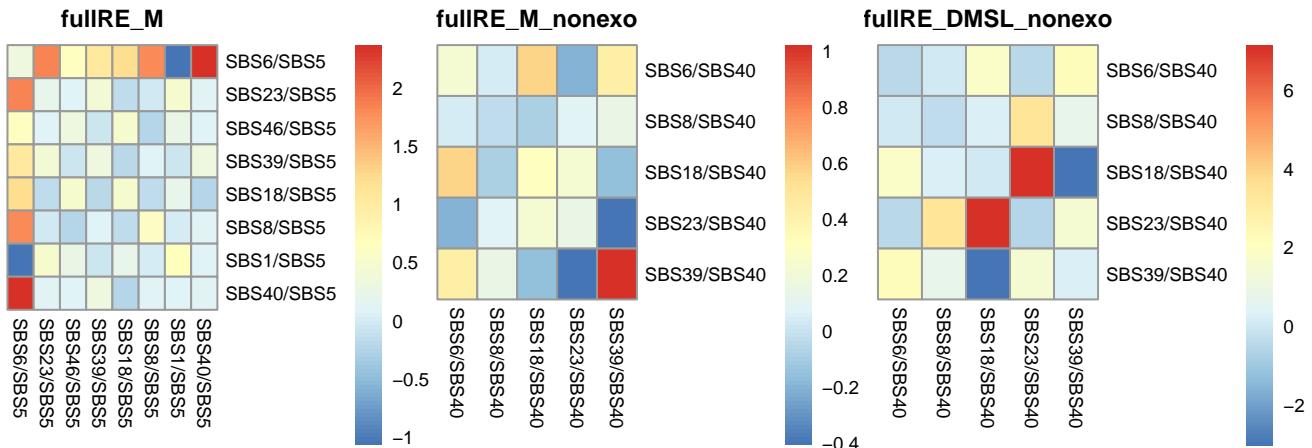
We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 0.0677062.

Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```



Simulation under inferred data

```

obj_CNS_Medullo_nonexo <- give_subset_sigs_TMBobj(obj_CNS_Medullo, nonexogenous$V1)

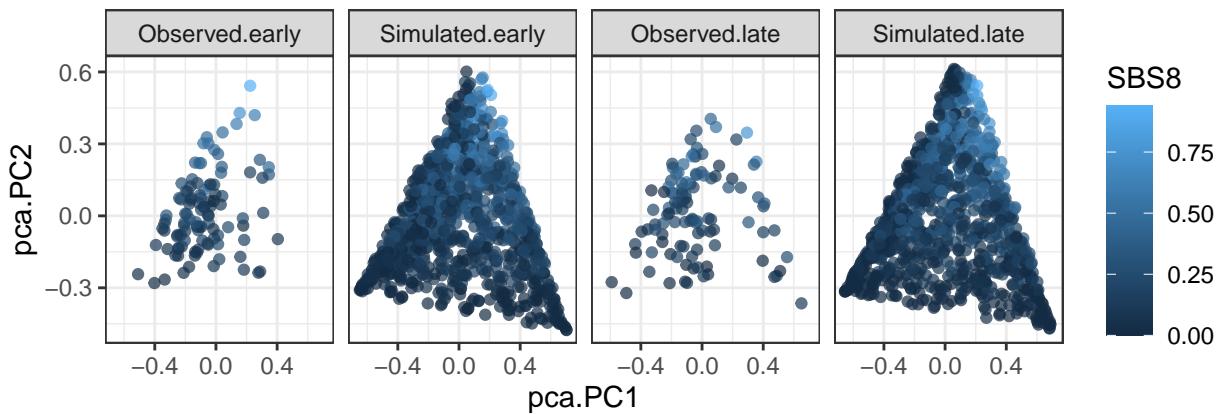
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)

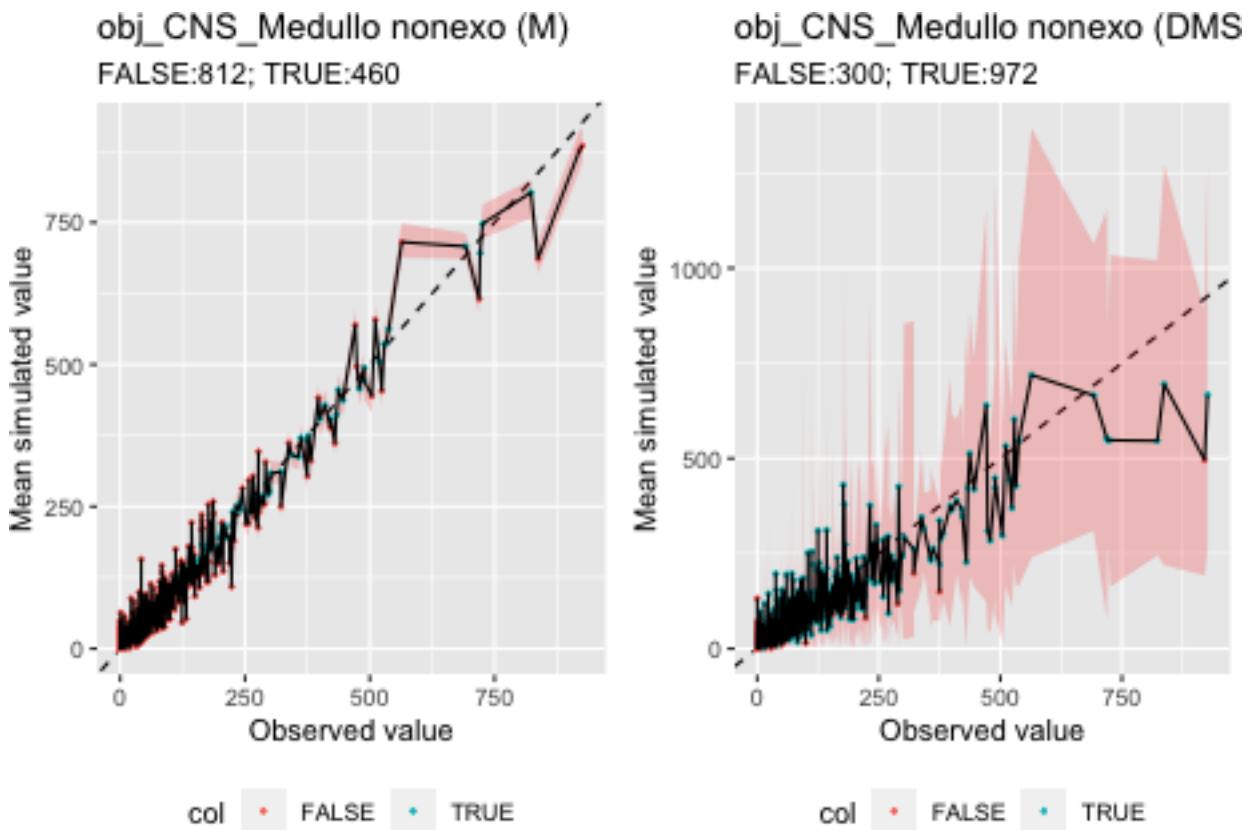
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite

```

Simulation of CNS-Medullo samples



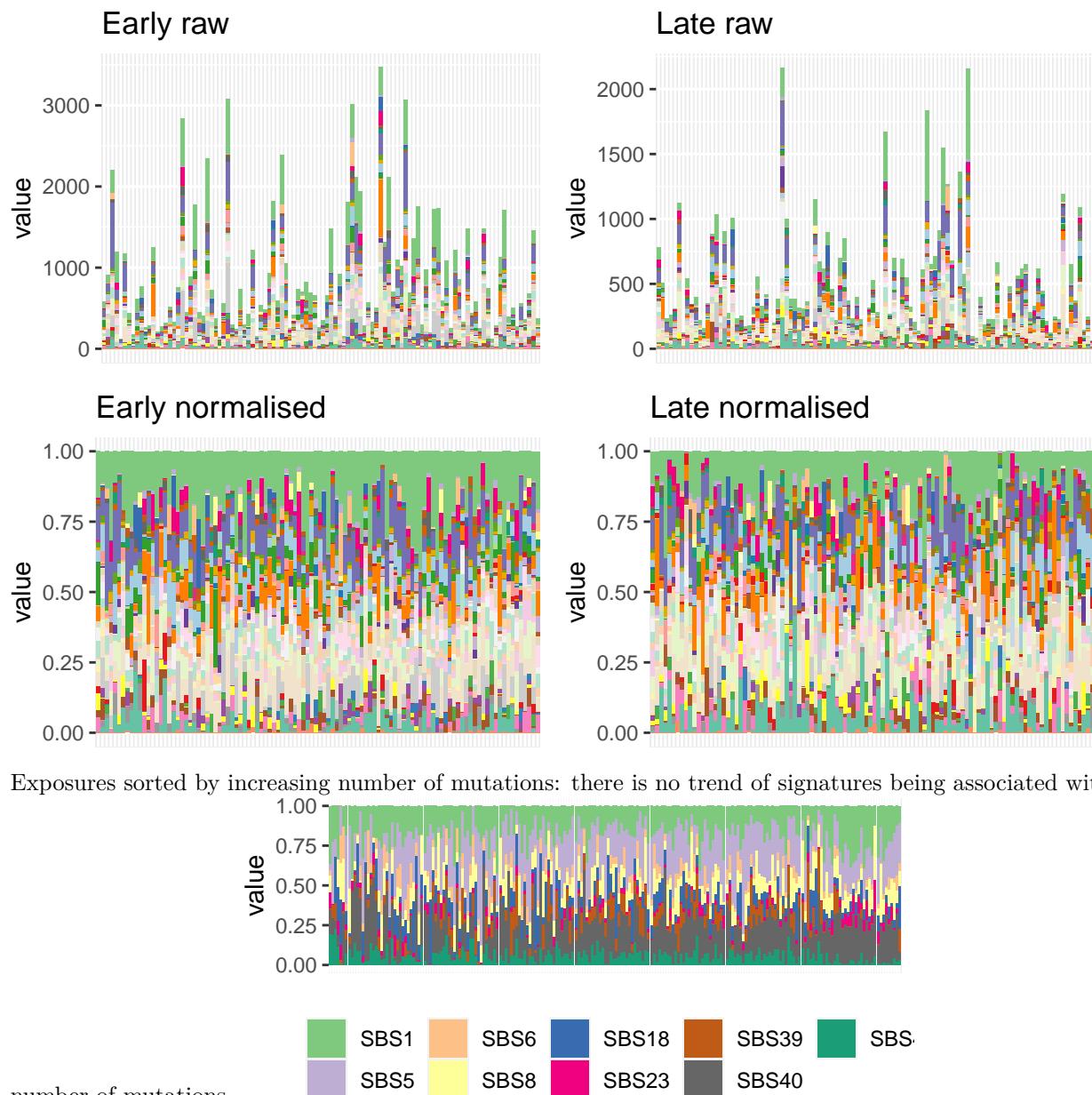
Ranked plot for coverage



Signatures from mutSigExtractor

The signatures from mutSigExtractor are a bit more chaotic:

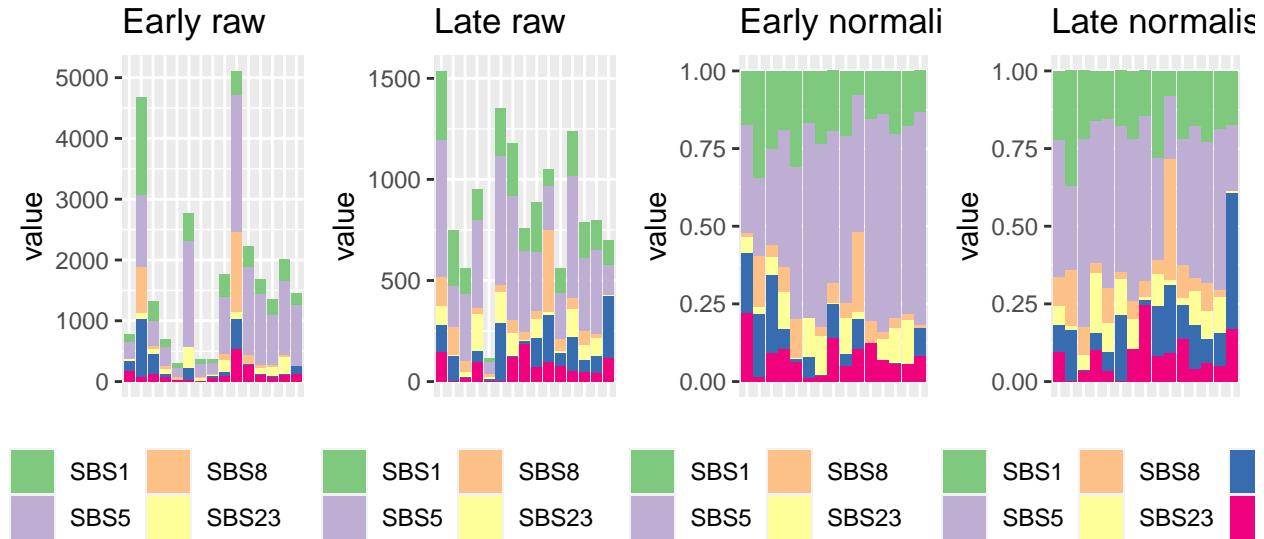
```
## [1] 106
```



CNS-Oligo

Barplot and general statistics

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



The number of samples and signatures is:

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

The signatures are:

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

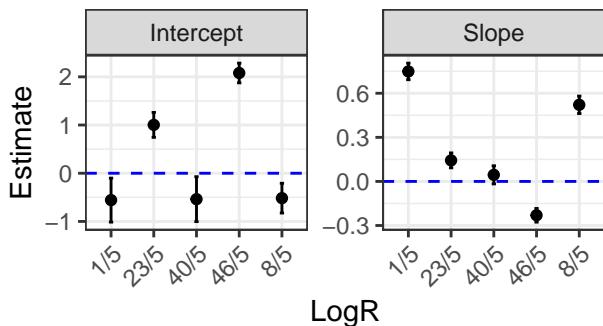
Convergence table

Pretty much everything has converged

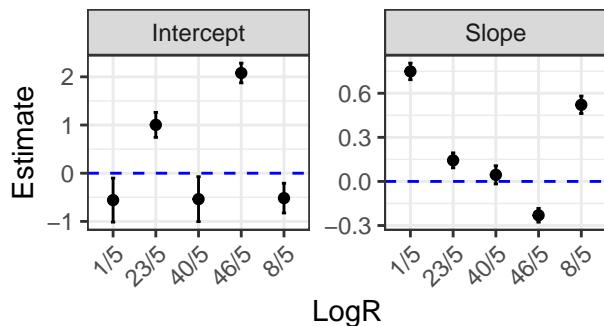
| | value | L2 | L1 |
|-----------------|----------------------------------|---------|--------------------------|
| ## 1 CNS-Oligo | hessian_positivedefinite_bool | | diagRE_M |
| ## 2 CNS-Oligo | hessian_positivedefinite_bool | | fullRE_M |
| ## 3 CNS-Oligo | hessian_positivedefinite_bool | | diagRE_DMDL |
| ## 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

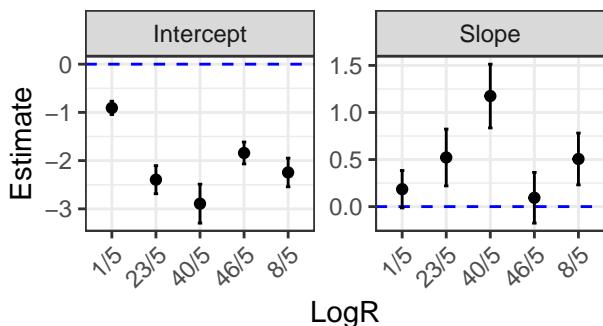
CNS-Oligo
diagRE_M



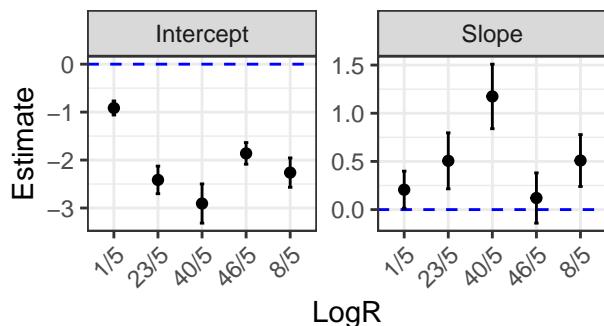
CNS-Oligo
fullRE_M



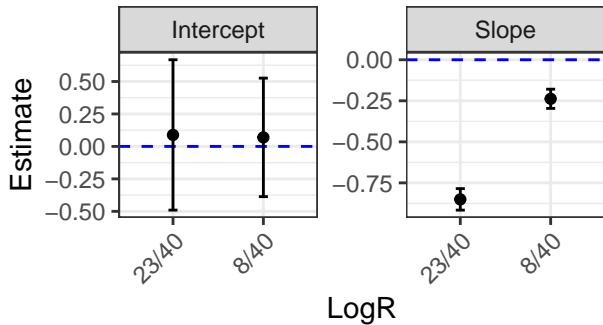
CNS-Oligo
diagRE_DMSL



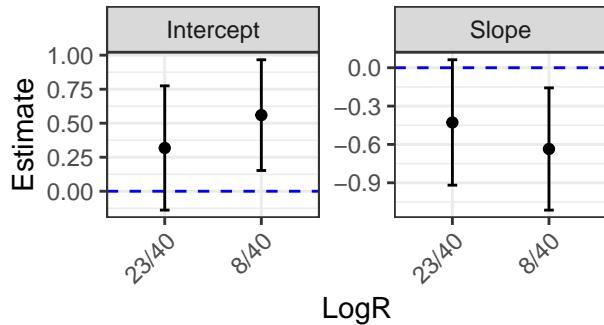
CNS-Oligo
fullRE_DMSL



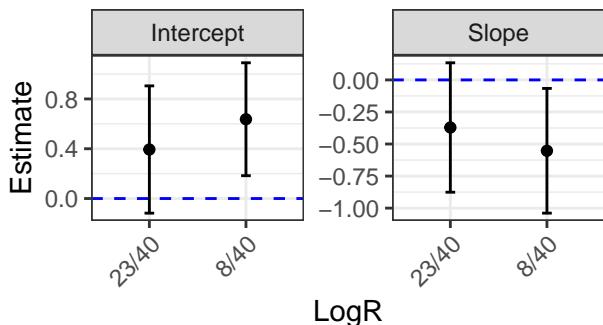
CNS-Oligo
fullRE_M_nonexo



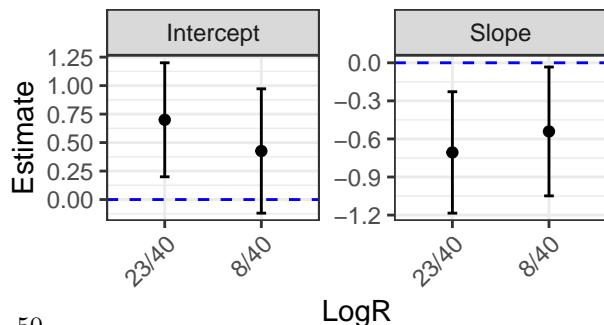
CNS-Oligo
diagRE_DMSL_nonexo



CNS-Oligo
fullRE_DMSL_nonexo



CNS-Oligo
fullRE_DMDL_nonexo



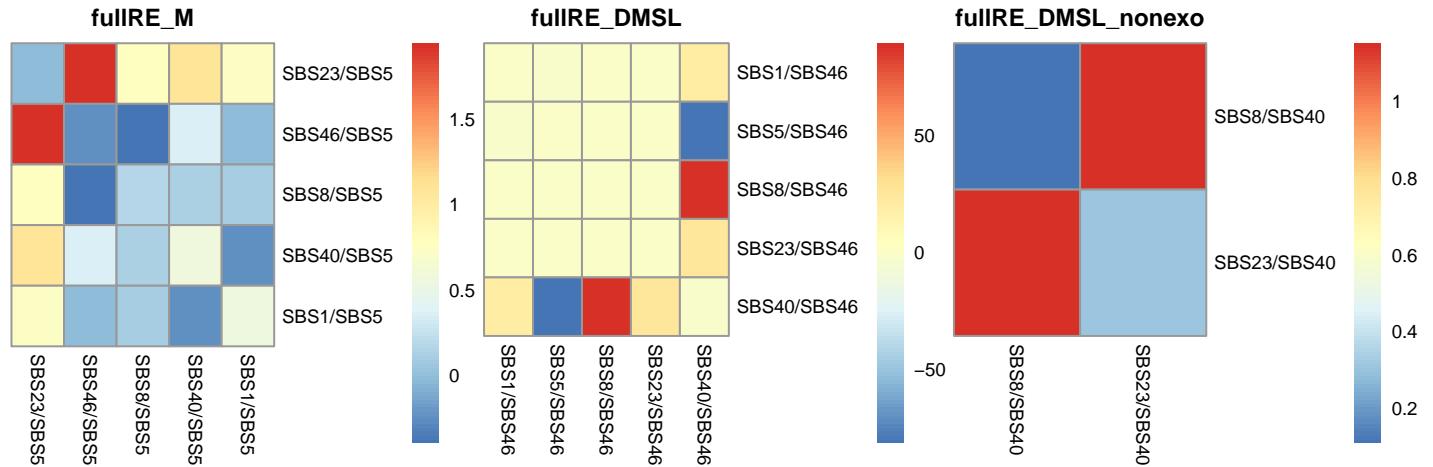
We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 0.5220955.

Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

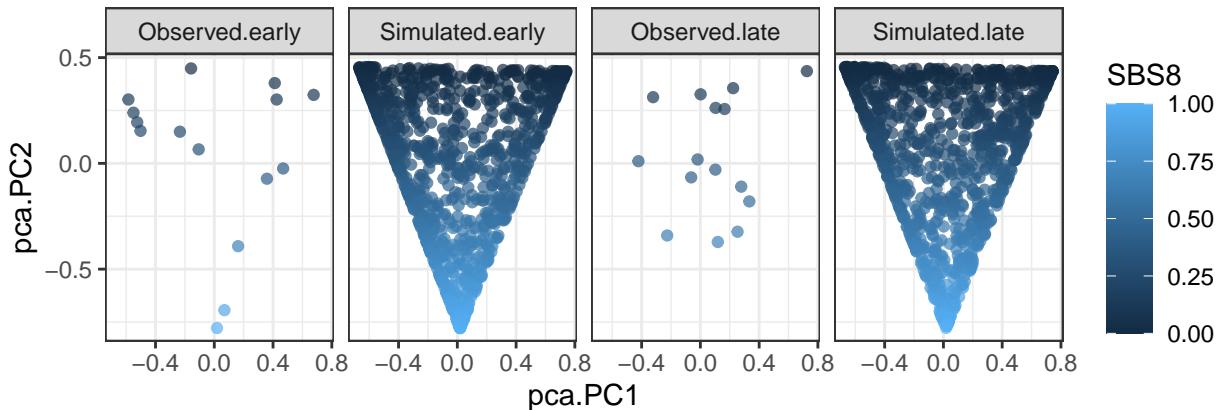


Simulation under inferred data

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
```

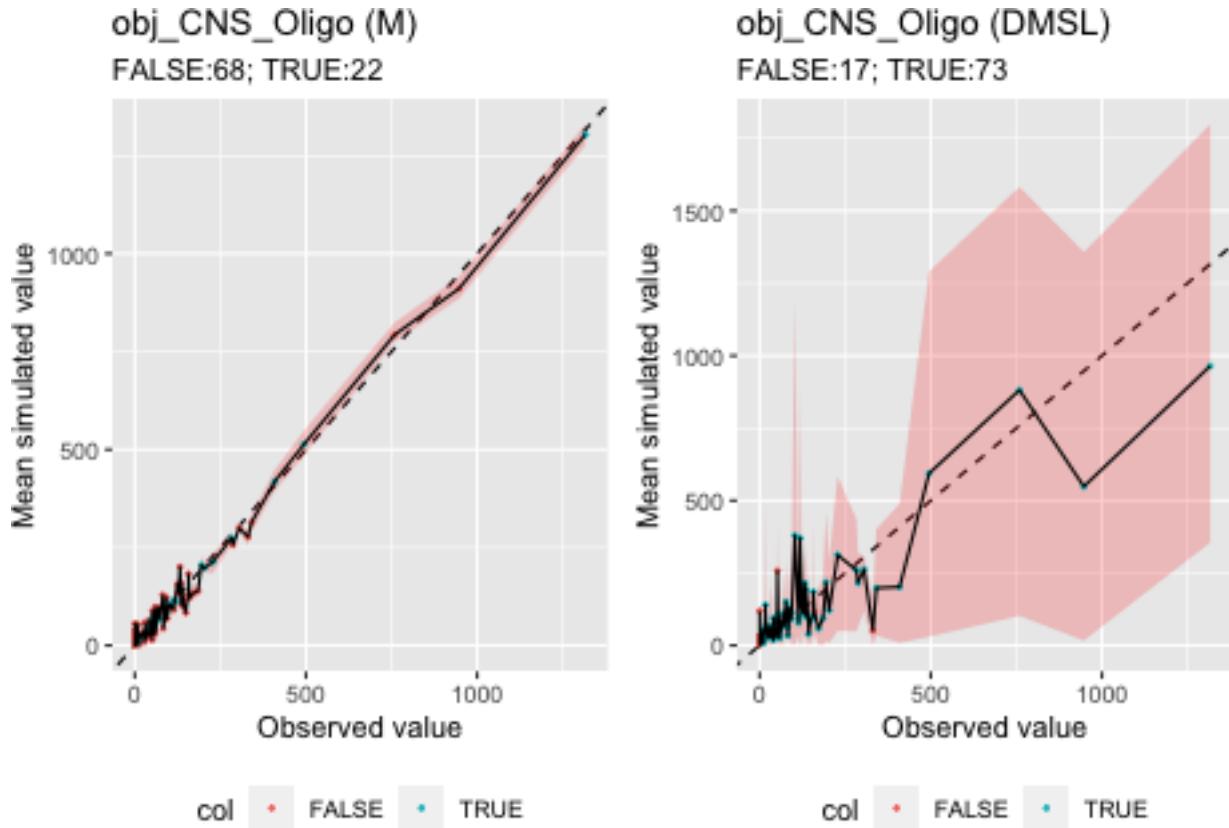
```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

Simulation of CNS-Oligo samples



Ranked plot for coverage

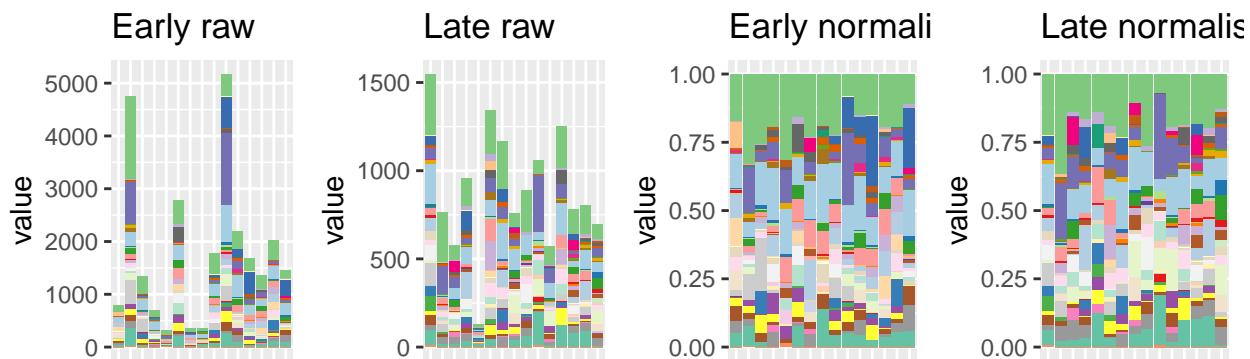
The values for DMSL nonexo look considerably better than for M nonexo.



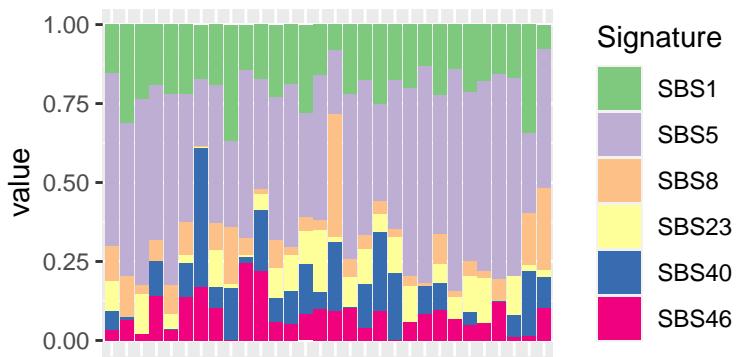
Signatures from mutSigExtractor

These are the signatures from mutSigExtractor:

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



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

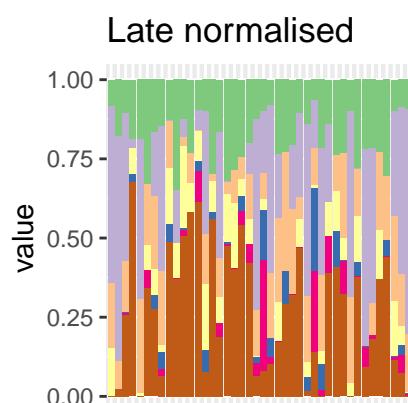
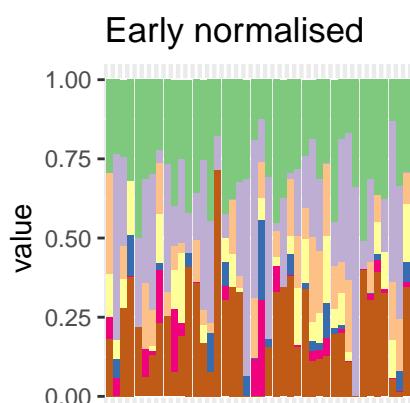
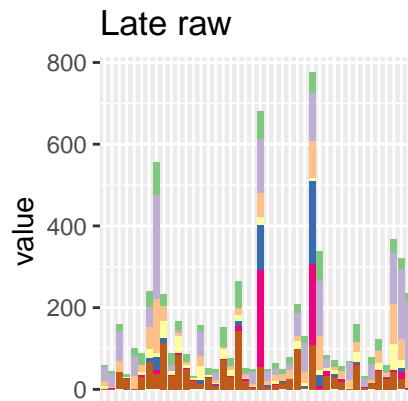
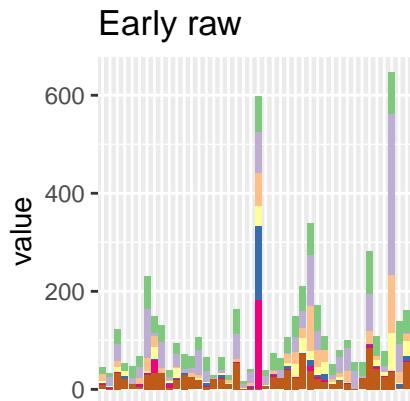


CNS-PiloAstro

CNS-PiloAstro

Barplot and general statistics

```
## [1] 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)
```

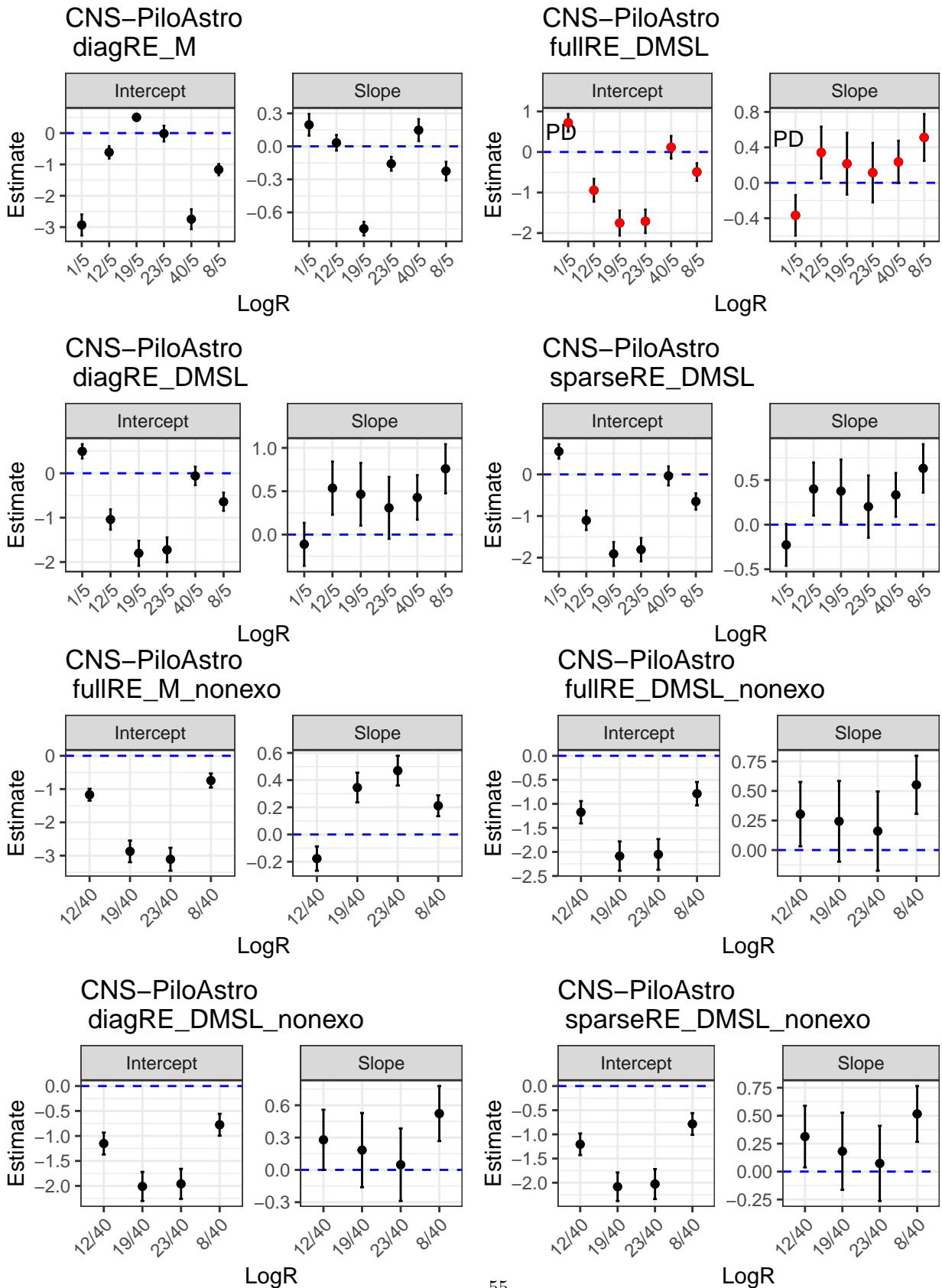
```
##      SBS1      SBS5      SBS8      SBS12      SBS19      SBS23      SBS40
## 0.0000000 0.2261905 0.2023810 0.2857143 0.5119048 0.5000000 0.1190476
```

```
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.

Betas



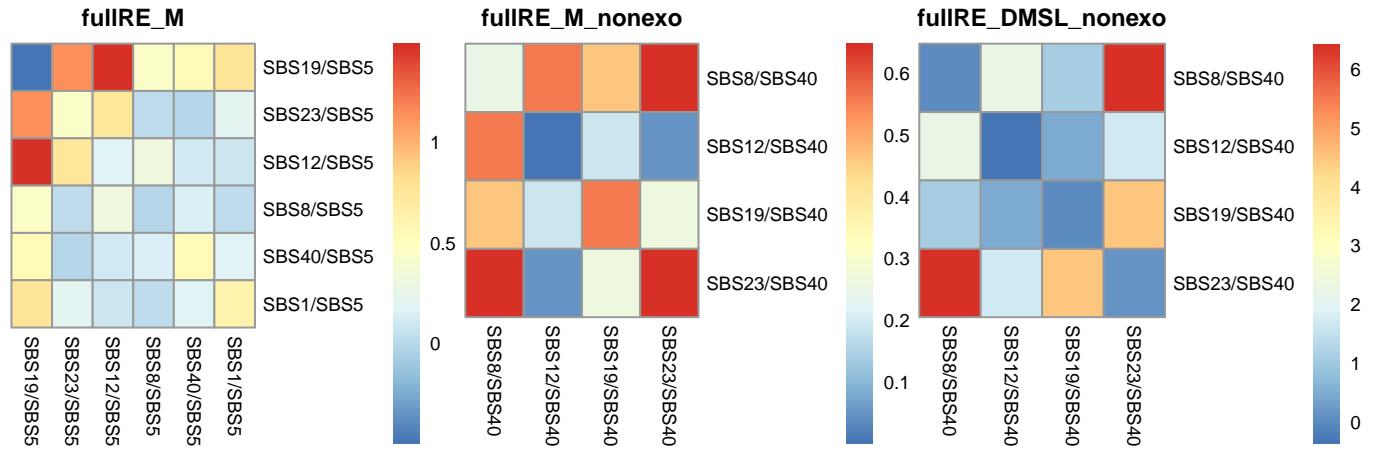
We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 0.2632004.

Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```



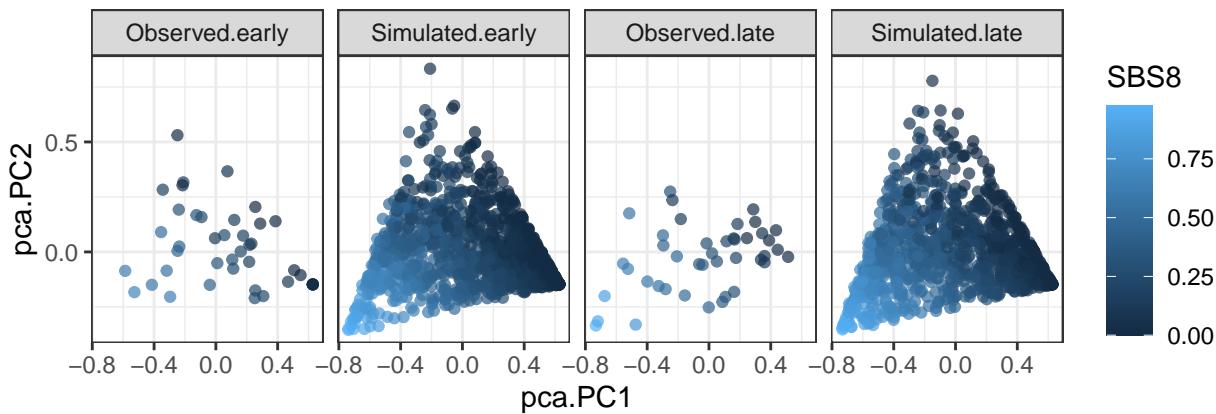
Simulation under inferred data

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

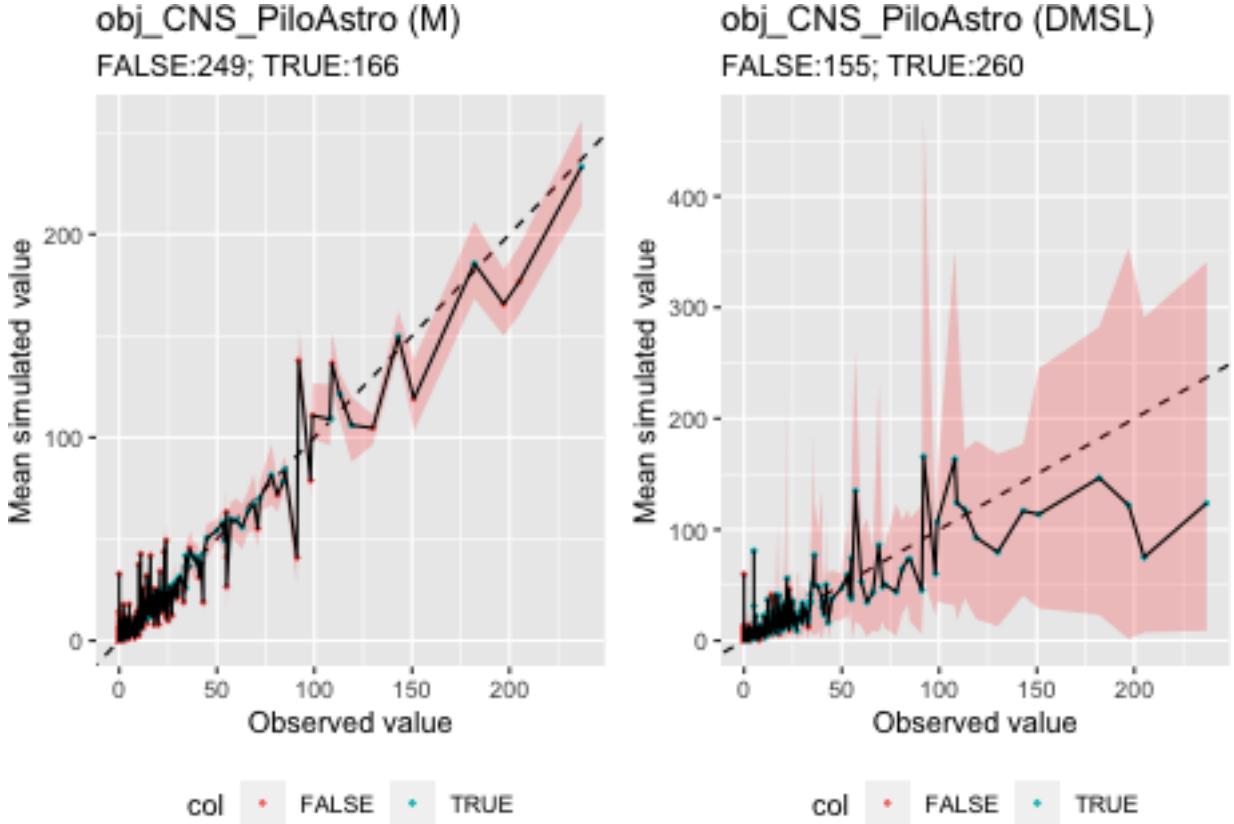
```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```

Simulation of CNS–PiloAstro samples



Ranked plot for coverage

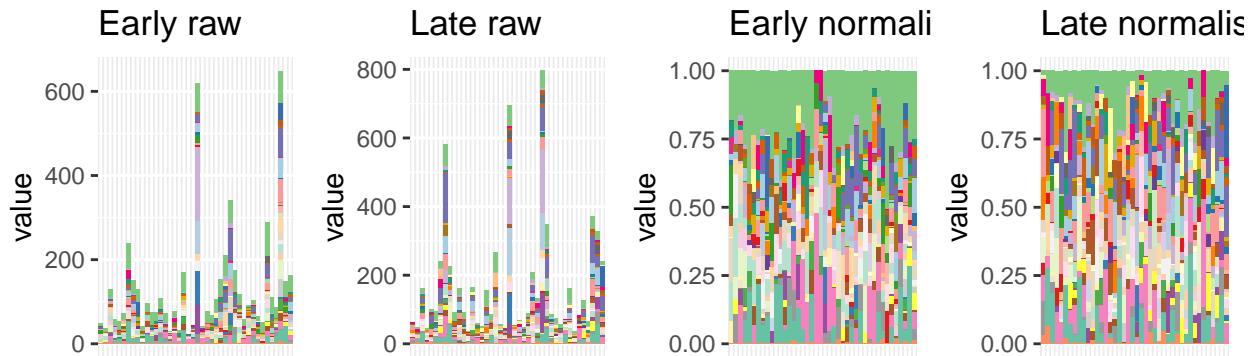
The strange pattern in DMSL is worth pointing out. The beta coefficients are too very different between M and DMSL for nonexo.



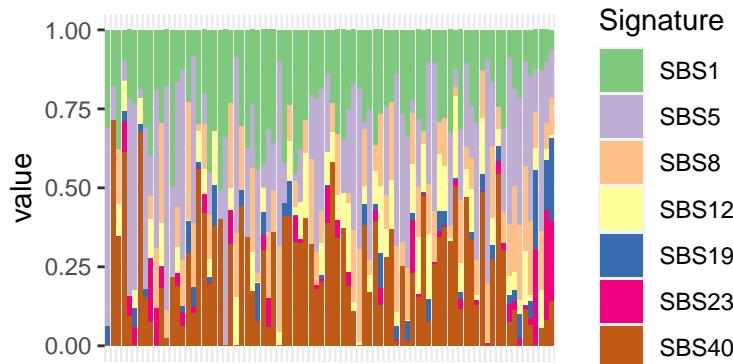
Signatures from mutSigExtractor

The signatures from mutSigExtractor are a bit more chaotic:

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



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.

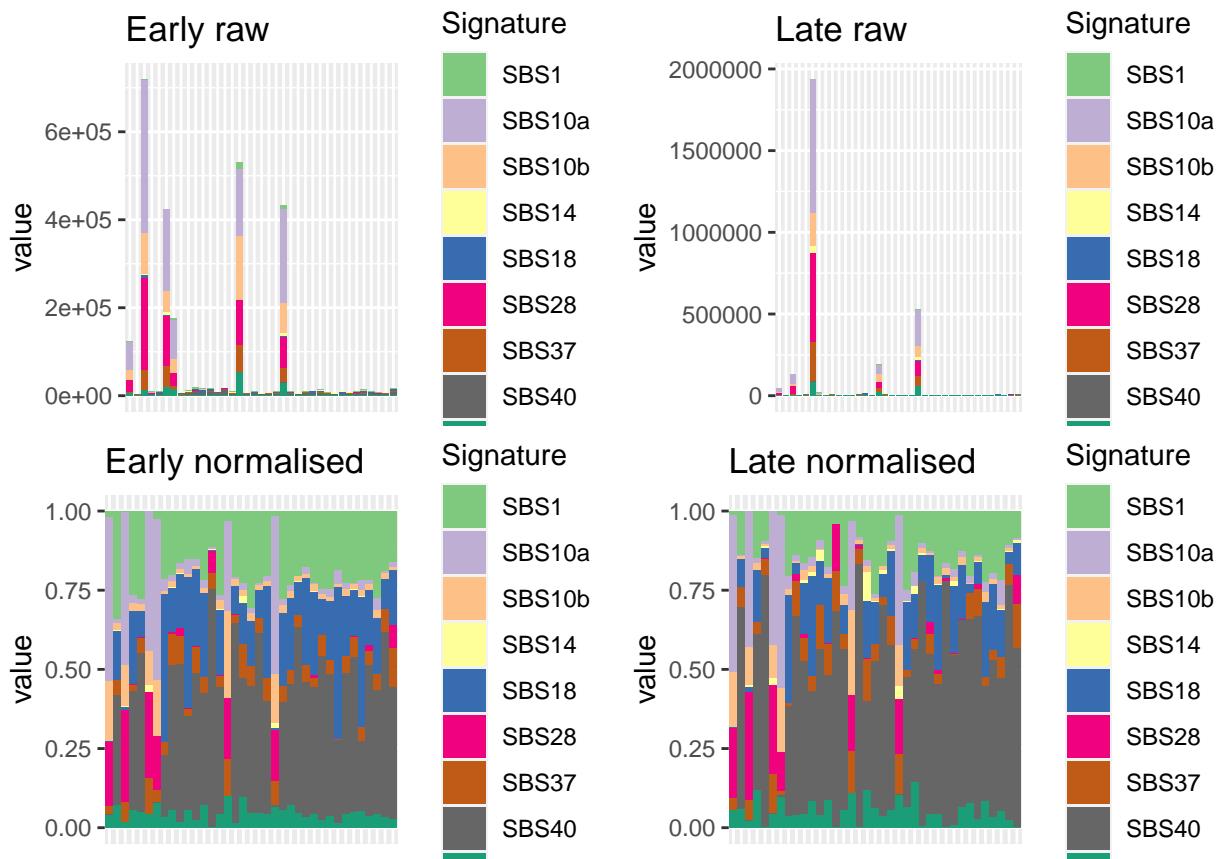


ColoRect-AdenoCA

ColoRect-AdenoCA

Barplot and general statistics

```
## [1] 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.

| | 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? 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

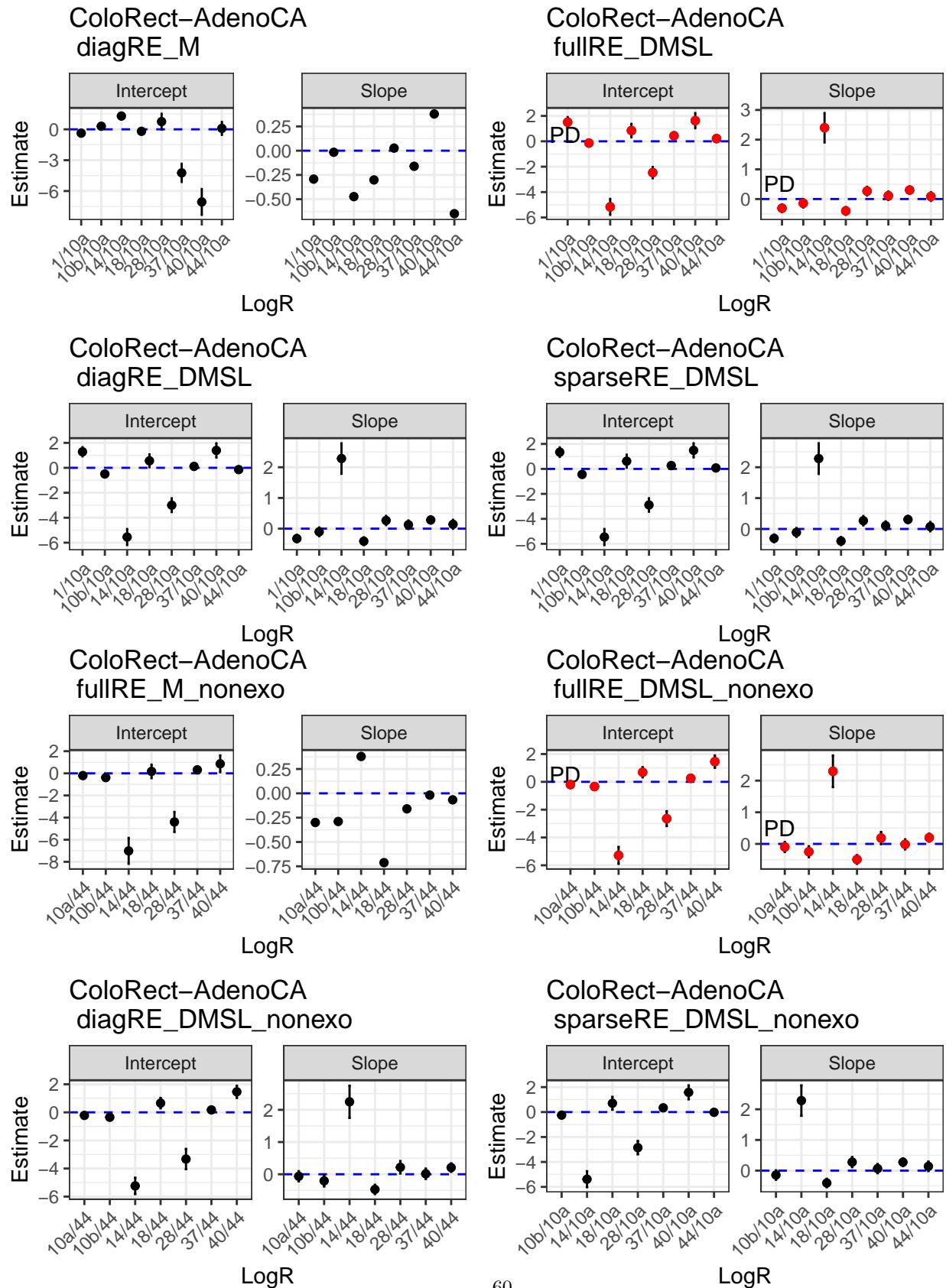
```
colSums(obj_ColoRect_AdenoCA$Y == 0) / nrow(obj_ColoRect_AdenoCA$Y)

##      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



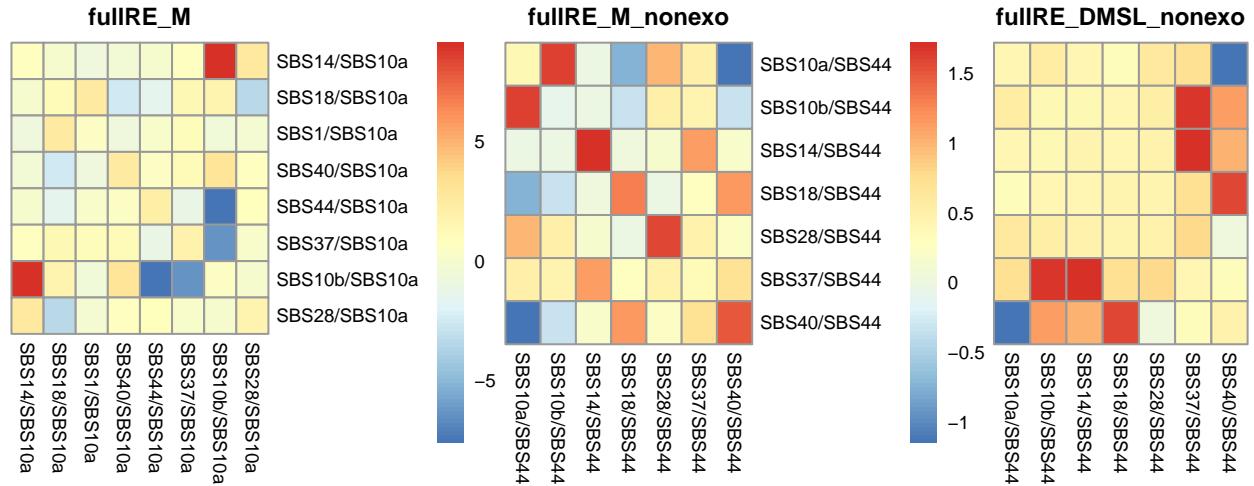
We use the results from the diagonal RE single lambda DM nonexo to test for differential abundance, giving a p-value of $8.8714208 \times 10^{-16}$.

Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```



Simulation under inferred data

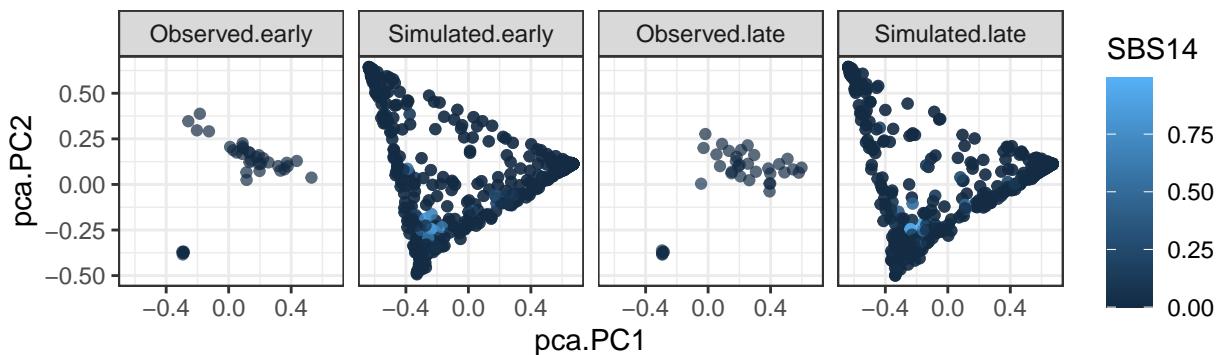
I am simulating using the full effects multinomial, because the function needs to be adapted to diagDMSL.

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
```

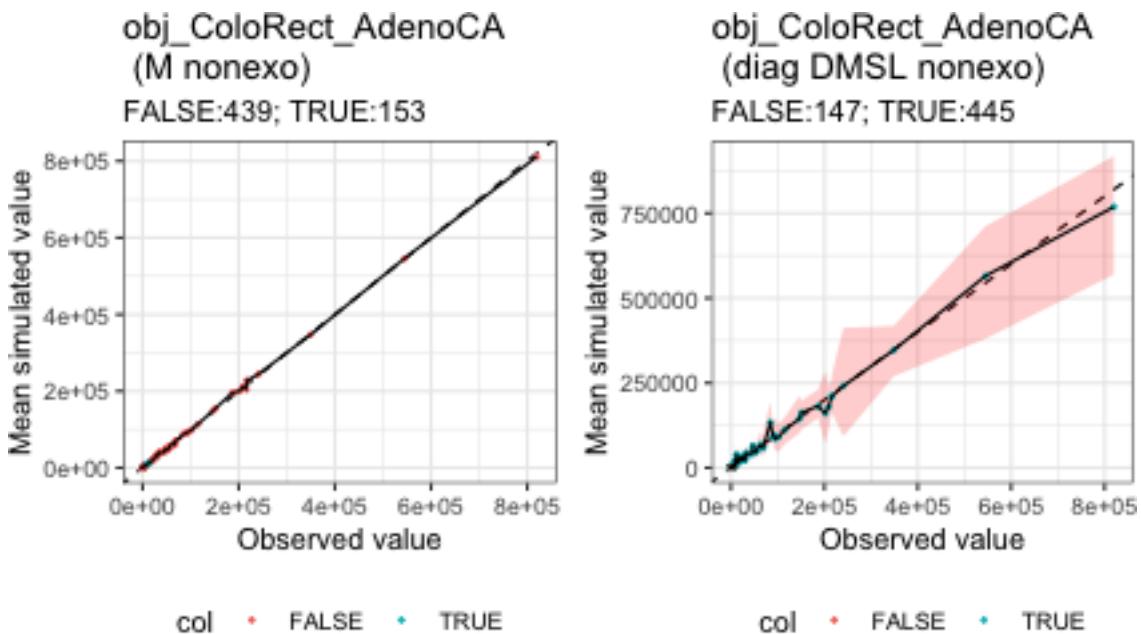
```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

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

Simulation of ColoRect–AdenoCA samples

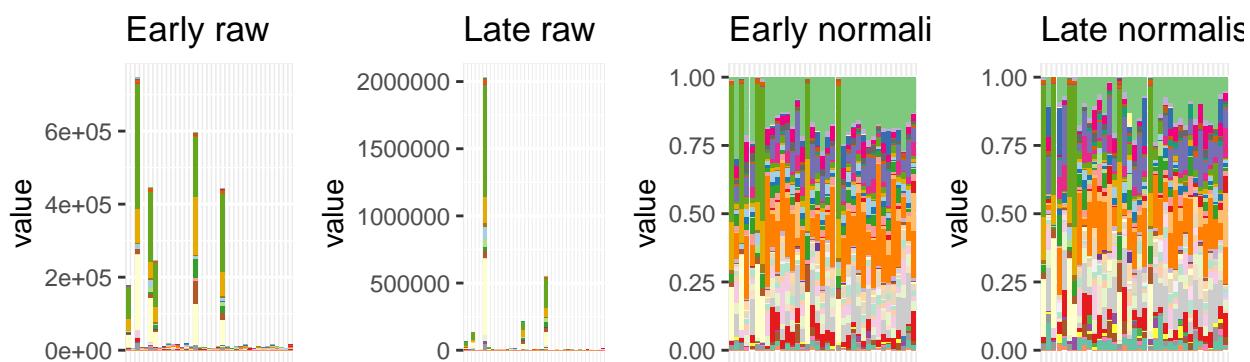


Ranked plot for coverage



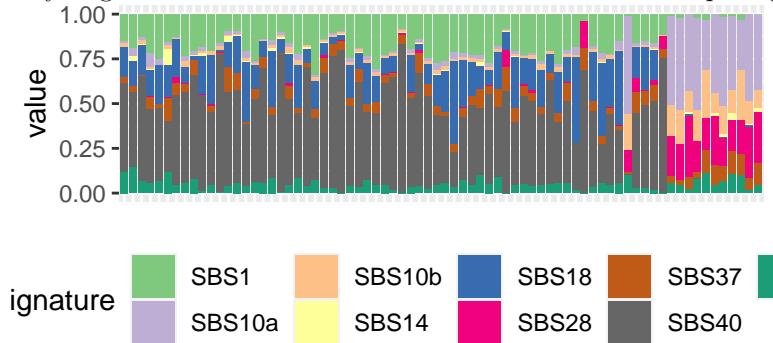
Signatures from mutSigExtractor

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



Exposures sorted by increasing number of mutations: very clearly there are a few samples with

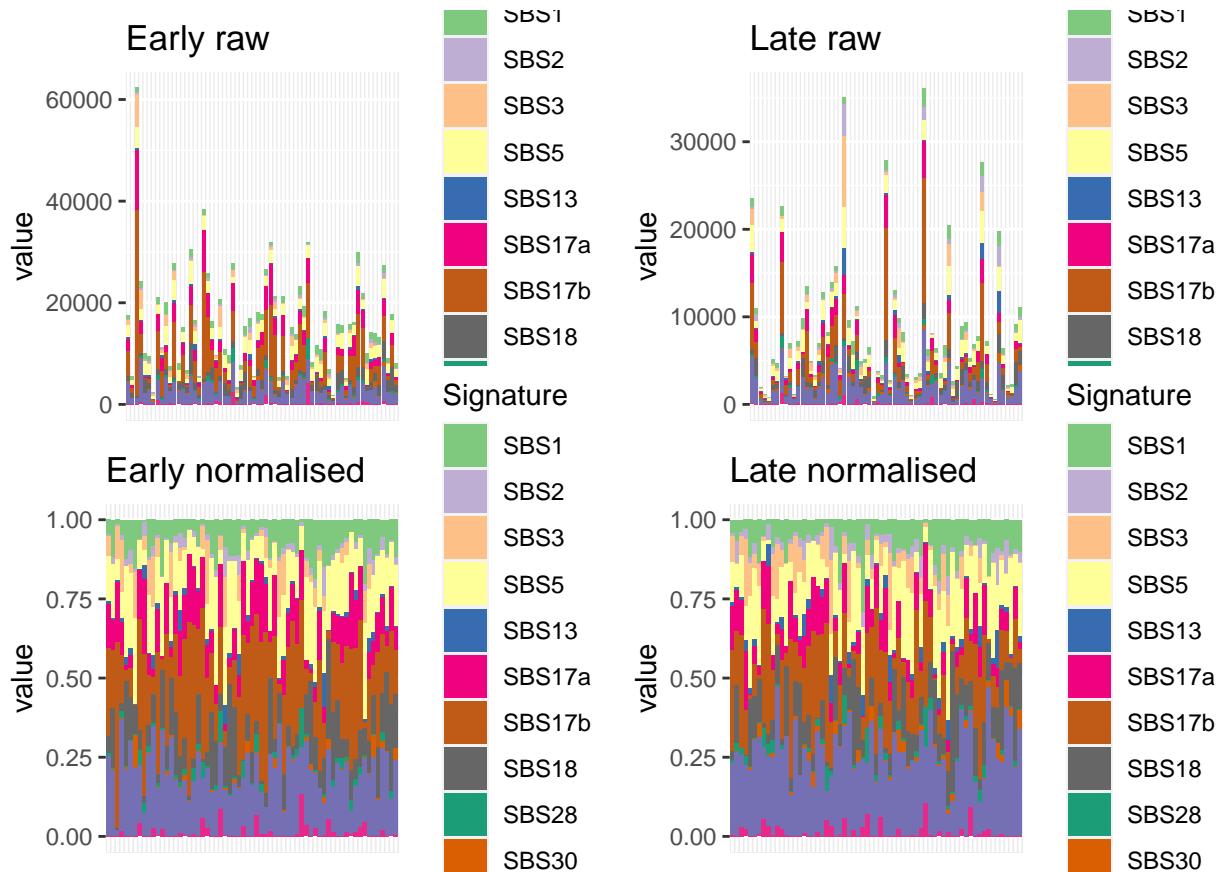
very high number of mutations that also have a completely different mutational signature exposure.



Eso-AdenoCA

Barplot and general statistics

```
## [1] 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
```

Running fullRE DMSL, this time without sorting, doesn't converge either:

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

Bafflingly, using two lambdas does:

Potentially problematic signatures

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

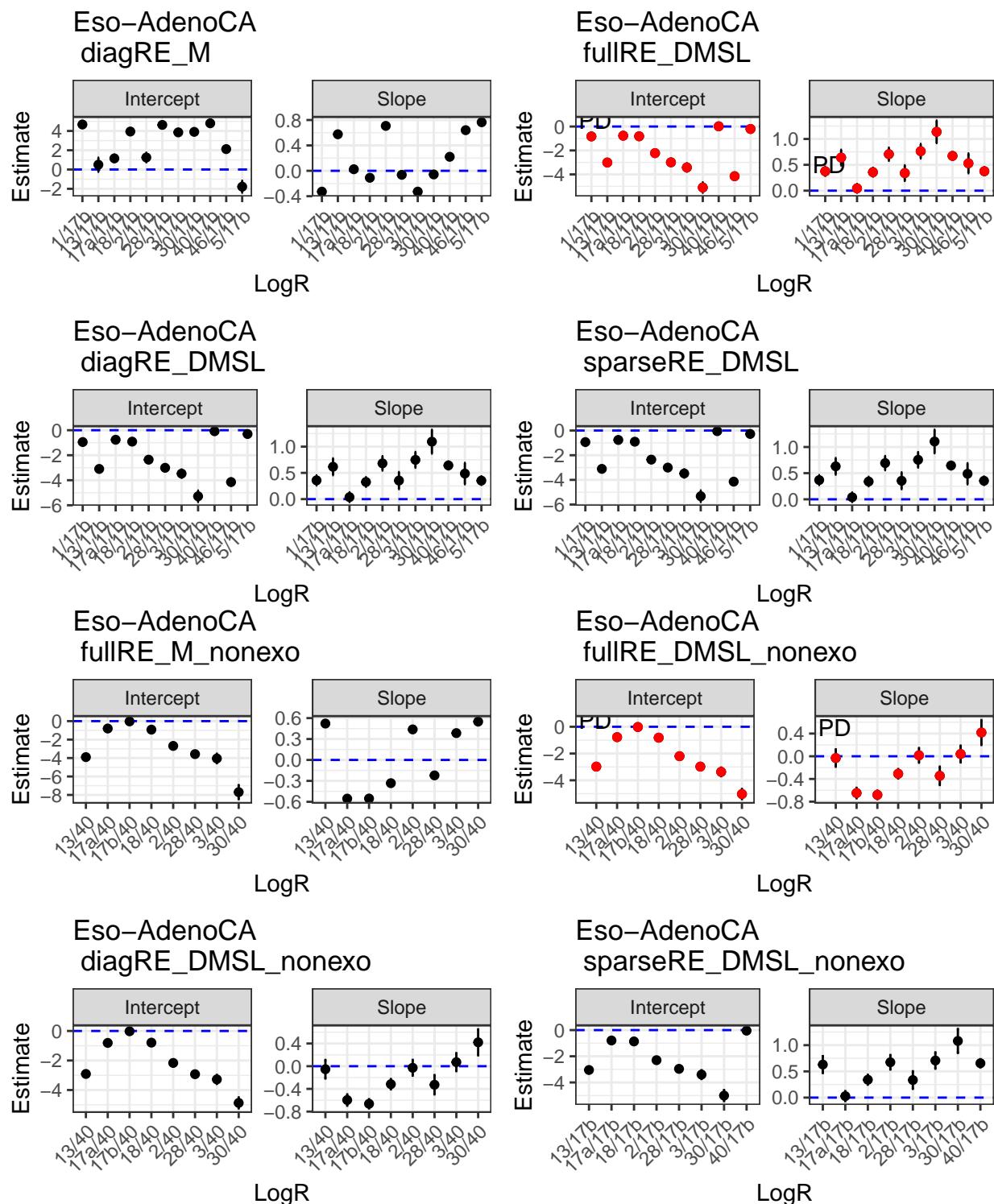
```
colSums(obj_Eso_AdenoCA$Y == 0)/nrow(obj_Eso_AdenoCA$Y)
```

```
##      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

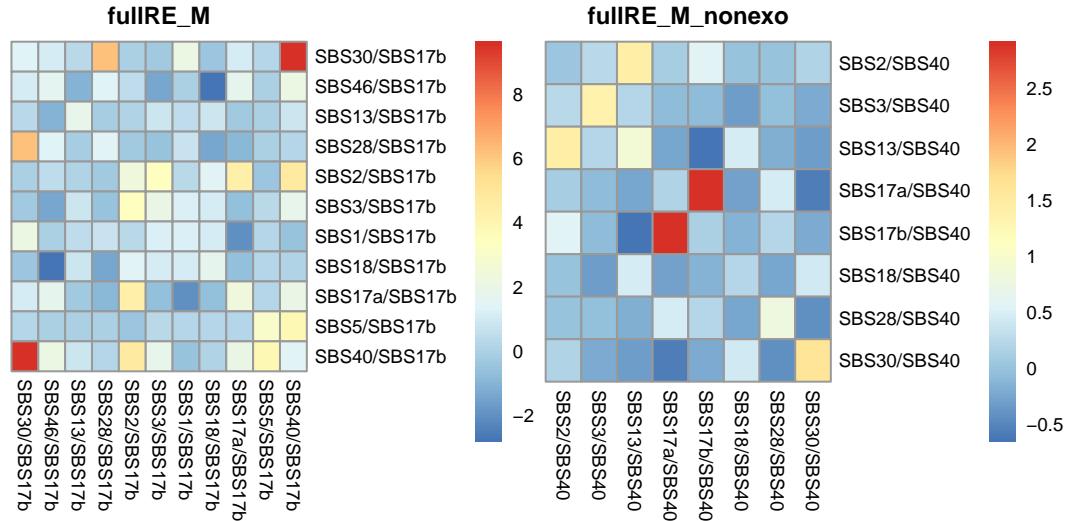


We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of $2.4465743 \times 10^{-18}$.

Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

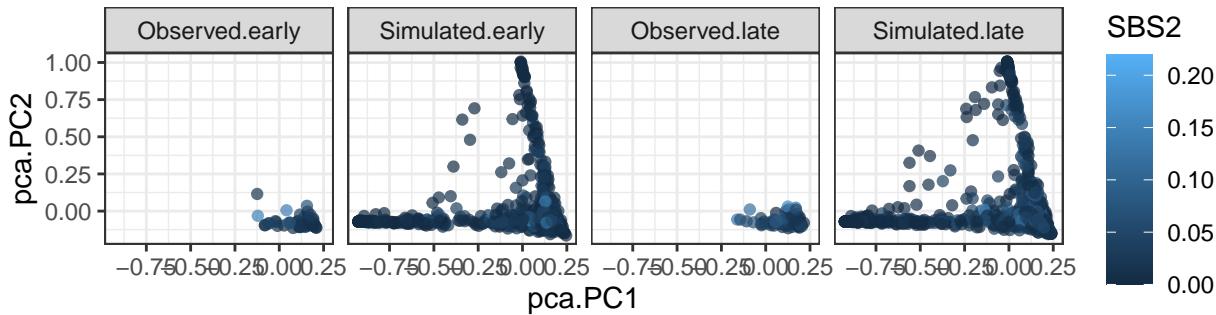


Simulation under inferred data

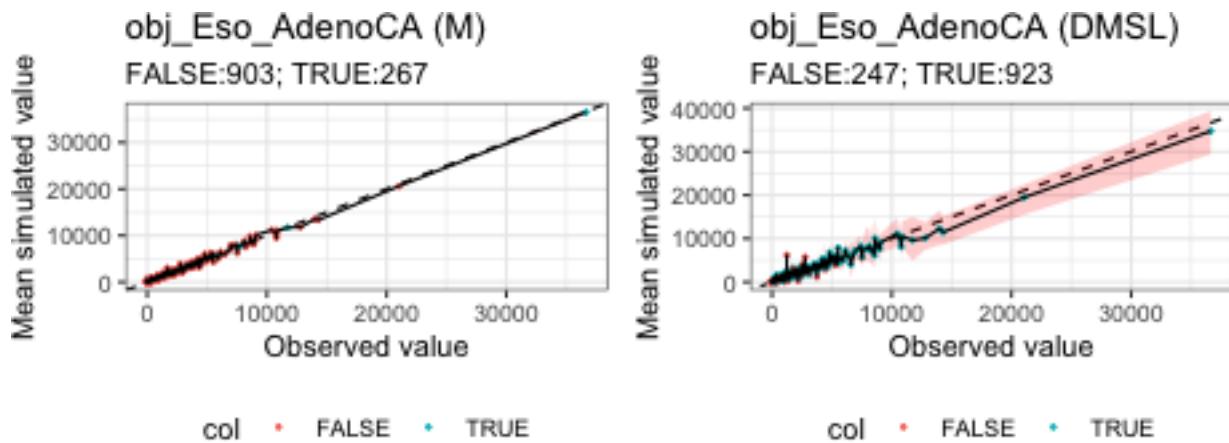
```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

Simulation of Eso-AdenoCA samples



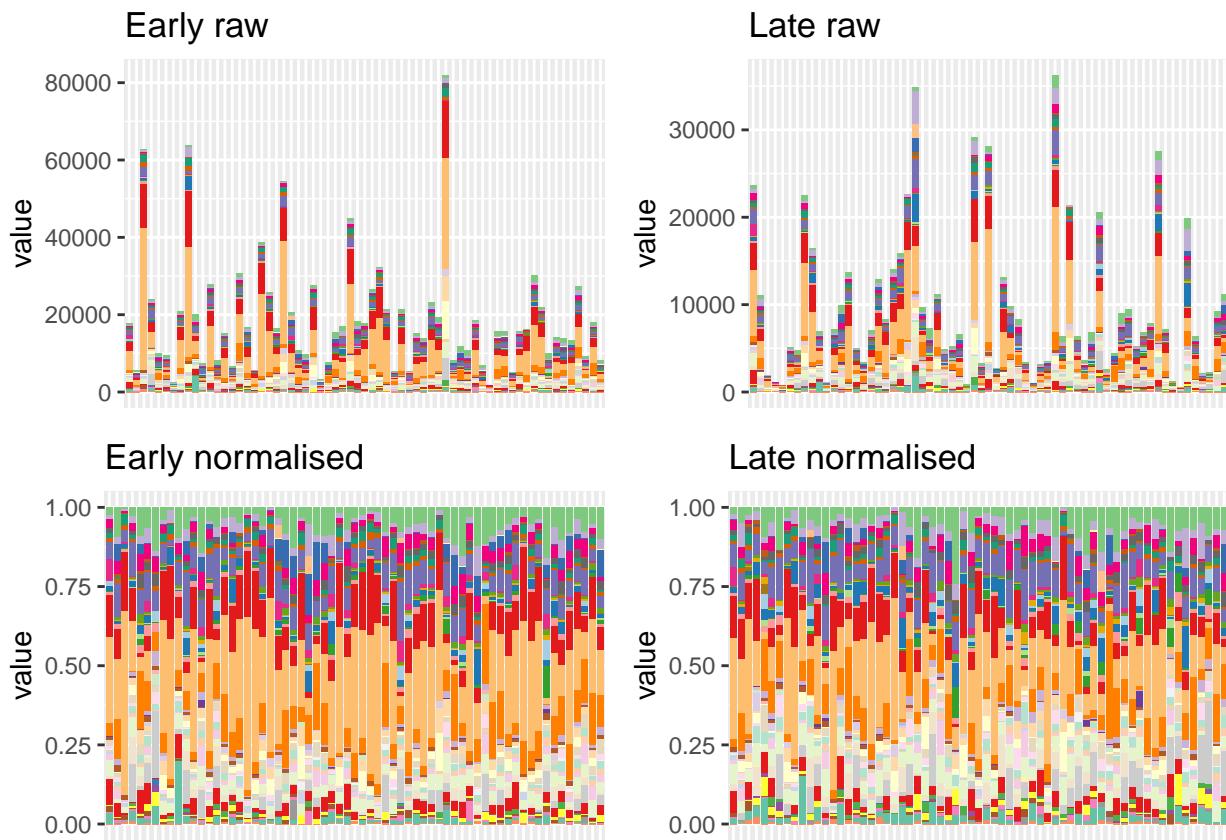
Ranked plot for coverage



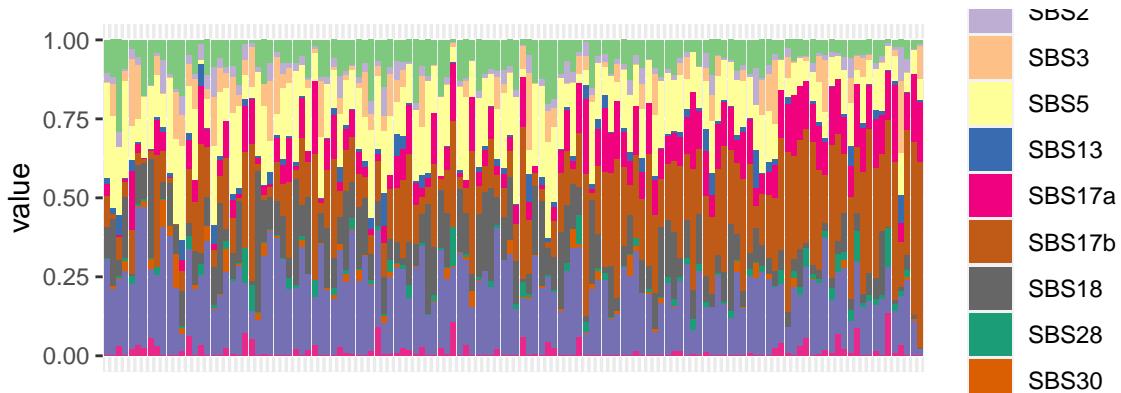
Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

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



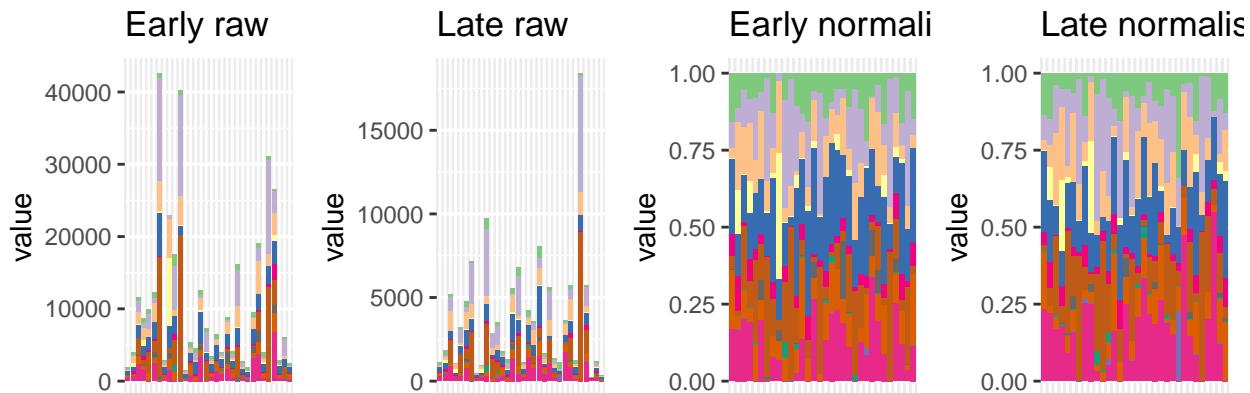
Exposures sorted by increasing number of mutations: there is a trend of samples with more mutations having more SBS17b and less SBS5, relatively.



Head-SCC

Barplot and general statistics

```
## [1] 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.

```

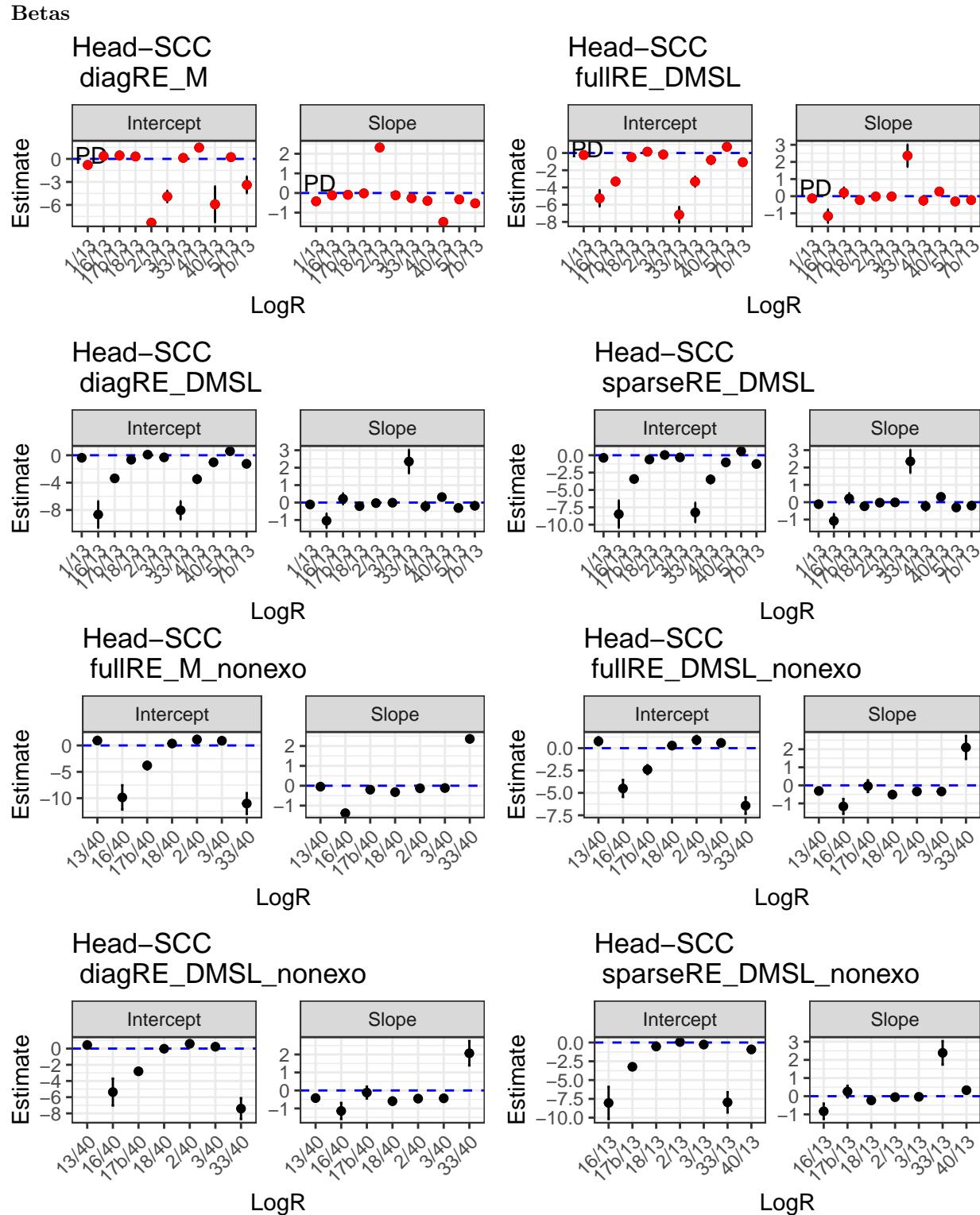
colSums(obj_Head(SCC$Y == 0)/nrow(obj_Head(SCC$Y)

##      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

```



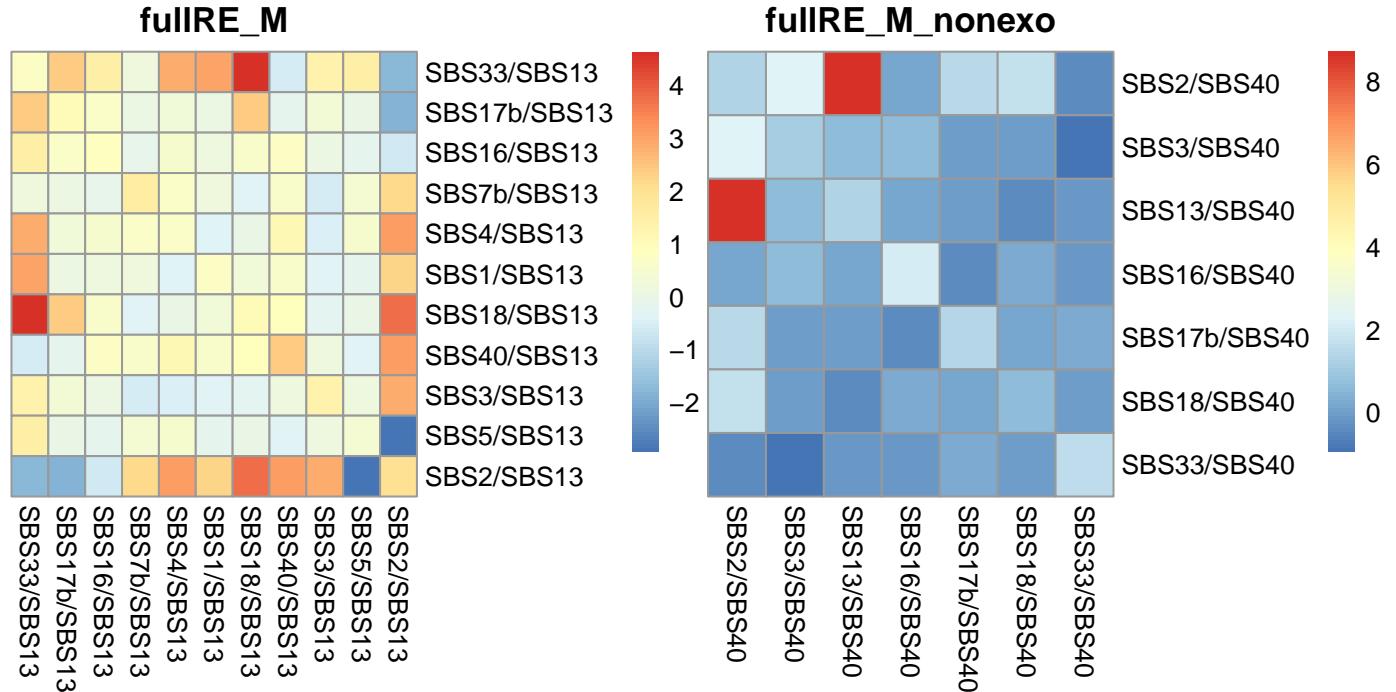
We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 8.4420109×10^{-5} .

Covariance matrices

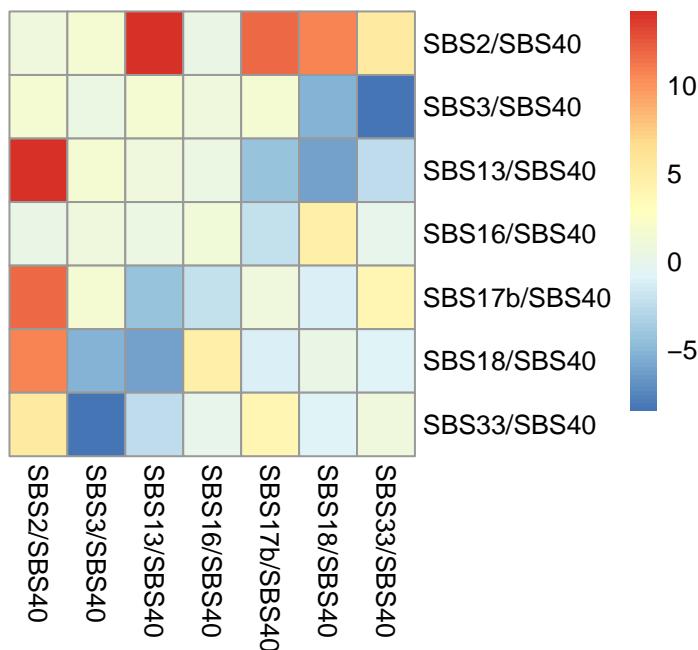
```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```



fullRE_DMSL_nonexo



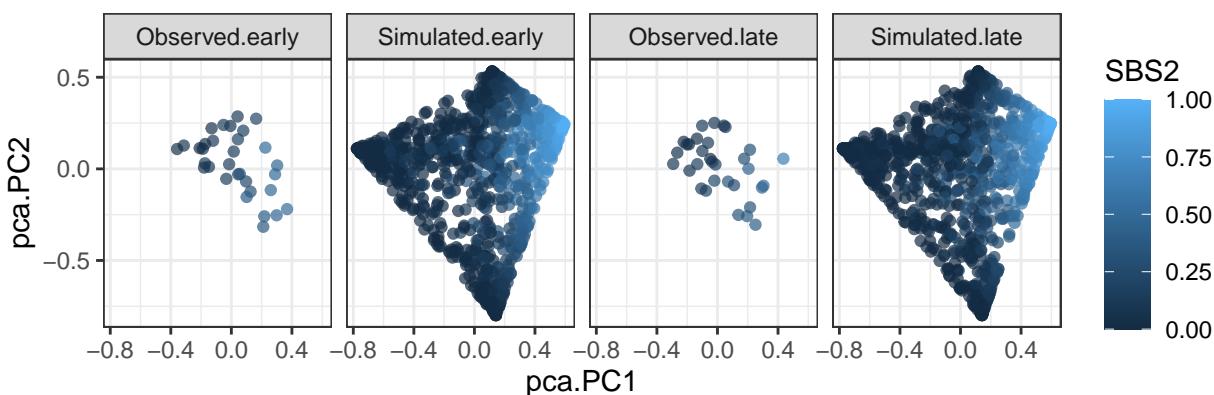
Simulation under inferred data

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)

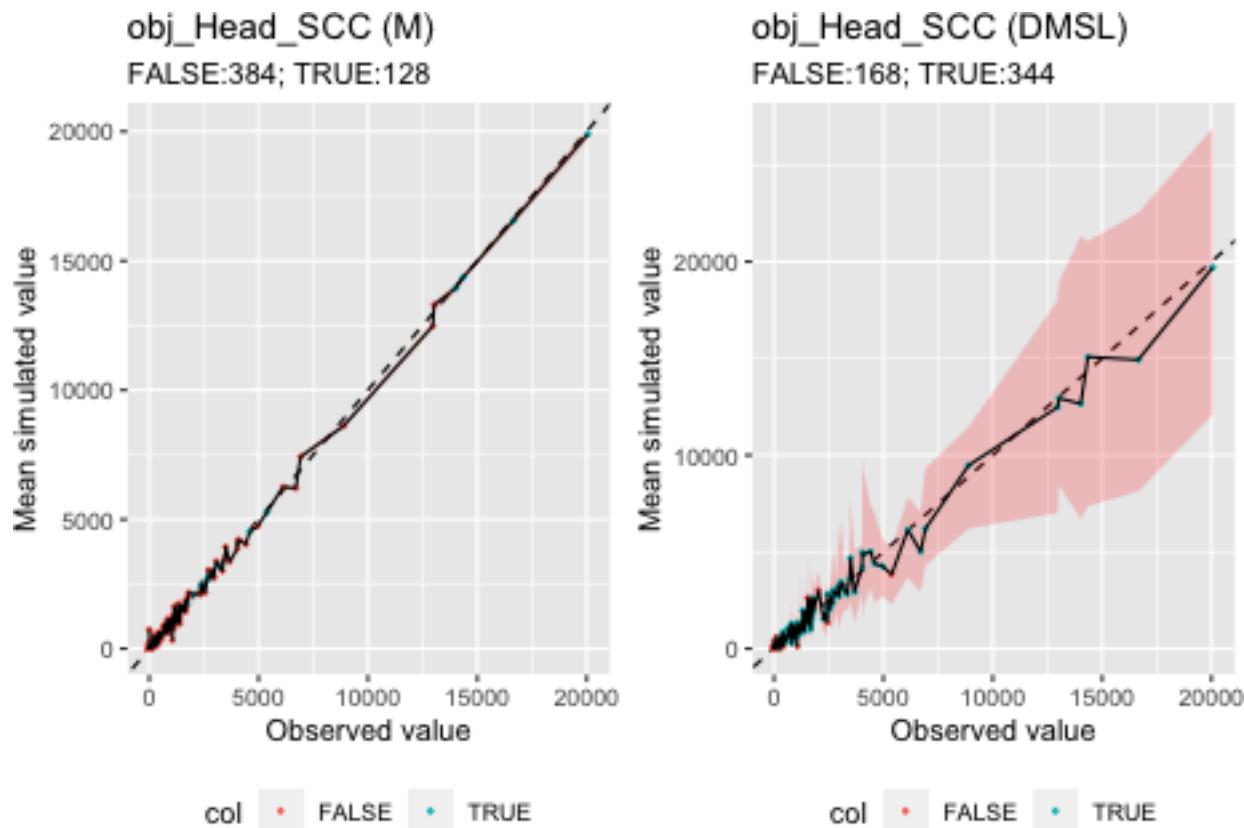
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)

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

Simulation of Head-SCC samples



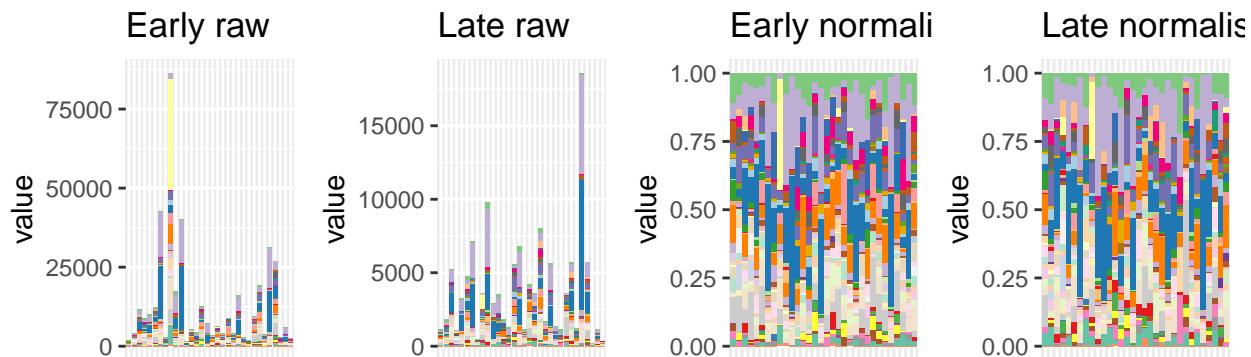
Ranked plot for coverage



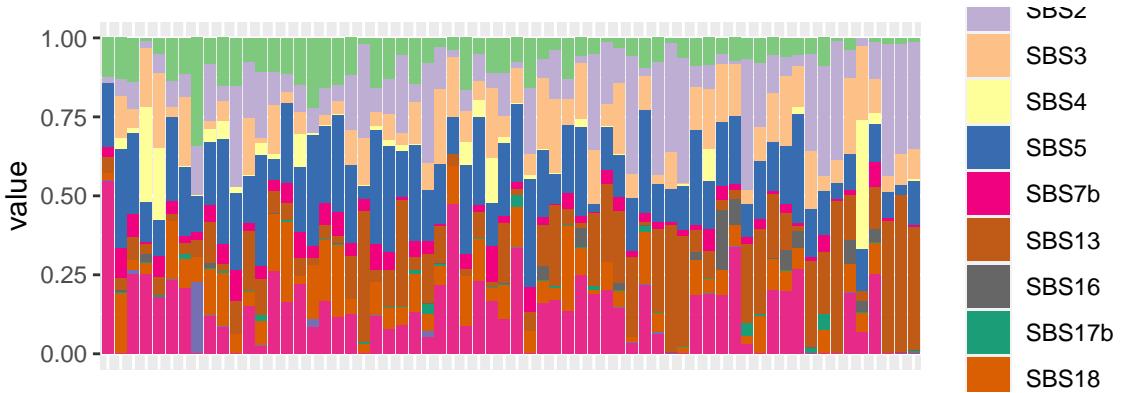
Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

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



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

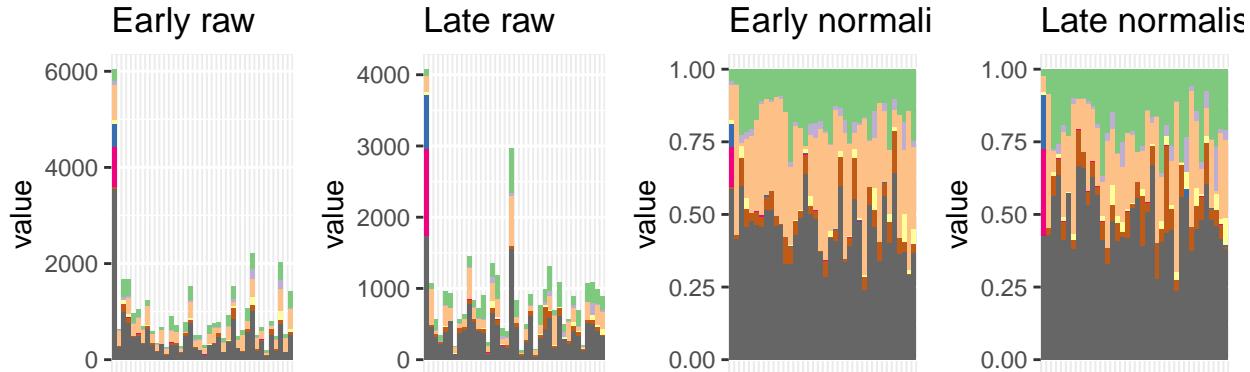


ber of mutations.

Kidney-ChRCC

Barplot and general statistics

```
## [1] 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

```

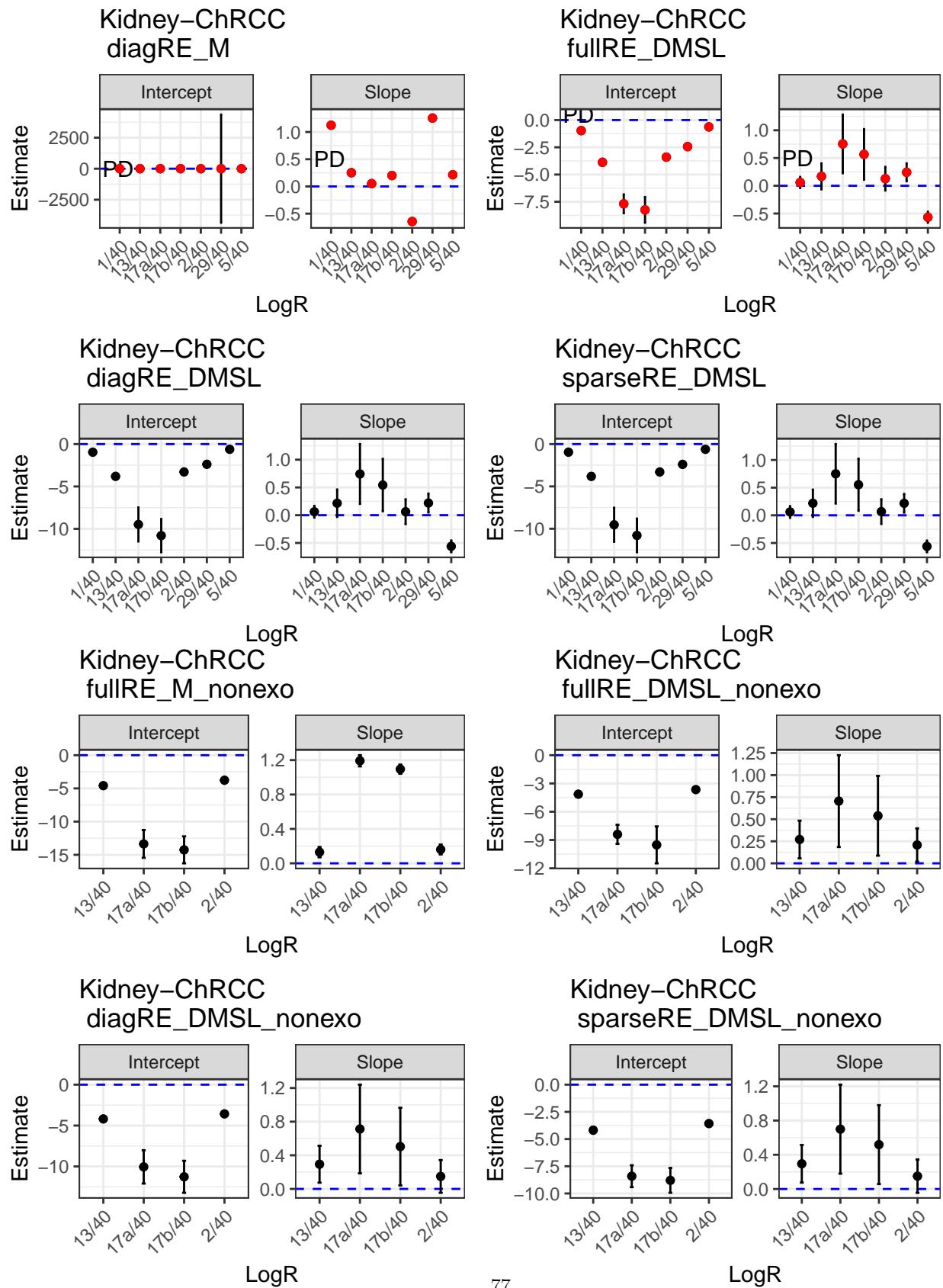
```
colSums(obj_Kidney_ChRCC$Y) / sum(obj_Kidney_ChRCC$Y)
```

```

##      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



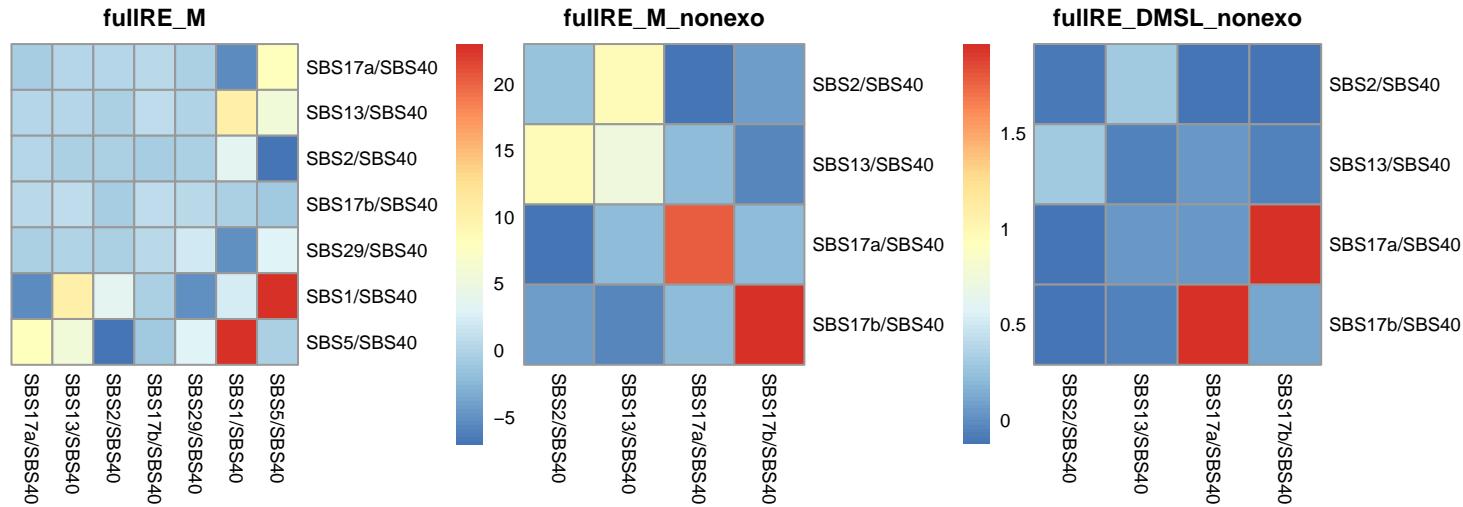
We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 0.2664763.

Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```



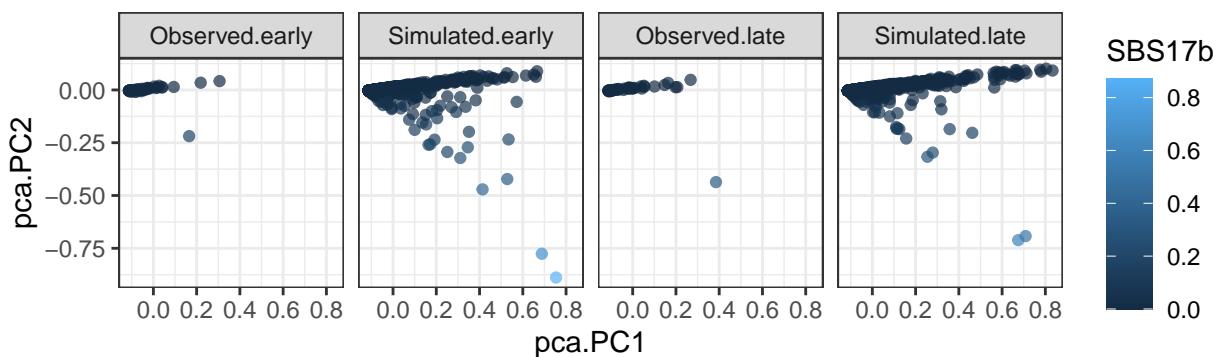
Simulation under inferred data

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
```

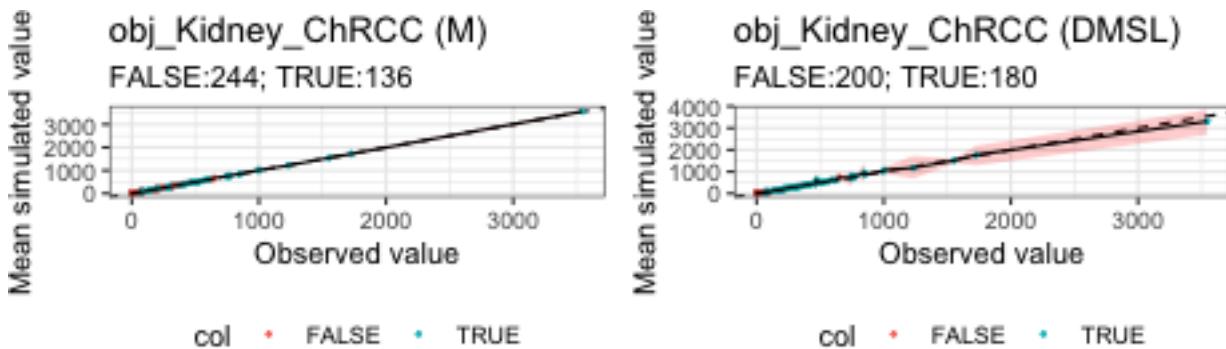
```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

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

Simulation of Kidney–ChRCC samples



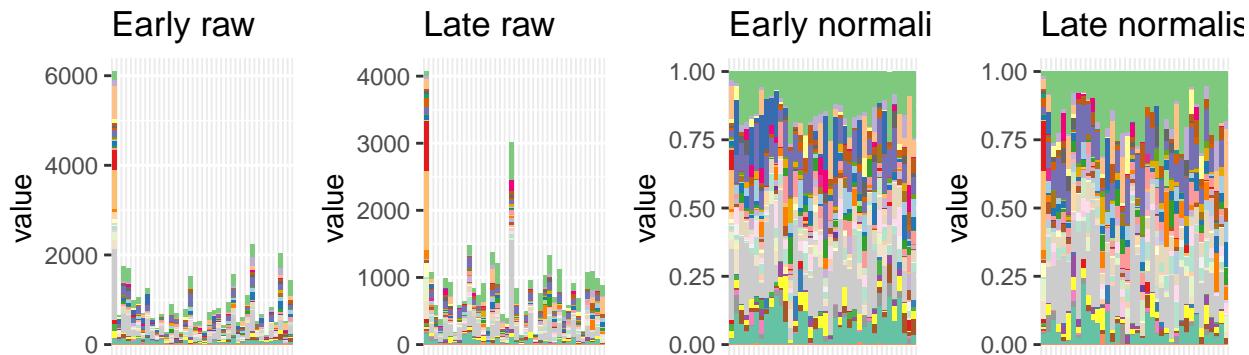
Ranked plot for coverage



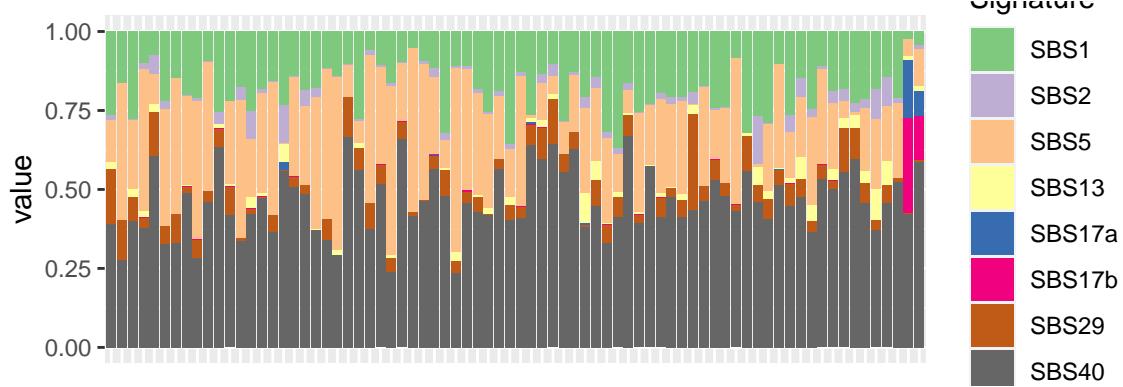
Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

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



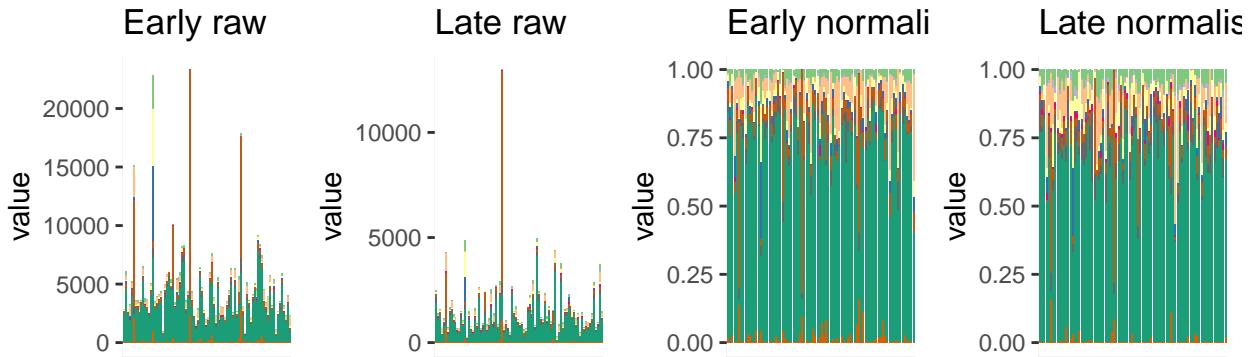
Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.



Kidney-RCC.clearcell

Barplot and general statistics

```
## [1] 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
##
##               value          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)

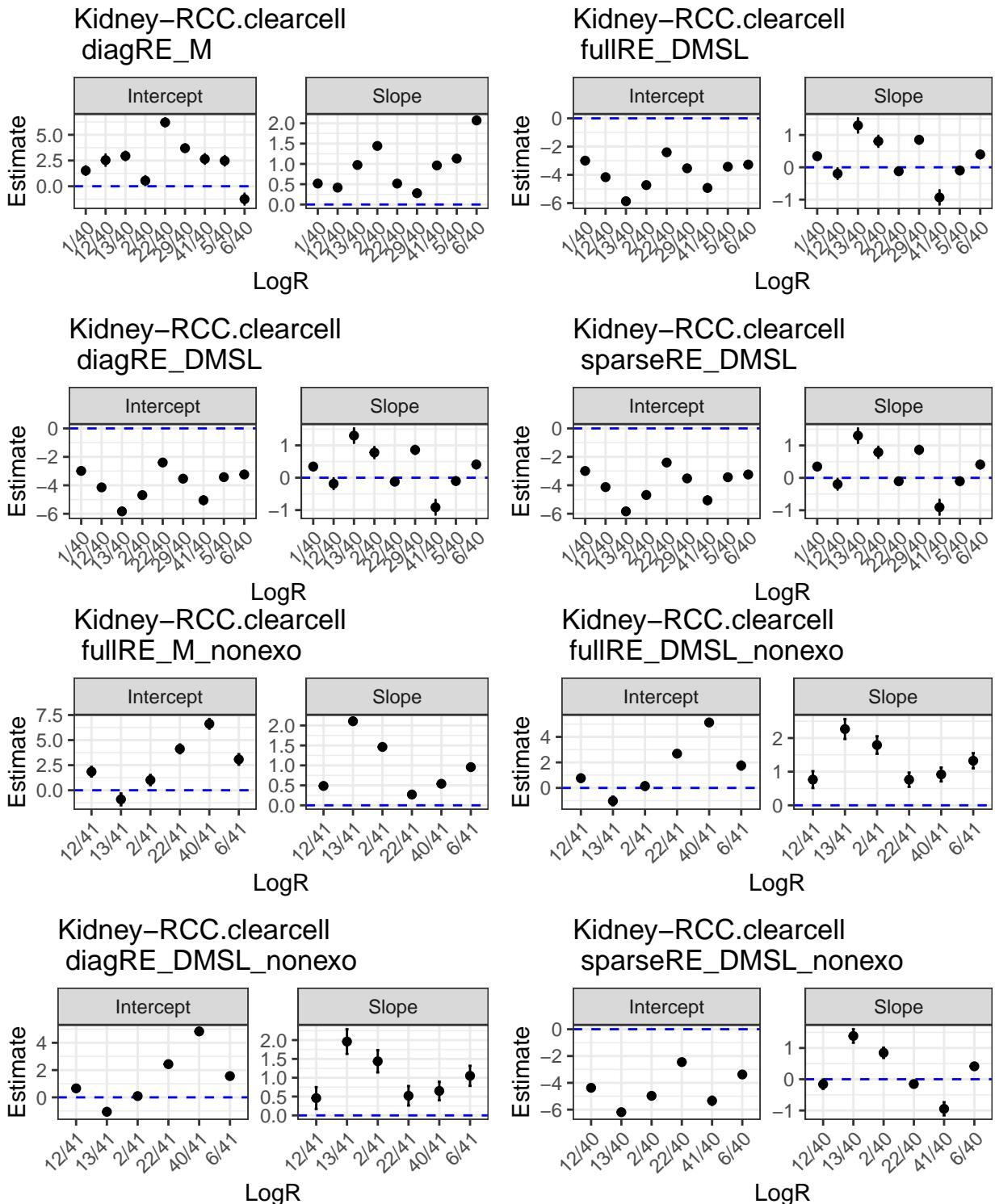
##      SBS1      SBS2      SBS5      SBS6      SBS12      SBS13      SBS22
## 0.02906977 0.26744186 0.33139535 0.11627907 0.35465116 0.52325581 0.00000000
##      SBS29      SBS40      SBS41
## 0.13372093 0.00000000 0.58720930

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
```

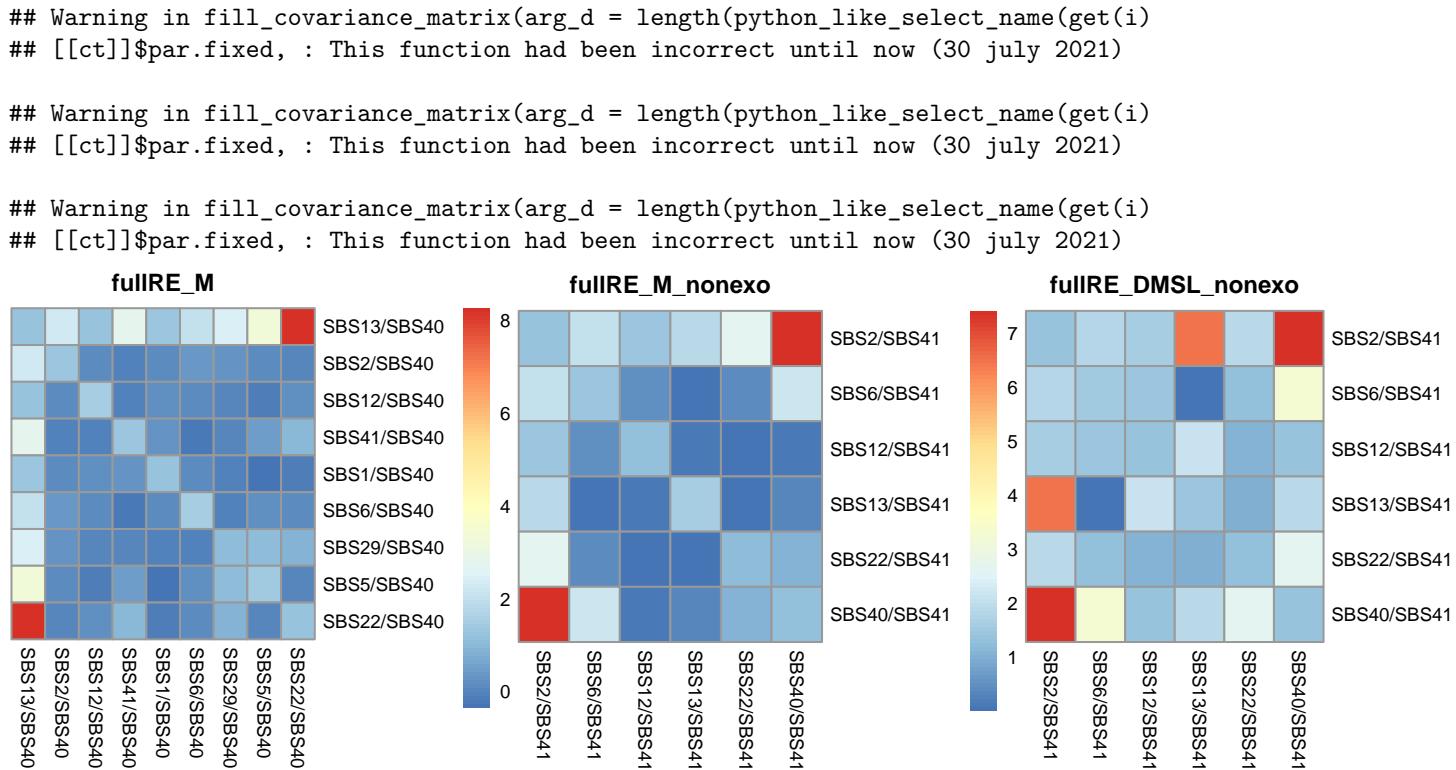
We would need to run `fullRE_DMSL`, because it timed out.

Betas



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



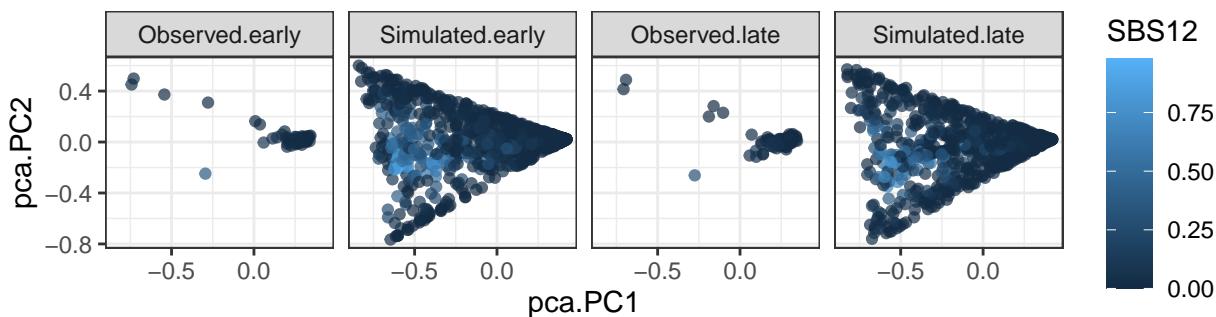
Simulation under inferred data

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)

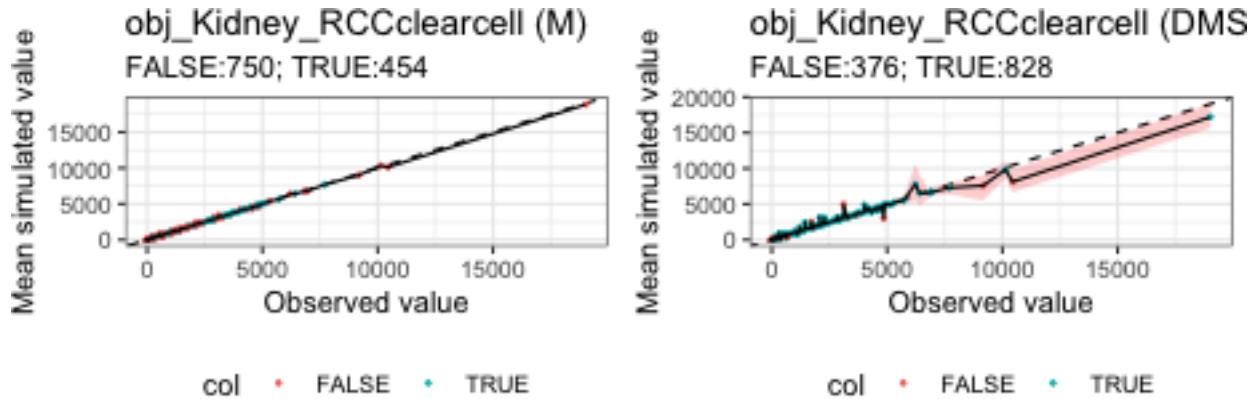
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)

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

Simulation of Kidney–RCC.clearcell samples



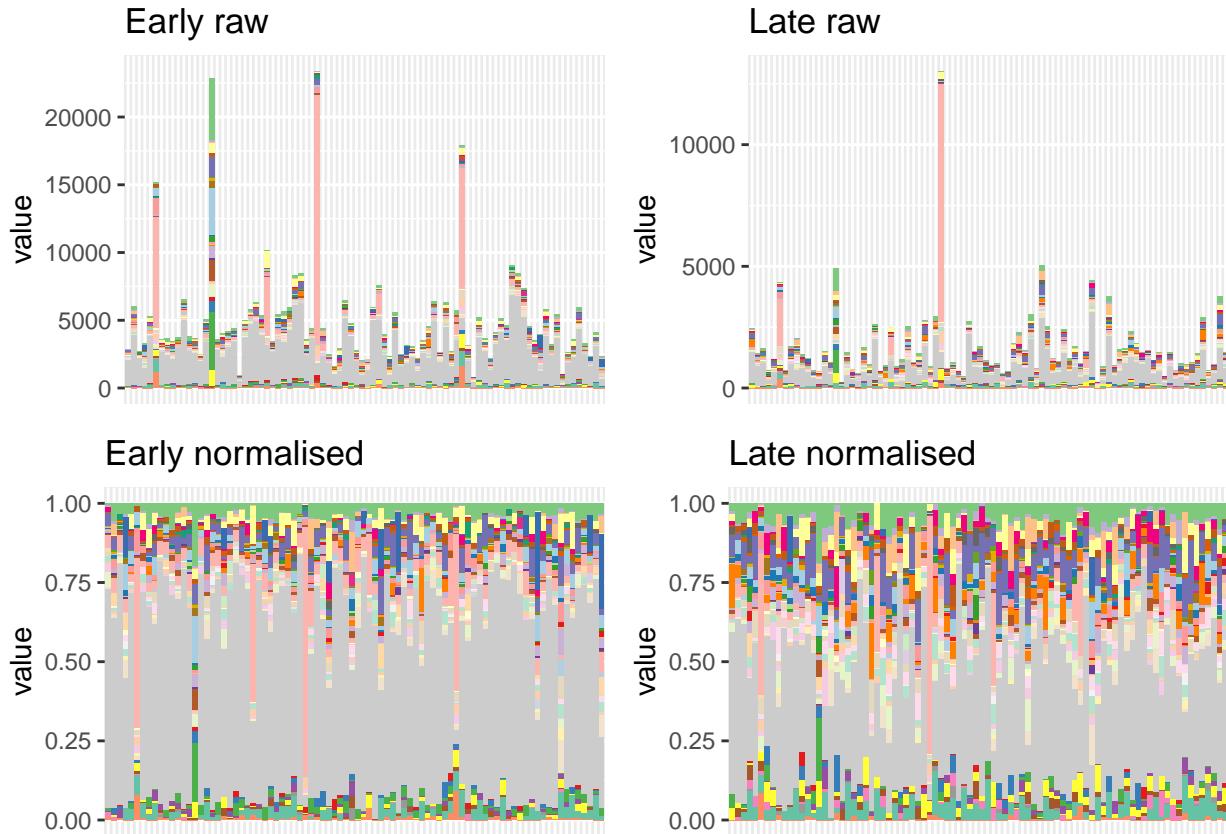
Ranked plot for coverage



Signatures from mutSigExtractor

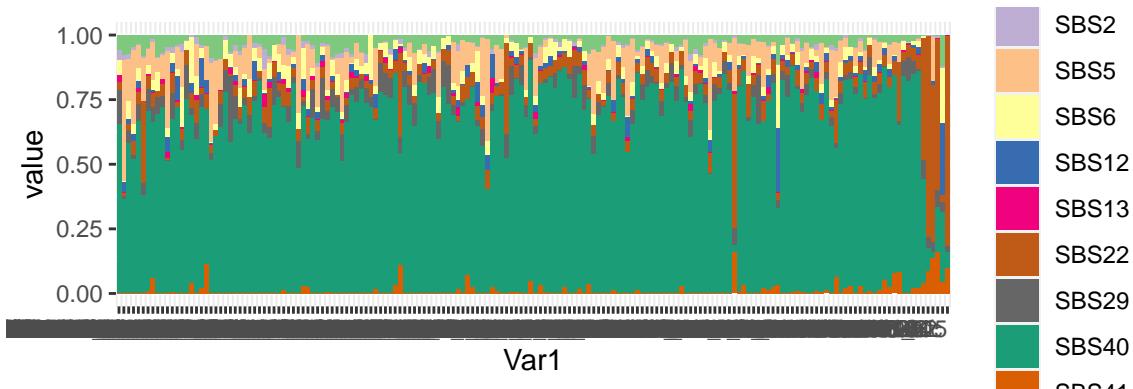
The signatures from mutSigExtractor are as follows:

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



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.

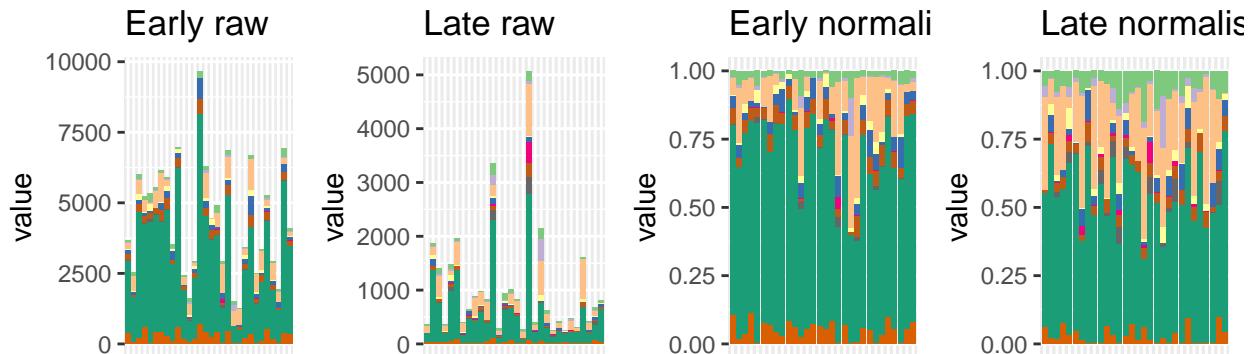


Kidney-RCC.papillary

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

Barplot and general statistics

```
## [1] 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)
```

```

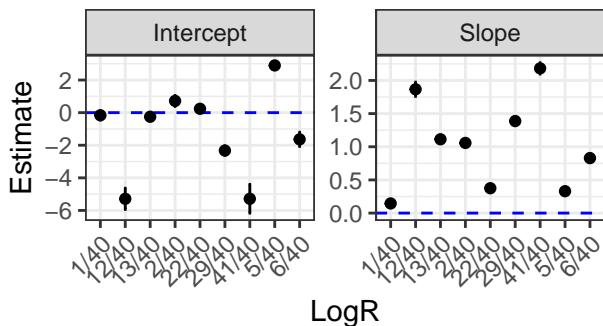
##      SBS1      SBS2      SBS5      SBS6      SBS12     SBS13
## 0.035736437 0.010720323 0.116403371 0.016521337 0.039719314 0.004438931
##      SBS22      SBS29      SBS40      SBS41
## 0.049284298 0.007187420 0.669488124 0.050500444

```

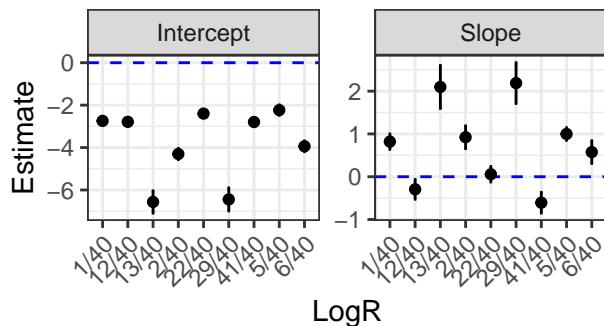
SBS29 is found in relatively small quantities.

Betas

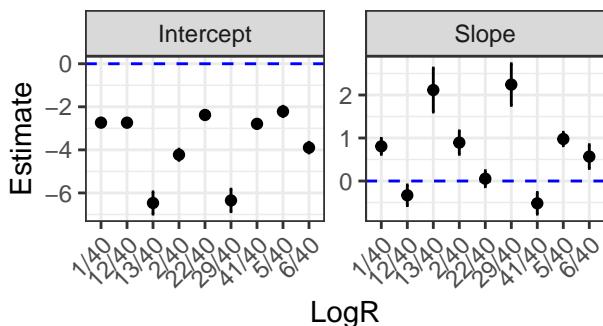
Kidney–RCC.papillary
diagRE_M



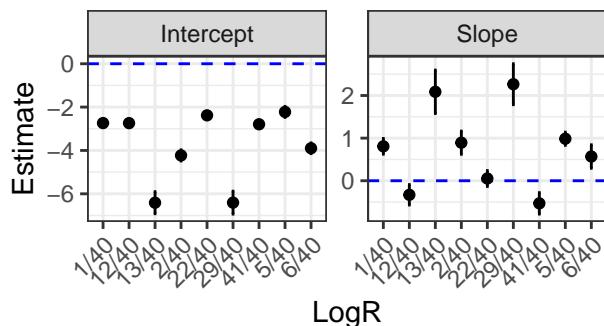
Kidney–RCC.papillary
fullRE_DMSL



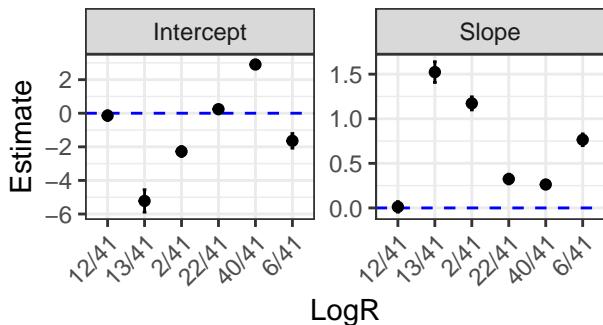
Kidney–RCC.papillary
diagRE_DMSL



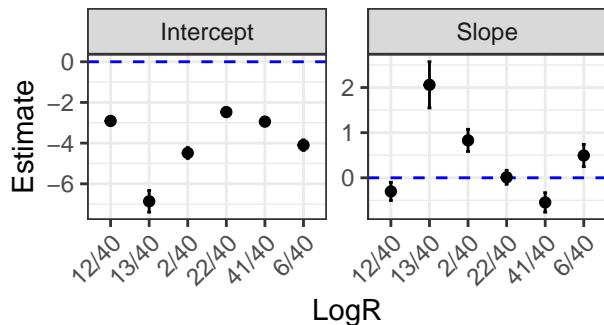
Kidney–RCC.papillary
sparseRE_DMSL



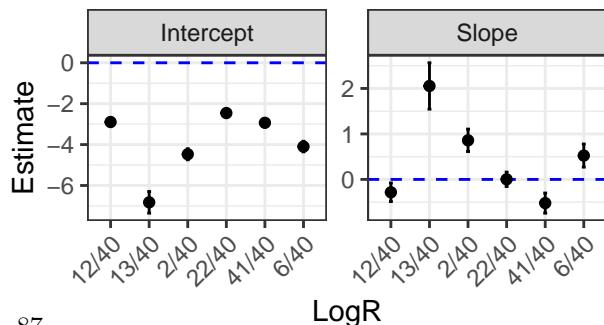
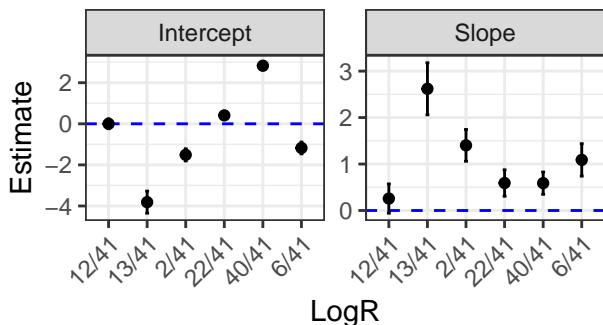
Kidney–RCC.papillary
fullRE_M_nonexo



Kidney–RCC.papillary
fullRE_DMSL_nonexo



Kidney–RCC.papillary
diagRE_DMSL_nonexo



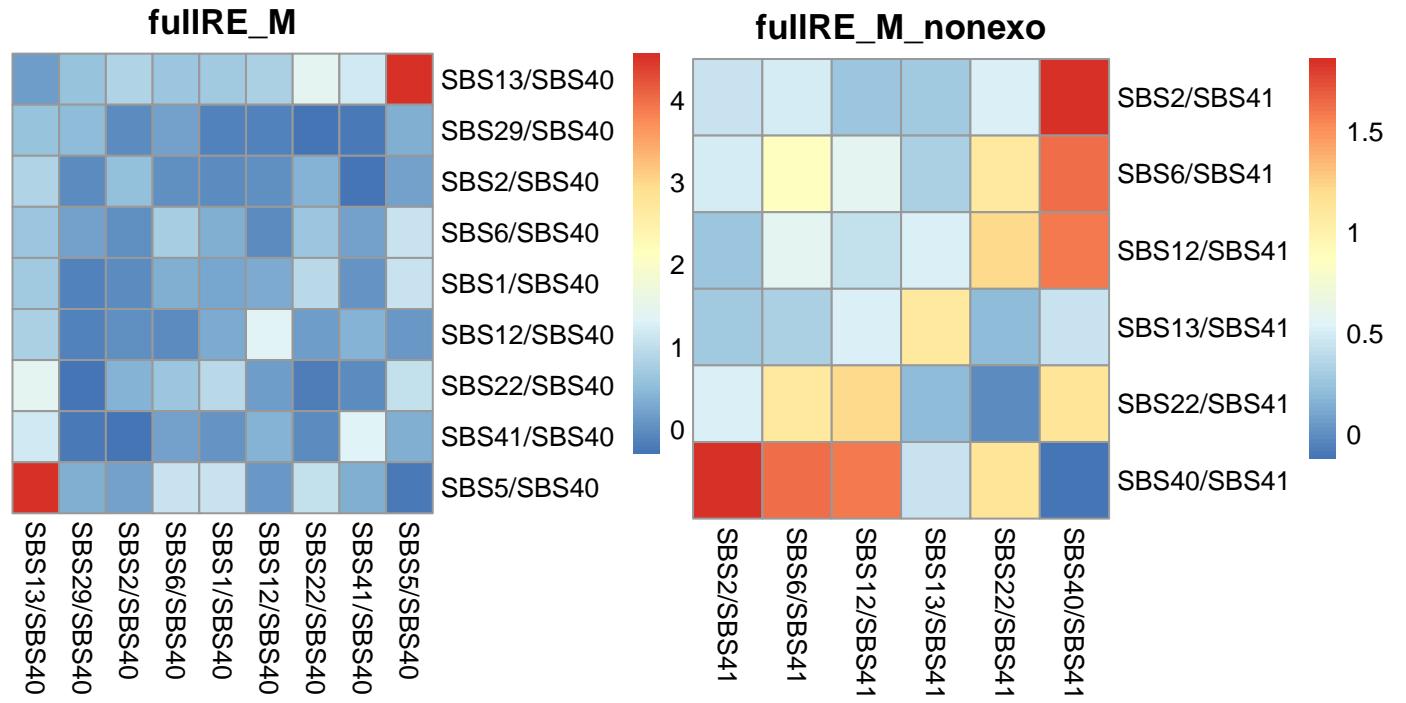
We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 2.591235×10^{-7} .

Covariance matrices

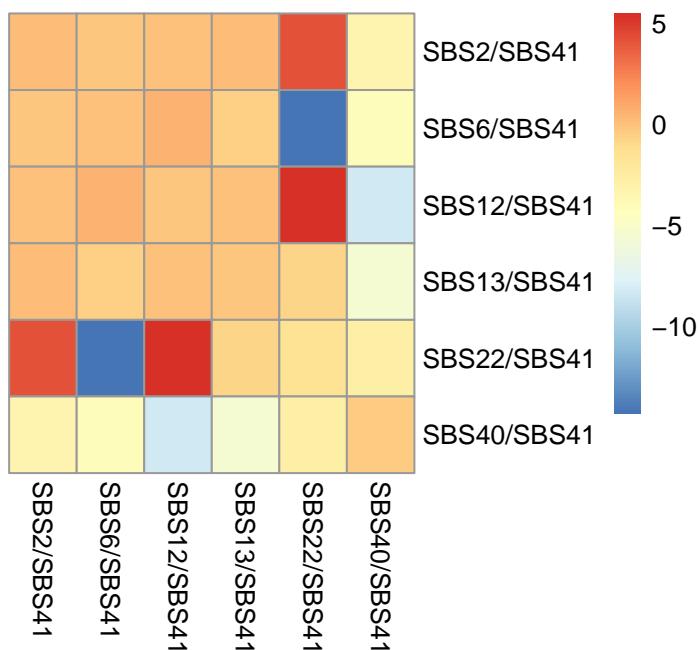
```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```



ditional_sortedDMSLnonexo



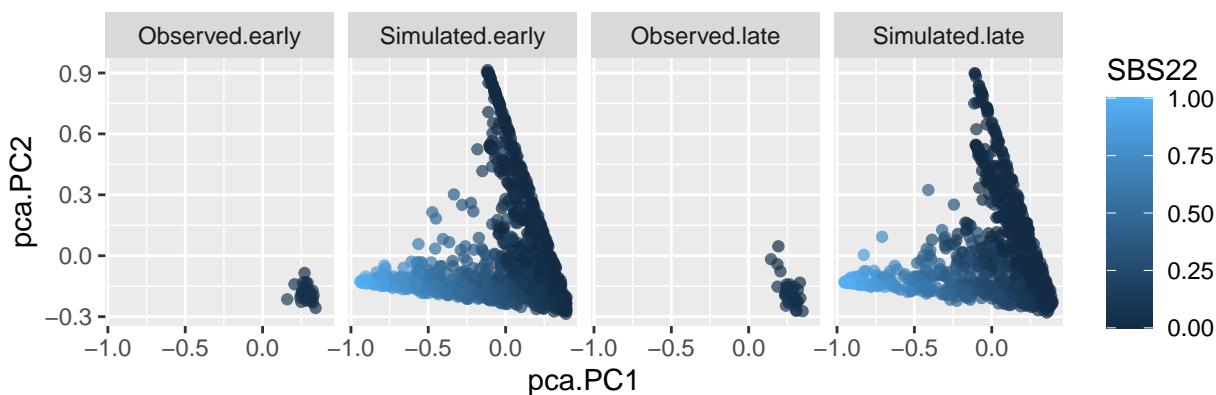
Simulation under inferred data

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)

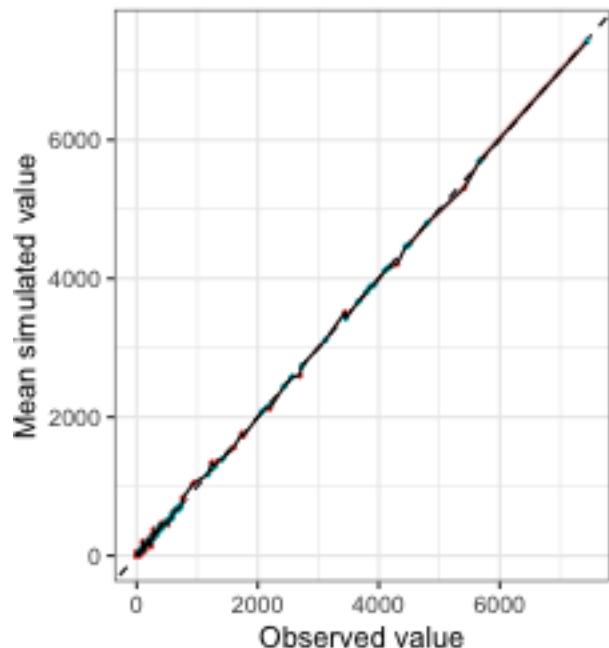
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```

Simulation of Kidney–RCC.papillary samples

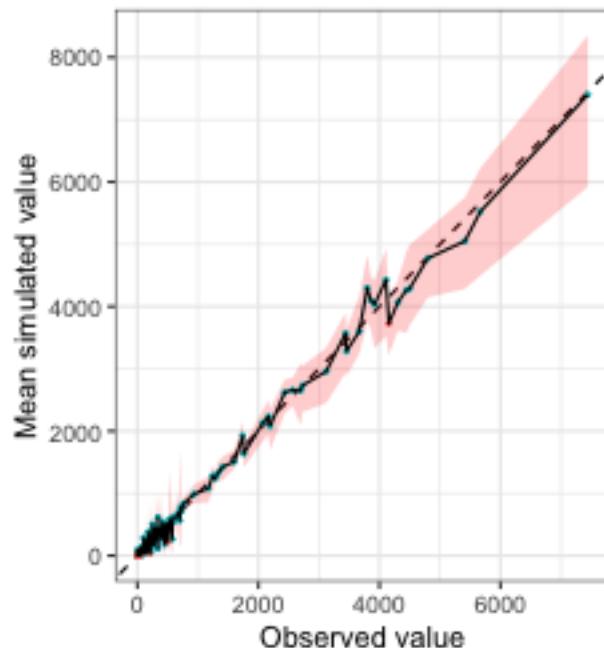


Ranked plot for coverage

obj_Kidney_RCCpapillary (M)
FALSE:224; TRUE:196



obj_Kidney_RCCpapillary (DMSI)
FALSE:114; TRUE:306



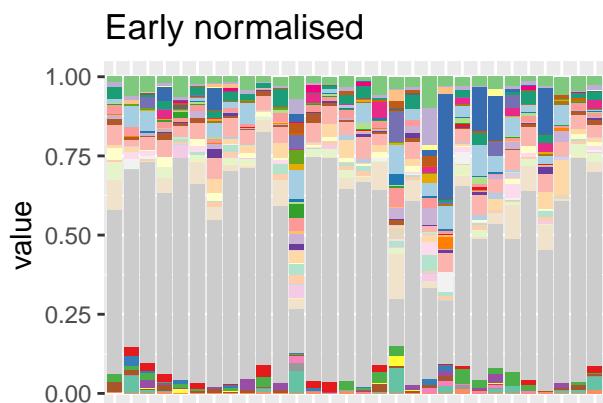
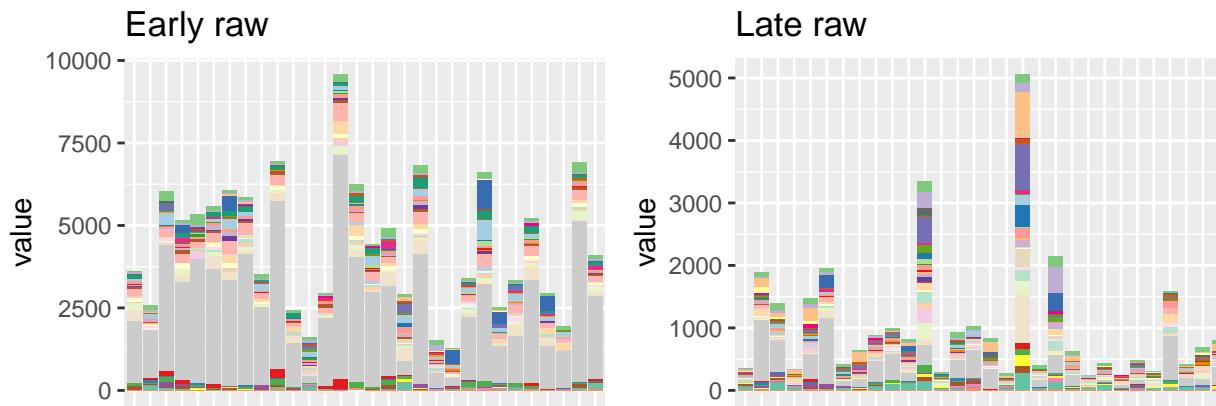
col * FALSE * TRUE

col * FALSE * TRUE

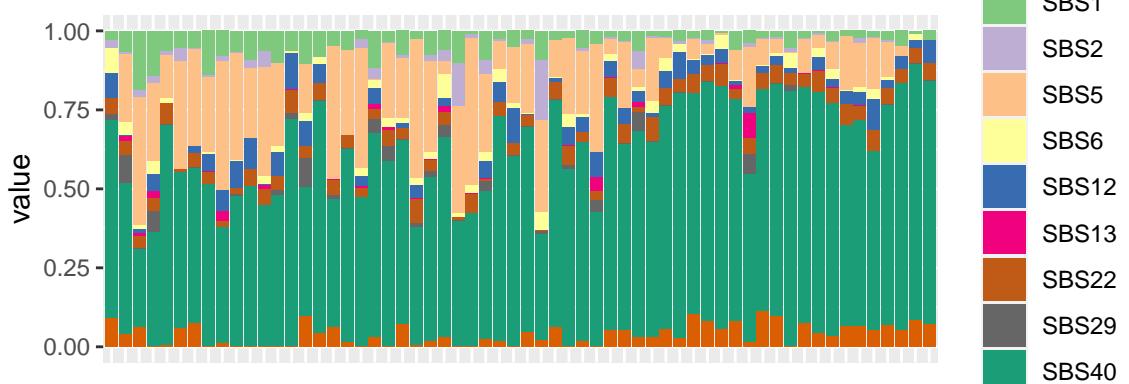
Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

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



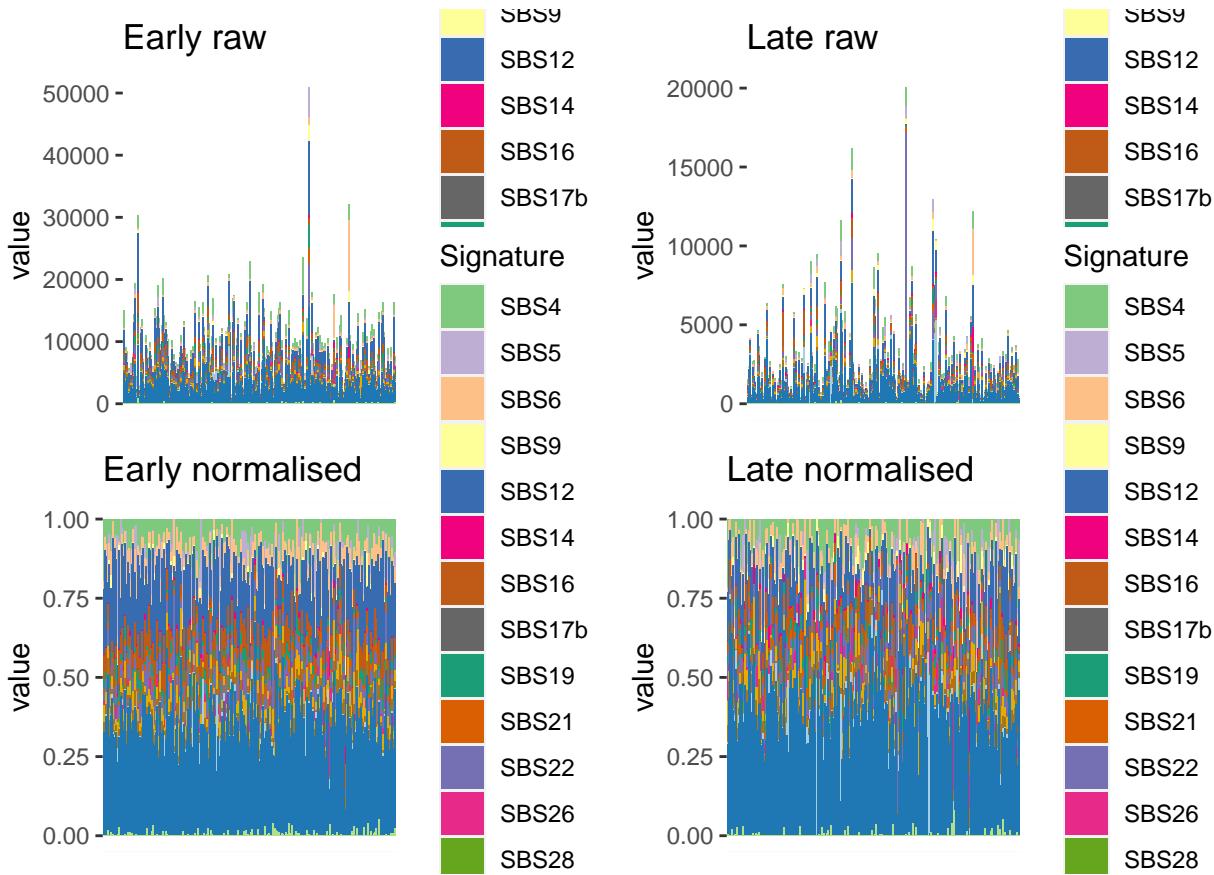
Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.



Liver-HCC

Barplot and general statistics

```
## [1] 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)
```

```

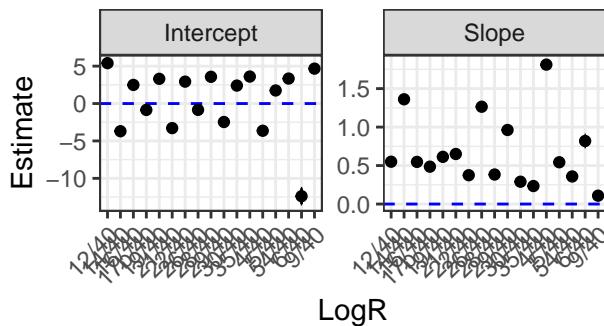
##      SBS4      SBS5      SBS6      SBS9      SBS12     SBS14
## 0.081740962 0.026465897 0.047036092 0.007670584 0.206143096 0.005884273
##      SBS16     SBS17b     SBS19     SBS21     SBS22     SBS26
## 0.068804779 0.001835835 0.028215636 0.016888238 0.058186725 0.011387208
##      SBS28     SBS29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

```

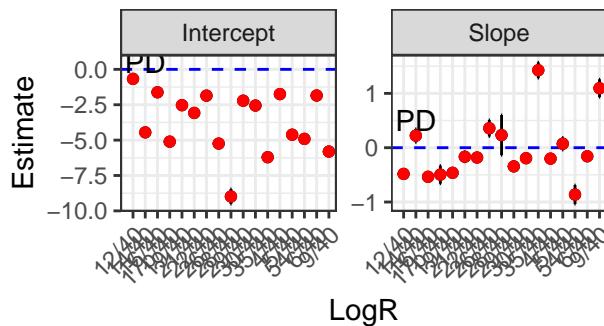
SBS28 is only present in 7% of samples and has extremely low exposure - we could consider removing it.

Betas

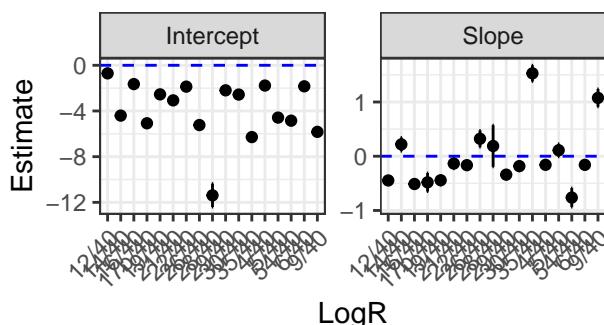
Liver-HCC
diagRE_M



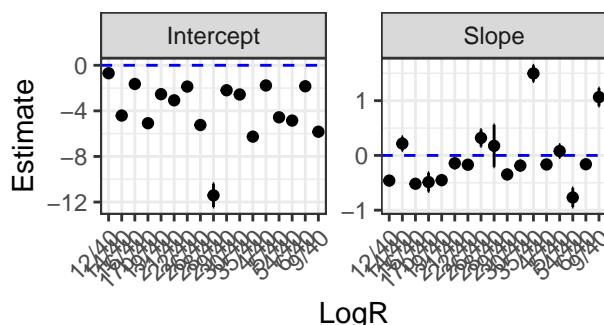
Liver-HCC
fullRE_DMSL



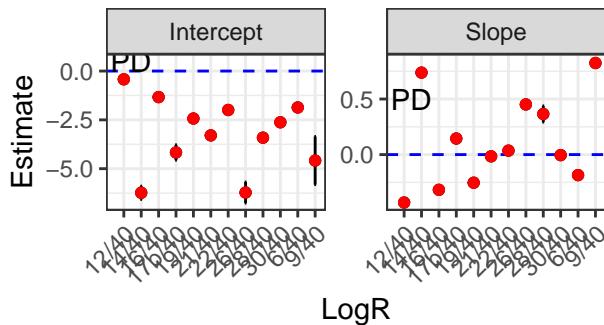
Liver-HCC
diagRE_DMSL



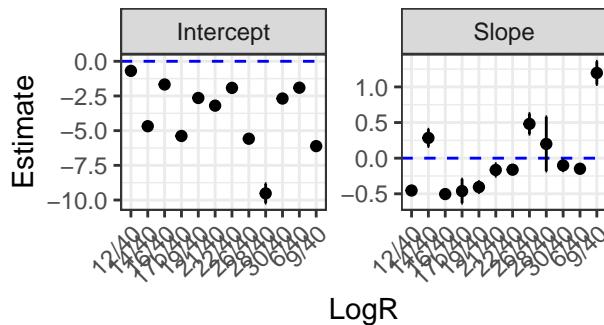
Liver-HCC
sparseRE_DMSL



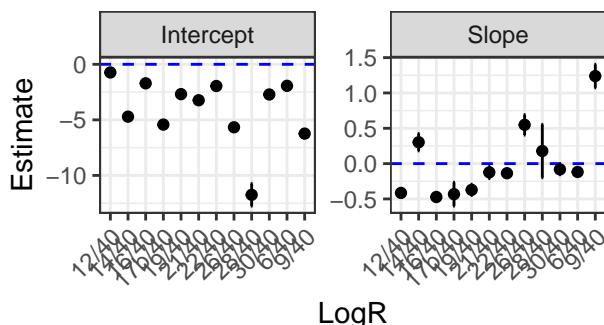
Liver-HCC
fullRE_M_nonexo



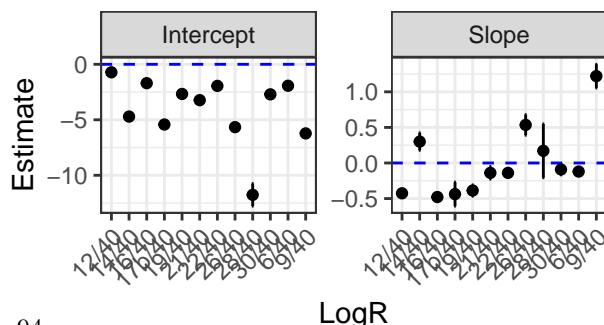
Liver-HCC
fullRE_DMSL_nonexo



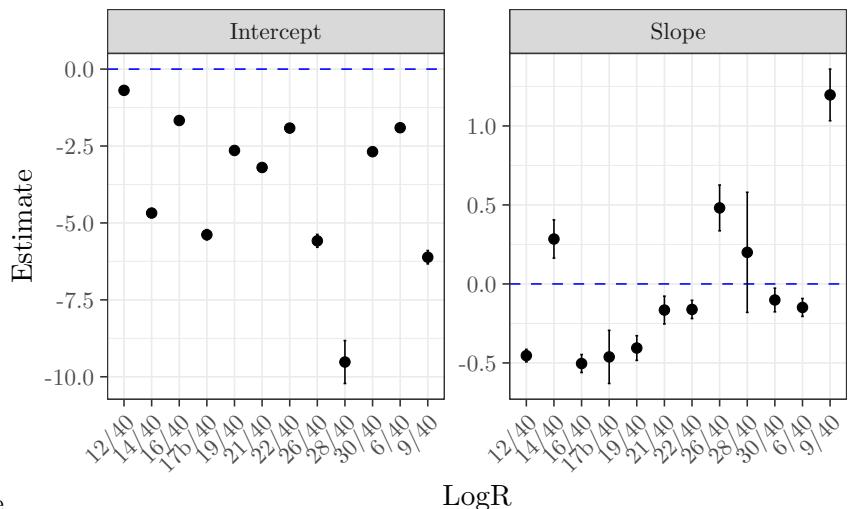
Liver-HCC
diagRE_DMSL_nonexo



Liver-HCC
sparseRE_DMSL_nonexo



Liver-HCCfullRE DMSL non-exogenous



Difficult to see the labels, so I replot it here

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

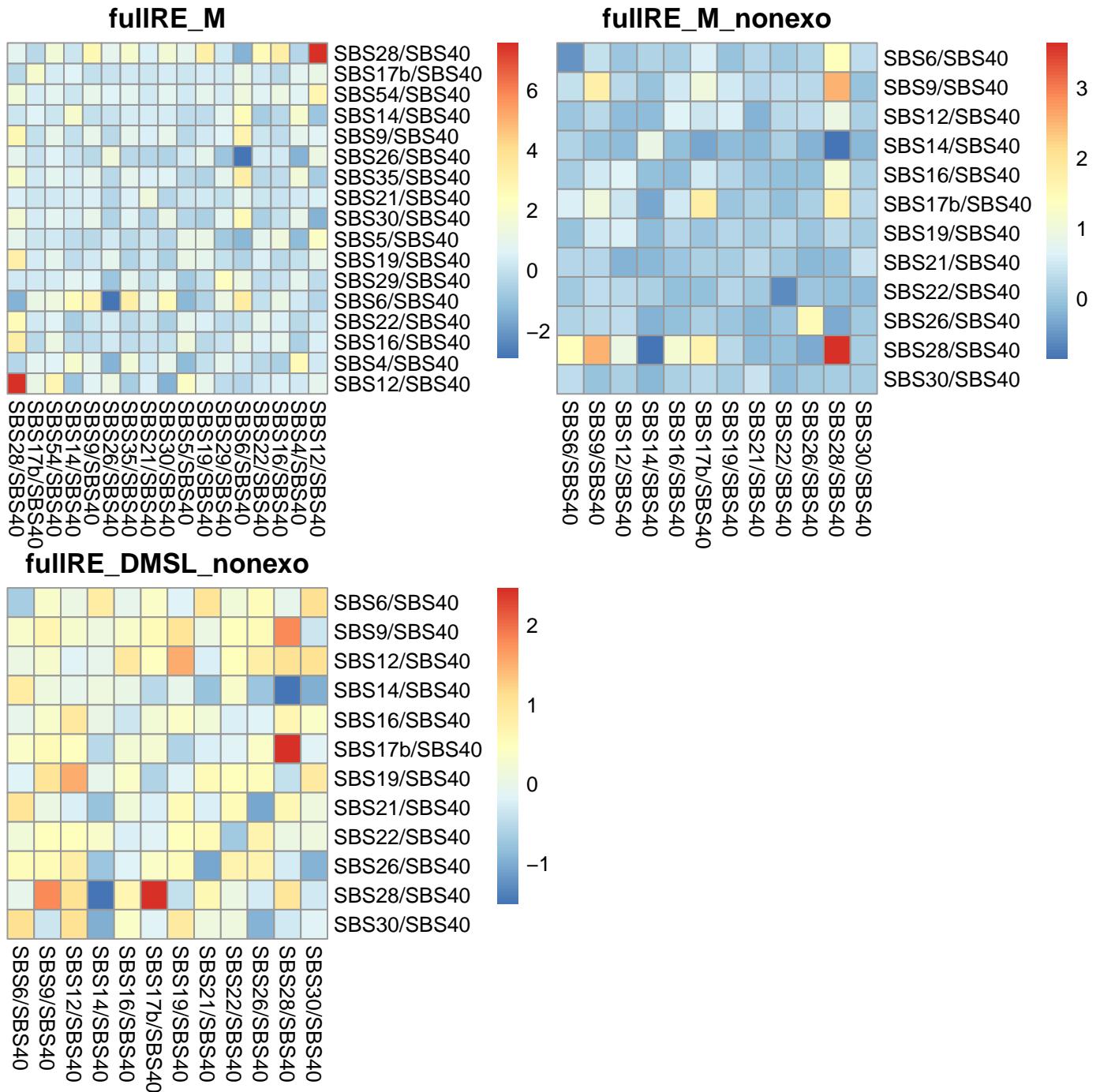
```

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

```



Simulation under inferred data

```

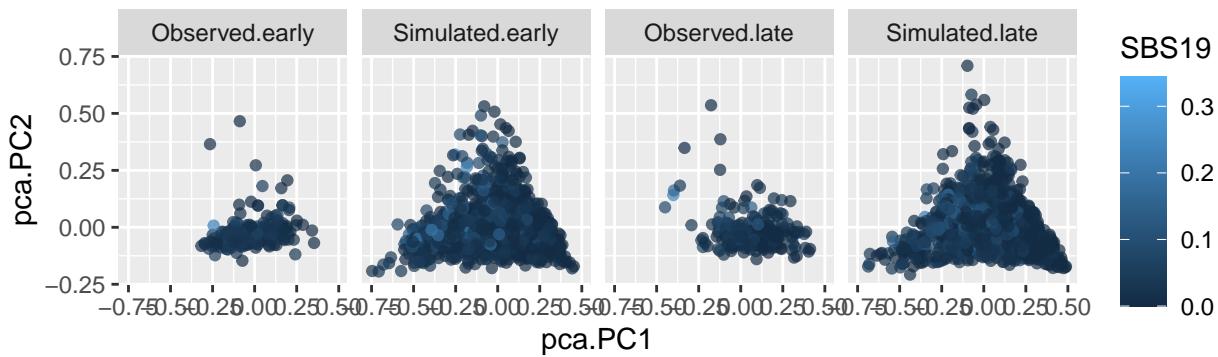
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)

```

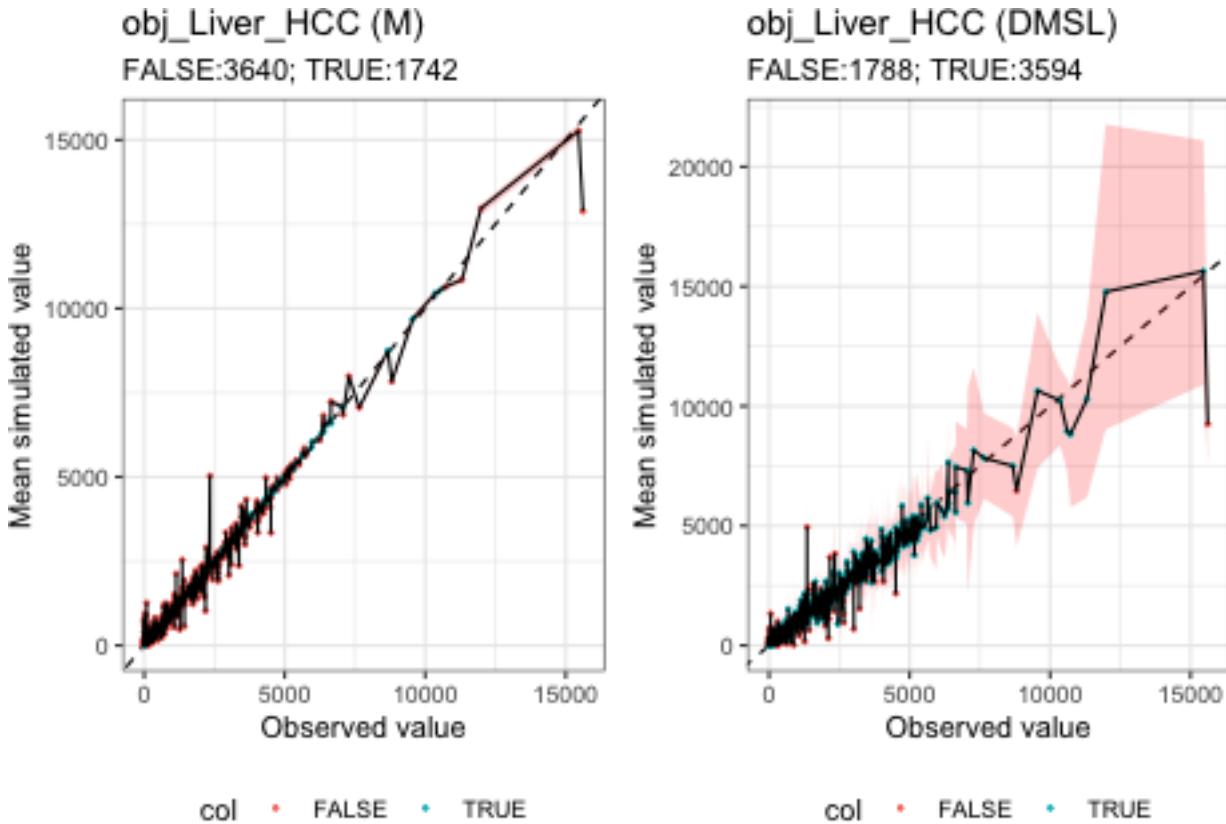
```
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```

Simulation of Liver–HCC samples



Ranked plot for coverage

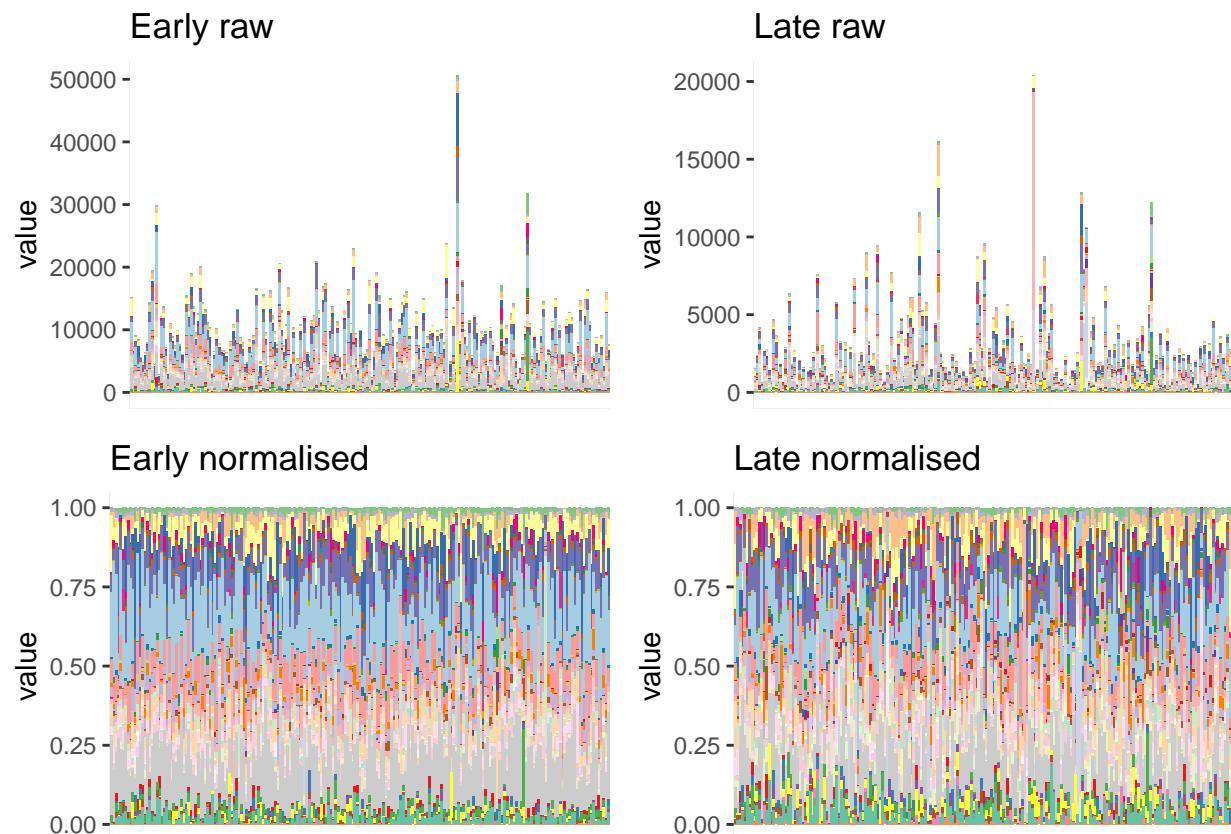
Remember that fullRE M has not converged, and it should be re-run:



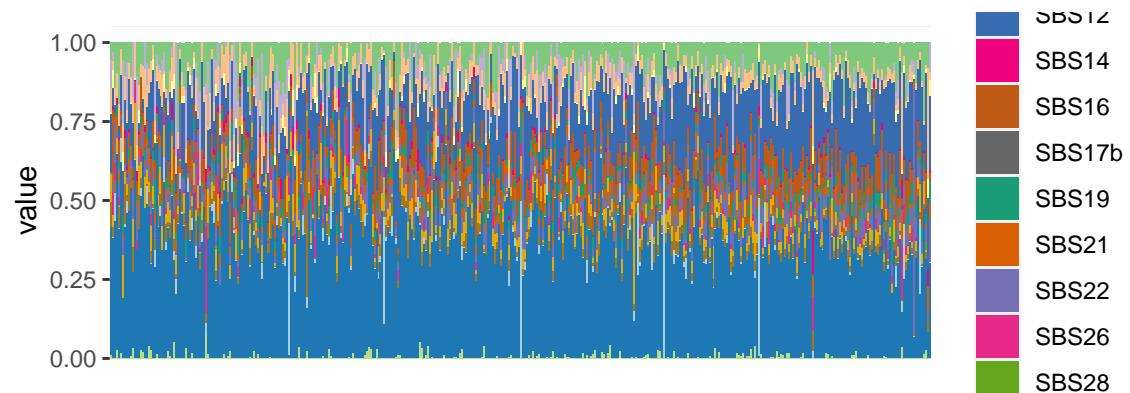
Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

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



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

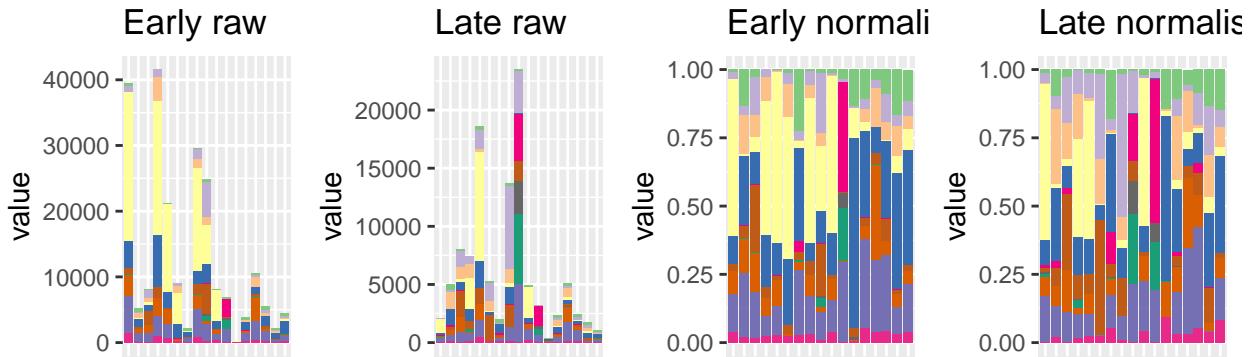


Lung-AdenoCA

How can we have such few samples?

Barplot and general statistics

```
## [1] 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)
```

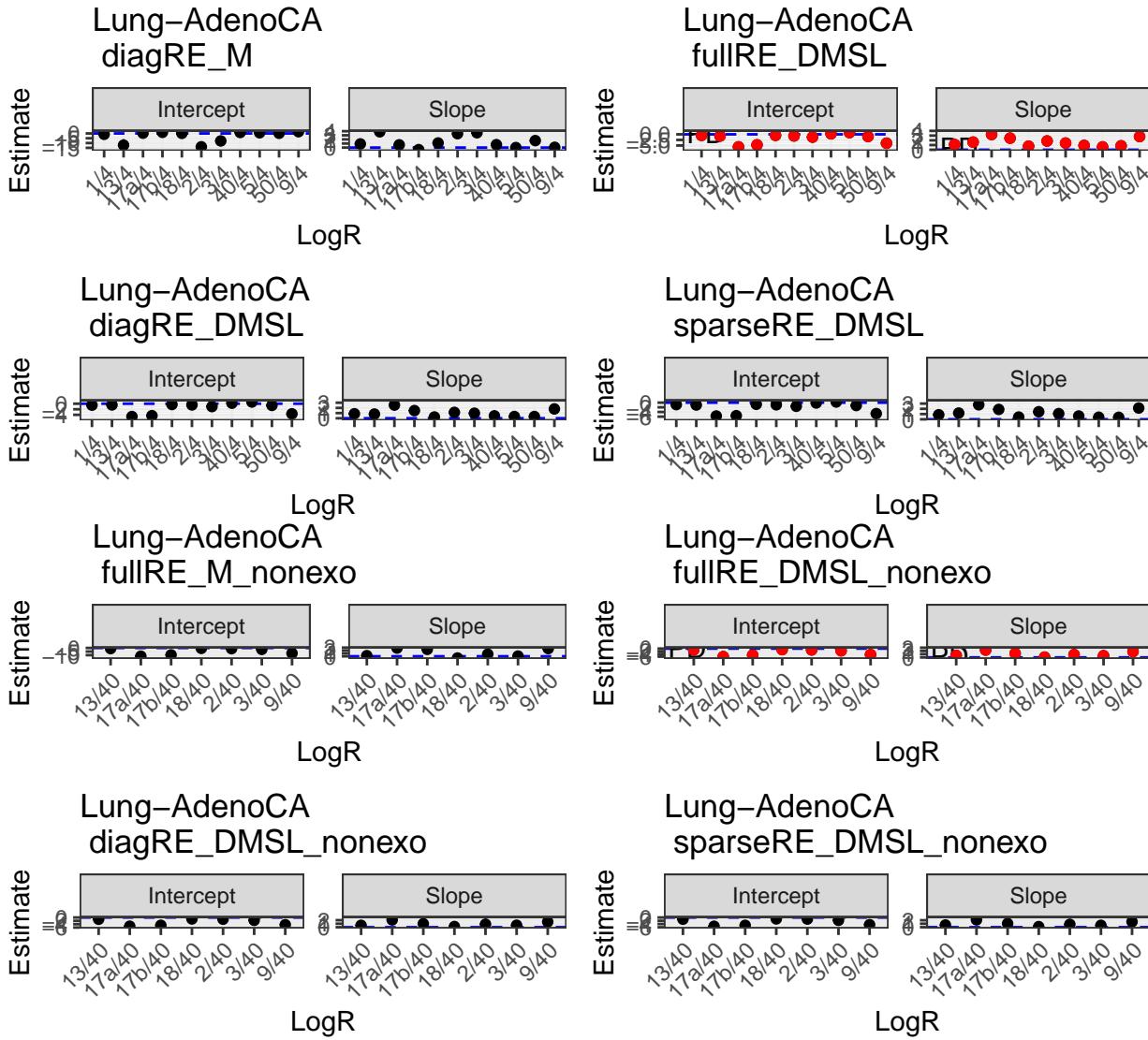
```
##      SBS1      SBS2      SBS3      SBS4      SBS5      SBS9      SBS13
## 0.02941176 0.02941176 0.26470588 0.17647059 0.08823529 0.58823529 0.08823529
##      SBS17a     SBS17b     SBS18     SBS40     SBS50
## 0.64705882 0.64705882 0.14705882 0.14705882 0.11764706
```

```
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

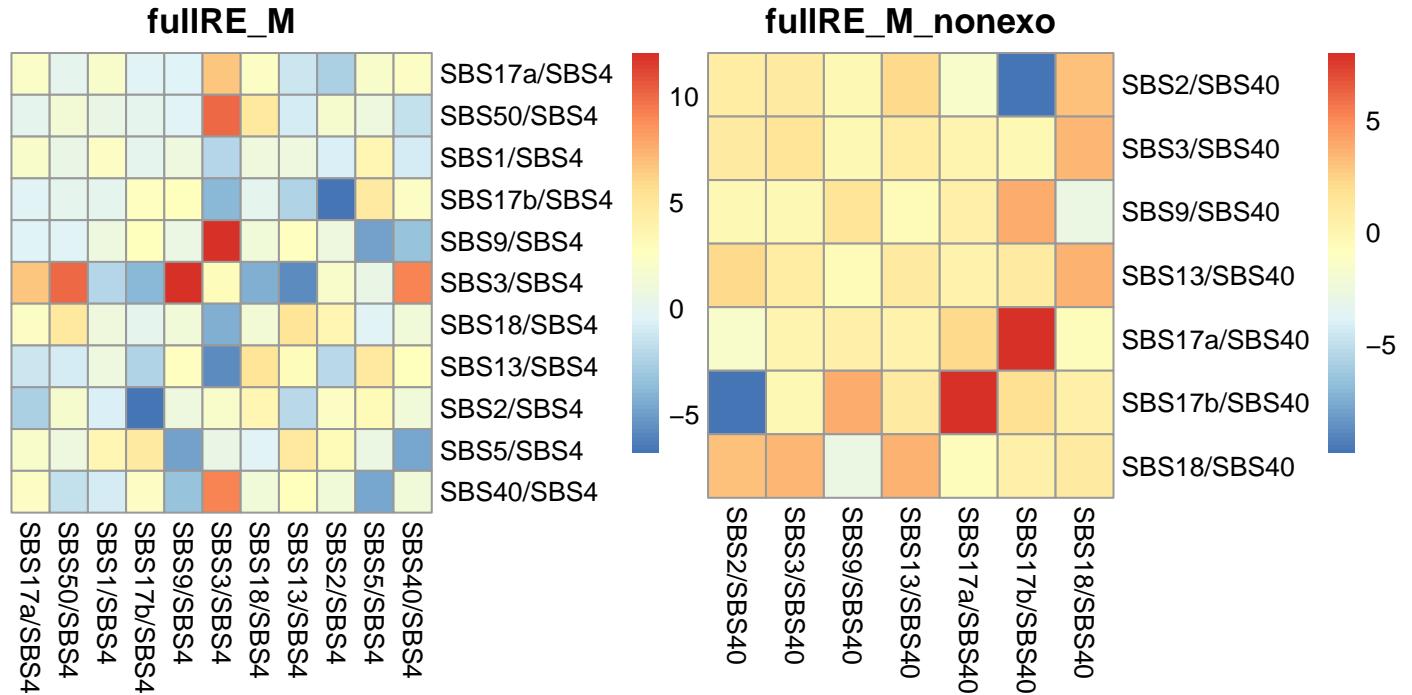


We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of 0.0034356.

Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

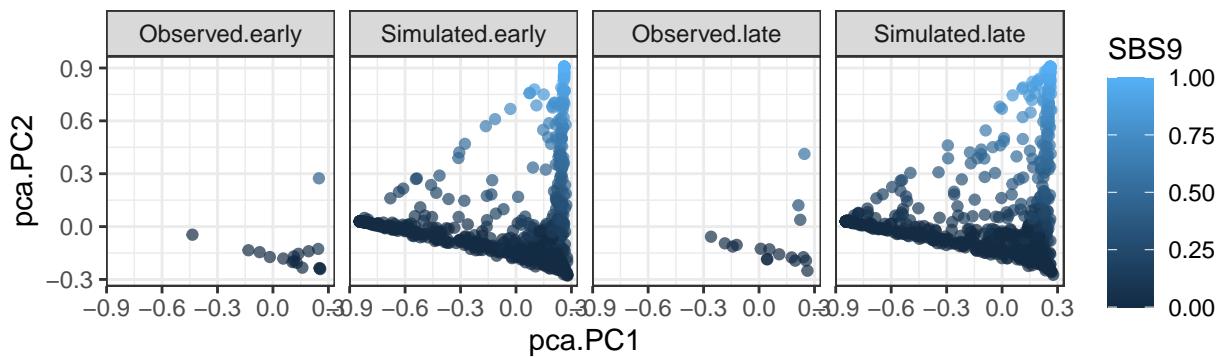


Simulation under inferred data

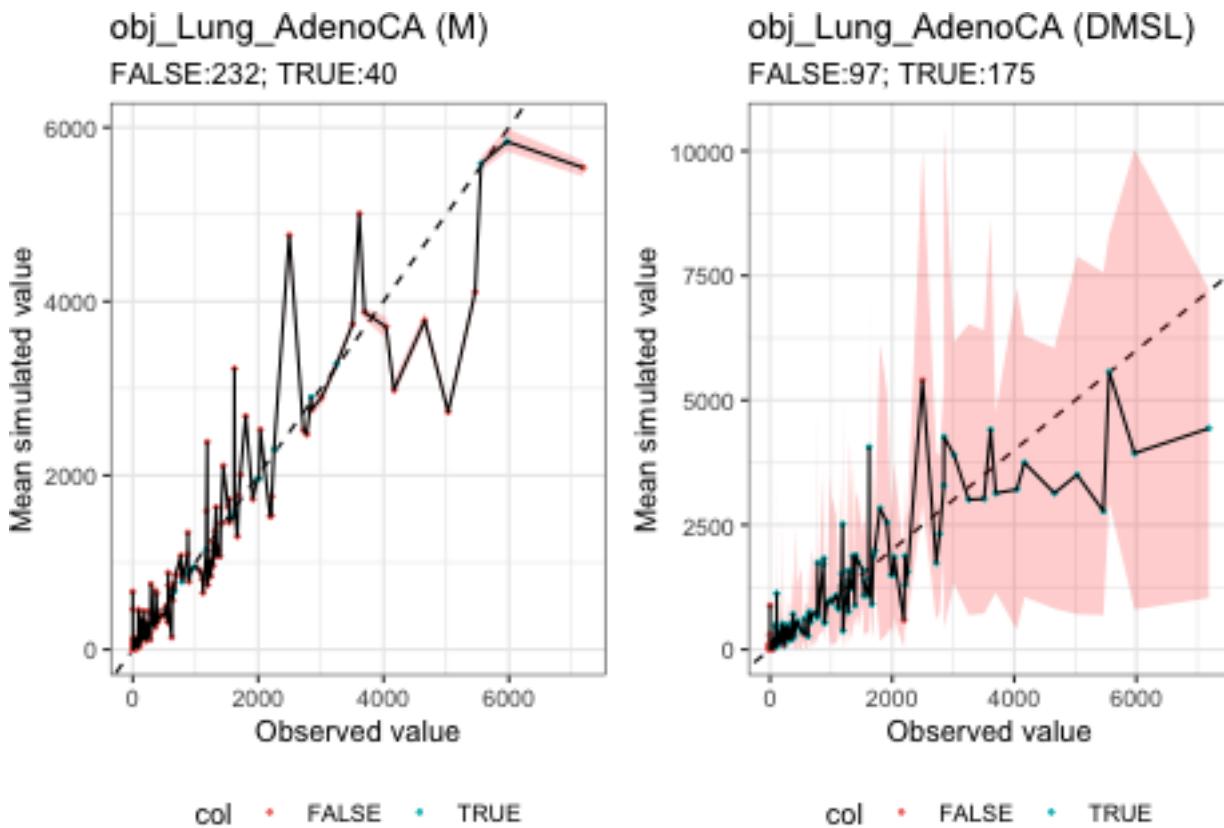
```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

Simulation of Lung–AdenoCA samples



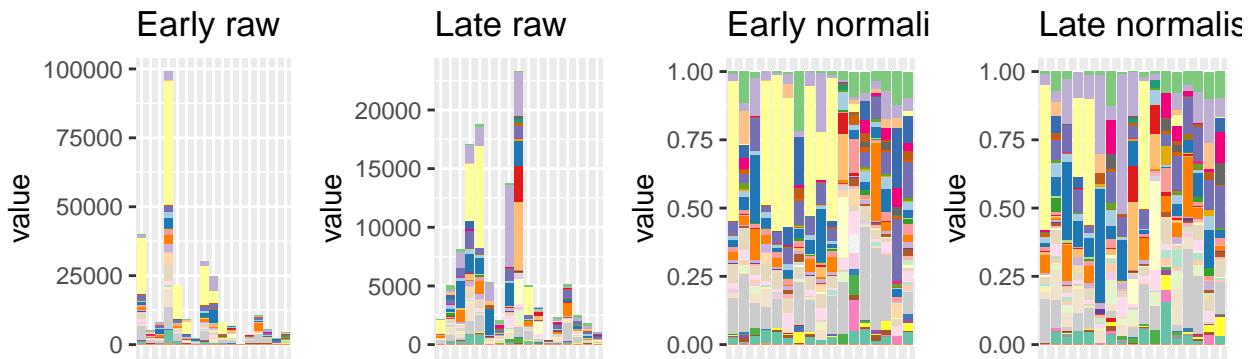
Ranked plot for coverage



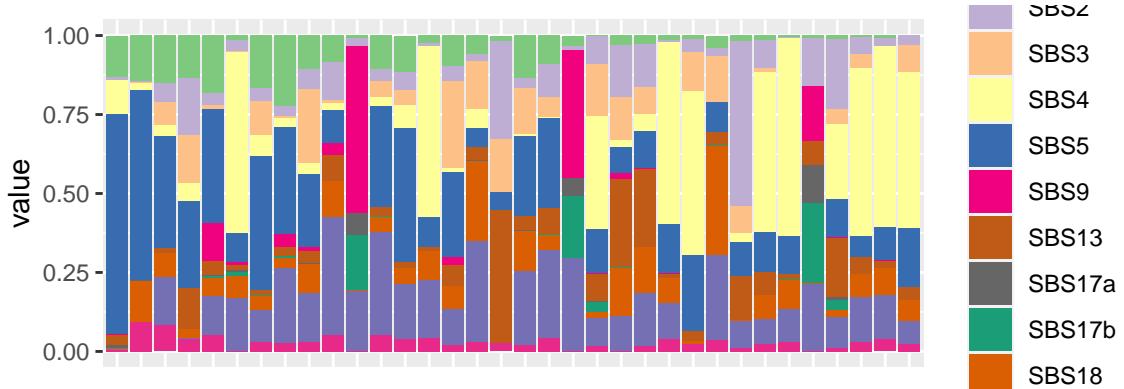
Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

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



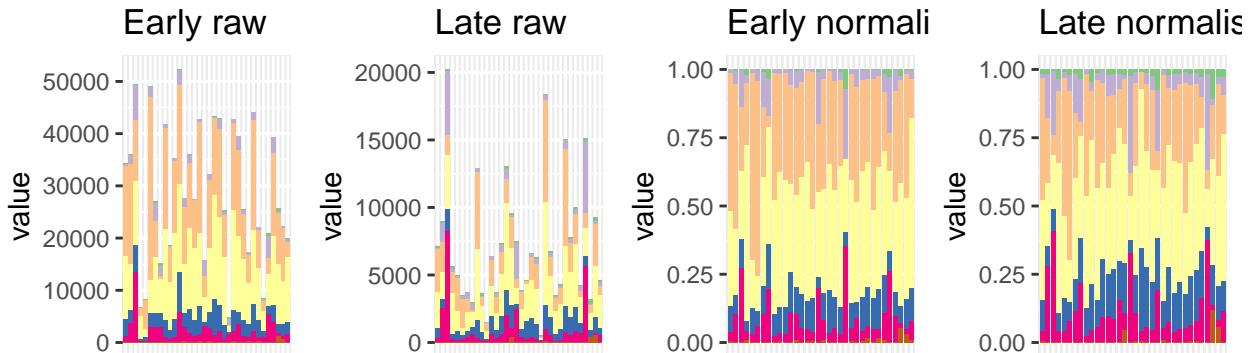
Exposures sorted by increasing number of mutations: there is a trend in which SBS5 decreases and SBS4 increases with the number of mutations.



Lung-SCC

Barplot and general statistics

```
## [1] 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_SCCT$Y == 0)/nrow(obj_Lung_SCCT$Y)

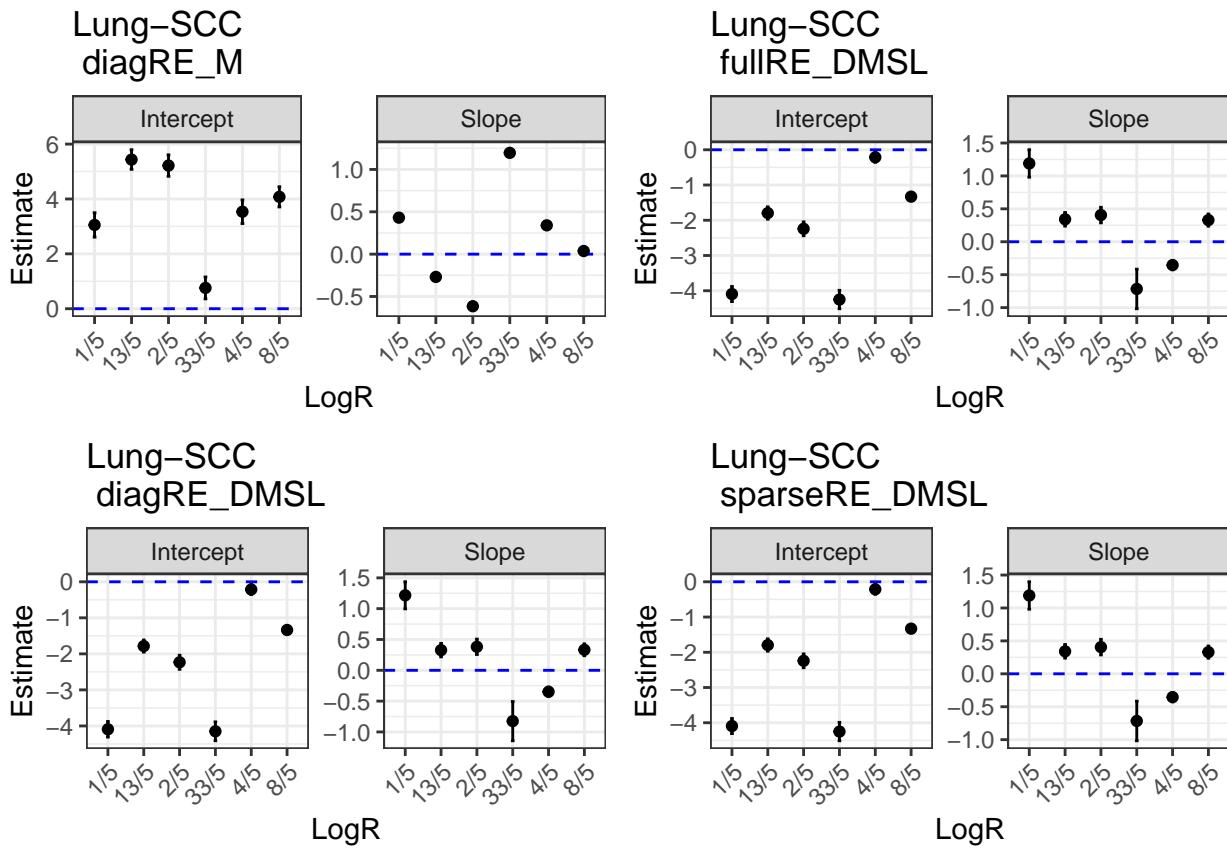
##           SBS1        SBS2        SBS4        SBS5        SBS8        SBS13       SBS33
## 0.11764706 0.01470588 0.01470588 0.00000000 0.00000000 0.00000000 0.35294118

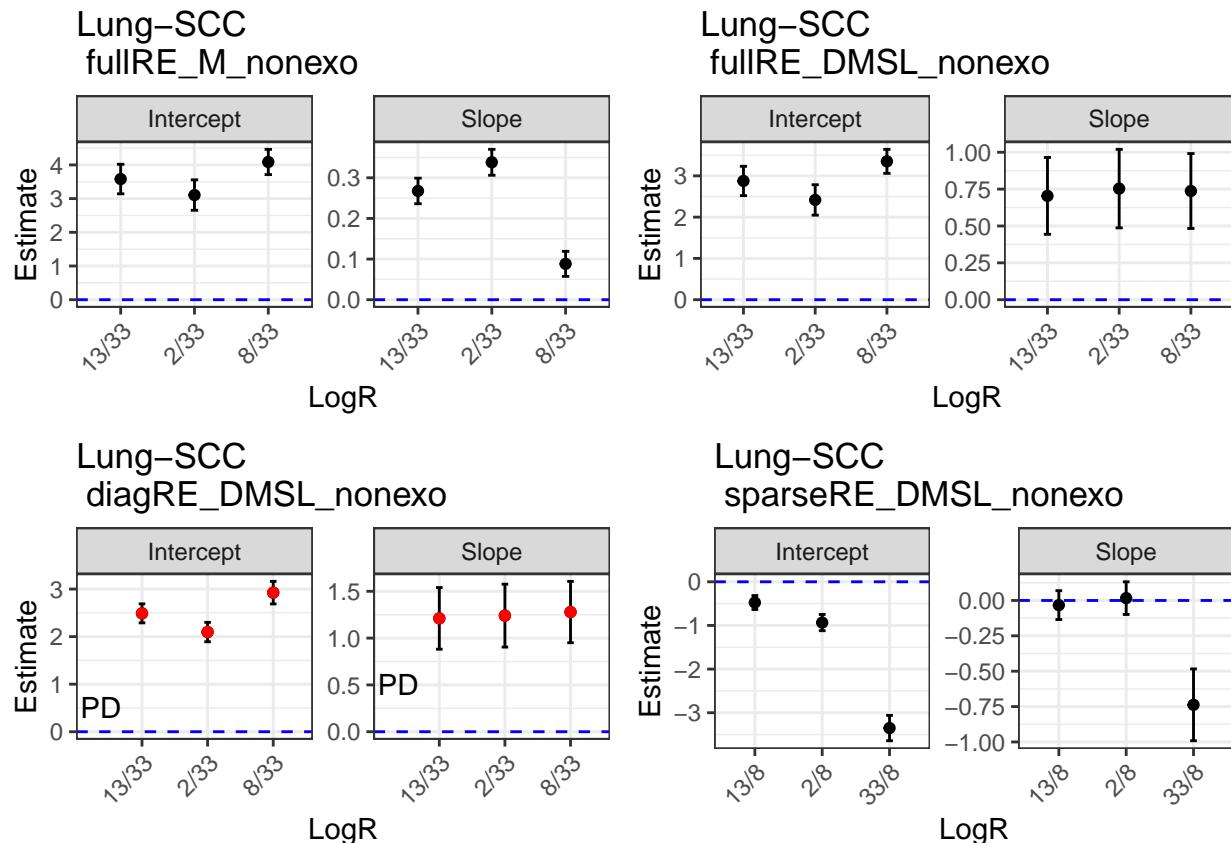
colSums(obj_Lung_SCCT$Y)/sum(obj_Lung_SCCT$Y)

##           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:





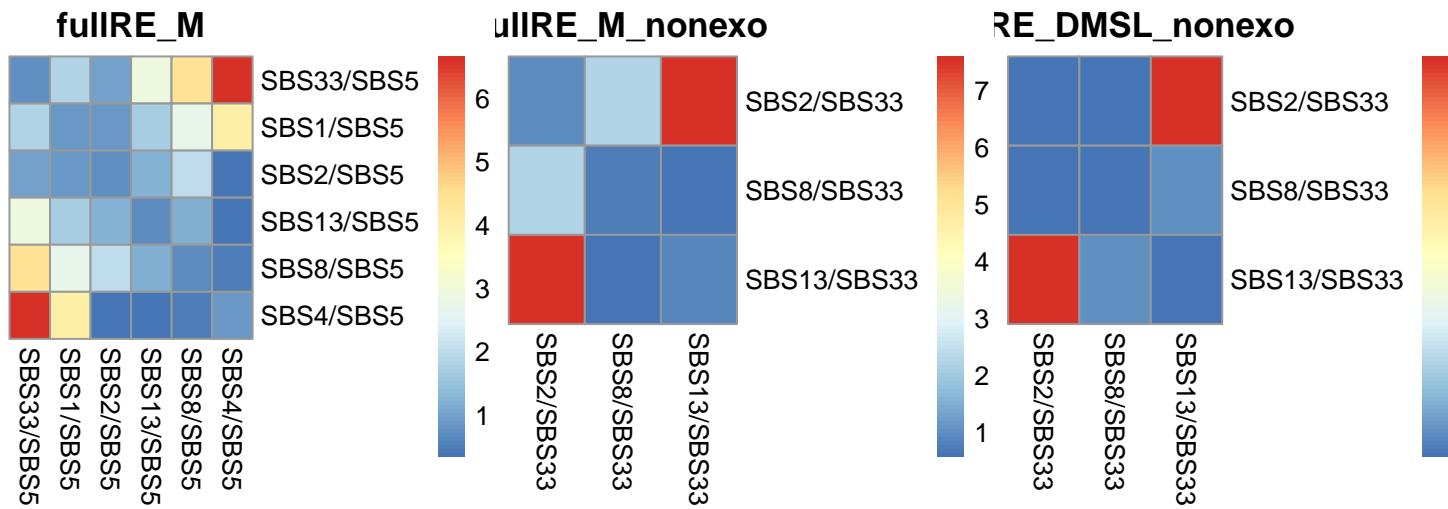
We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 0.0338506.

Covariance matrices

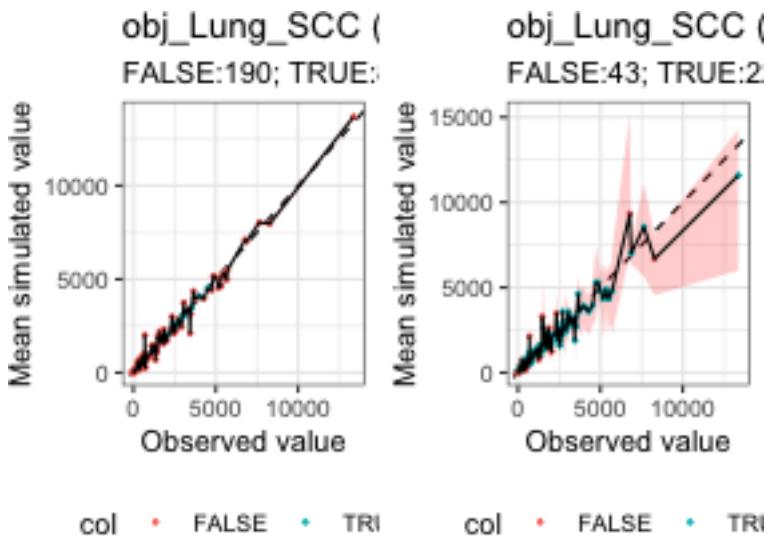
```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```



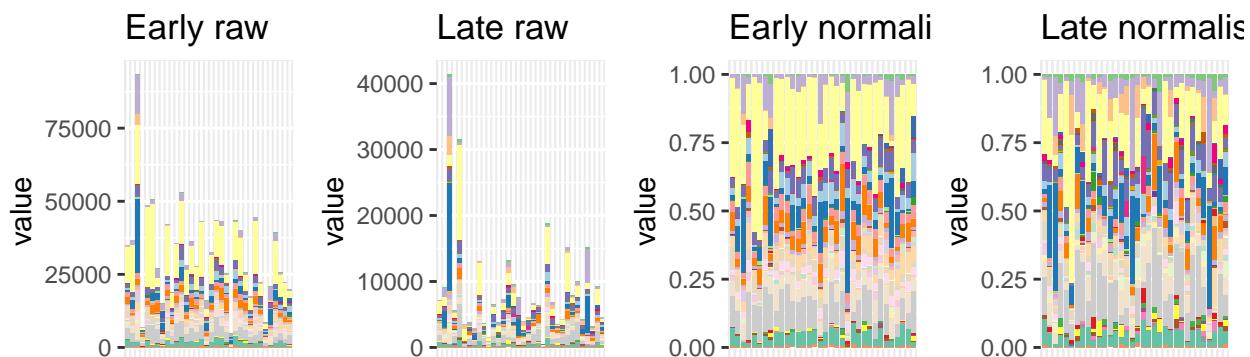
Ranked plot for coverage



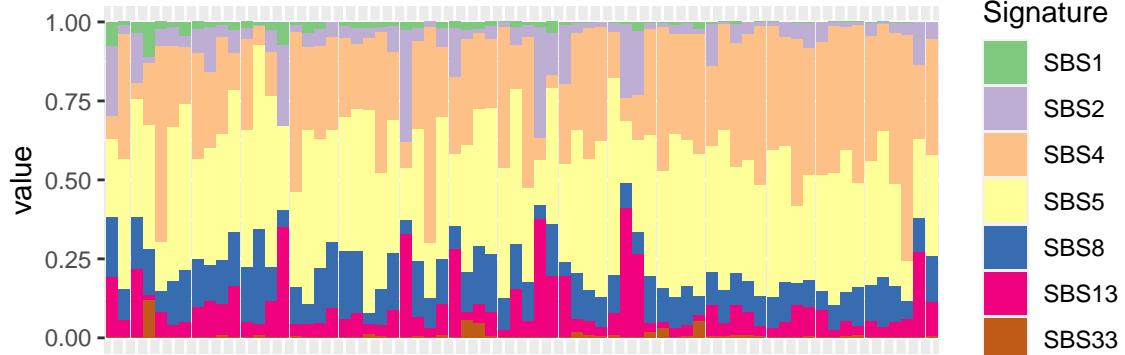
Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

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



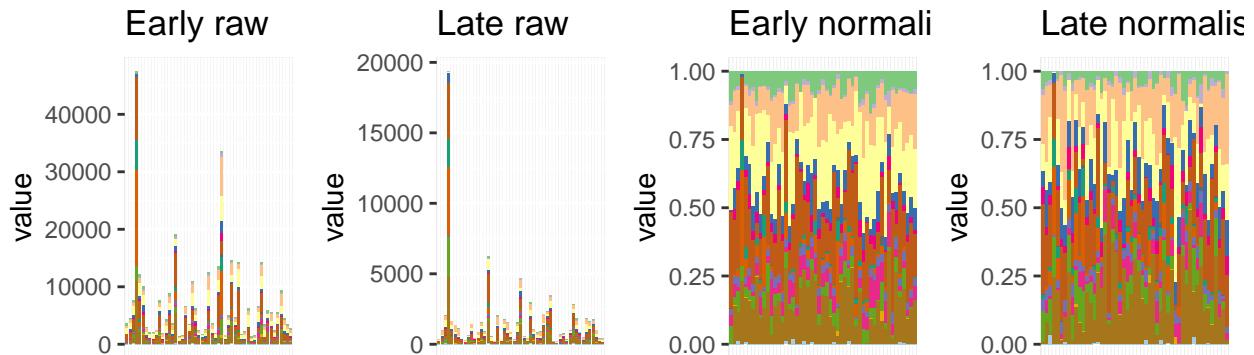
Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.



Lymph-BNHL

Barplot and general statistics

```
## [1] 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 | | fullRE_halfDM |
| ## 5 | Lymph-BNHL | | 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

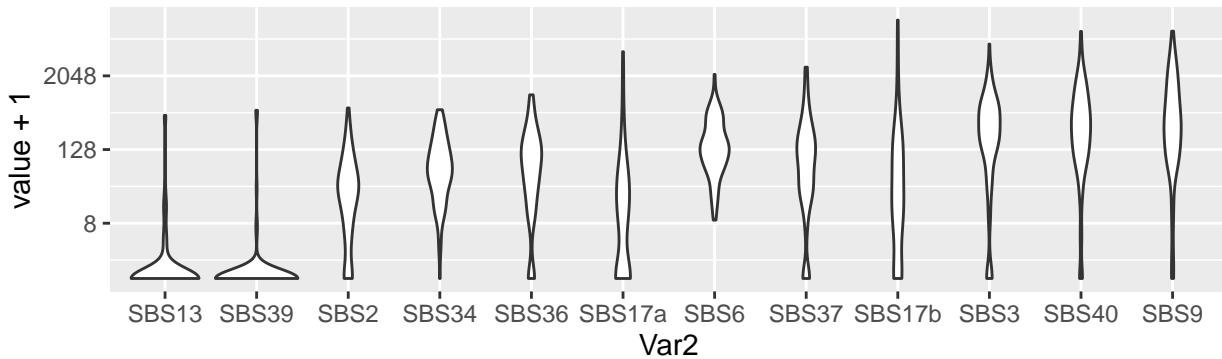
```

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?



SBS13 and SBS39 should definitely be removed.

Has fullRE M now converged? converge:

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

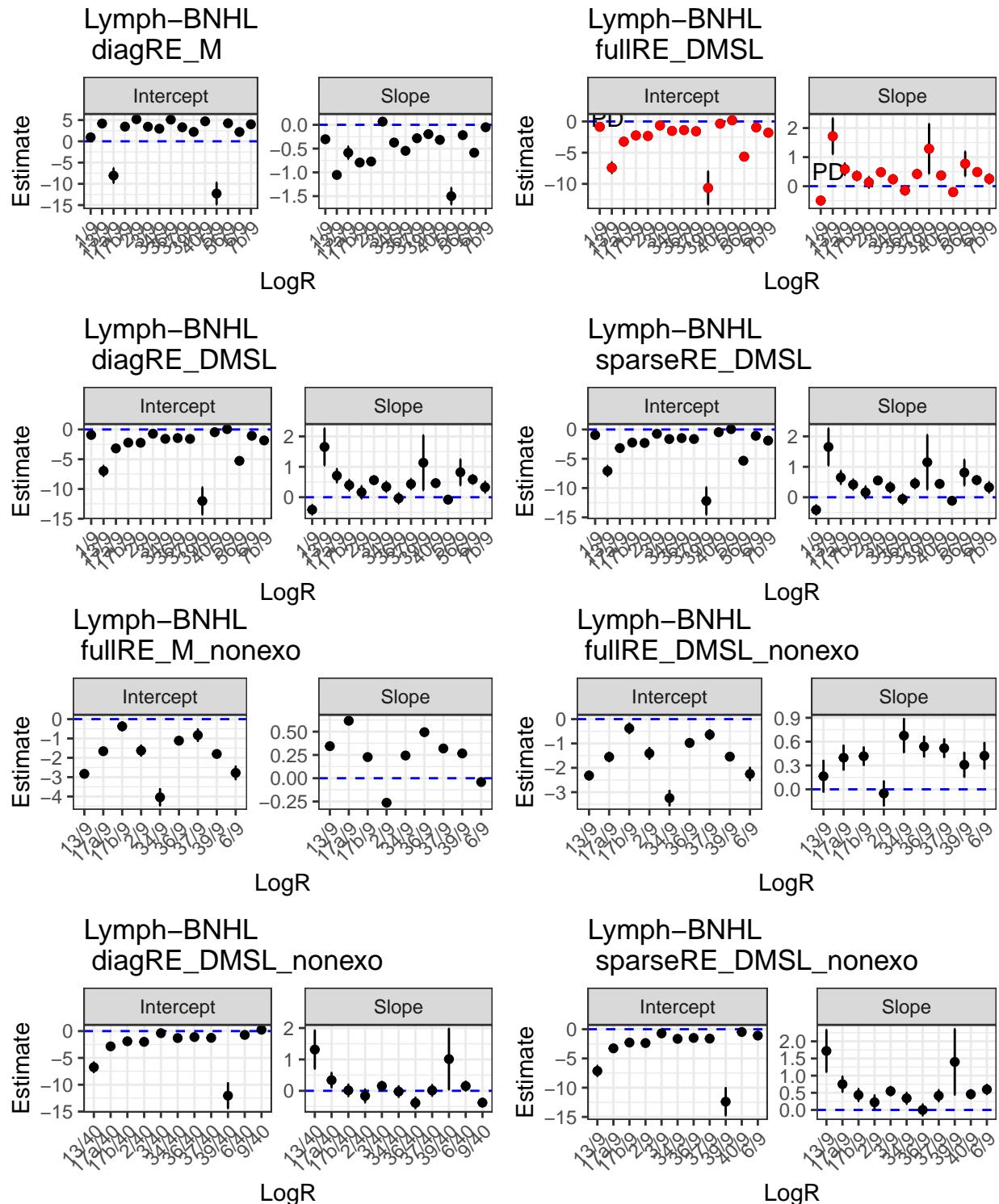
it has. I now run DM with this subset

Its convergence is as follows:

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

it has also converged

Betas



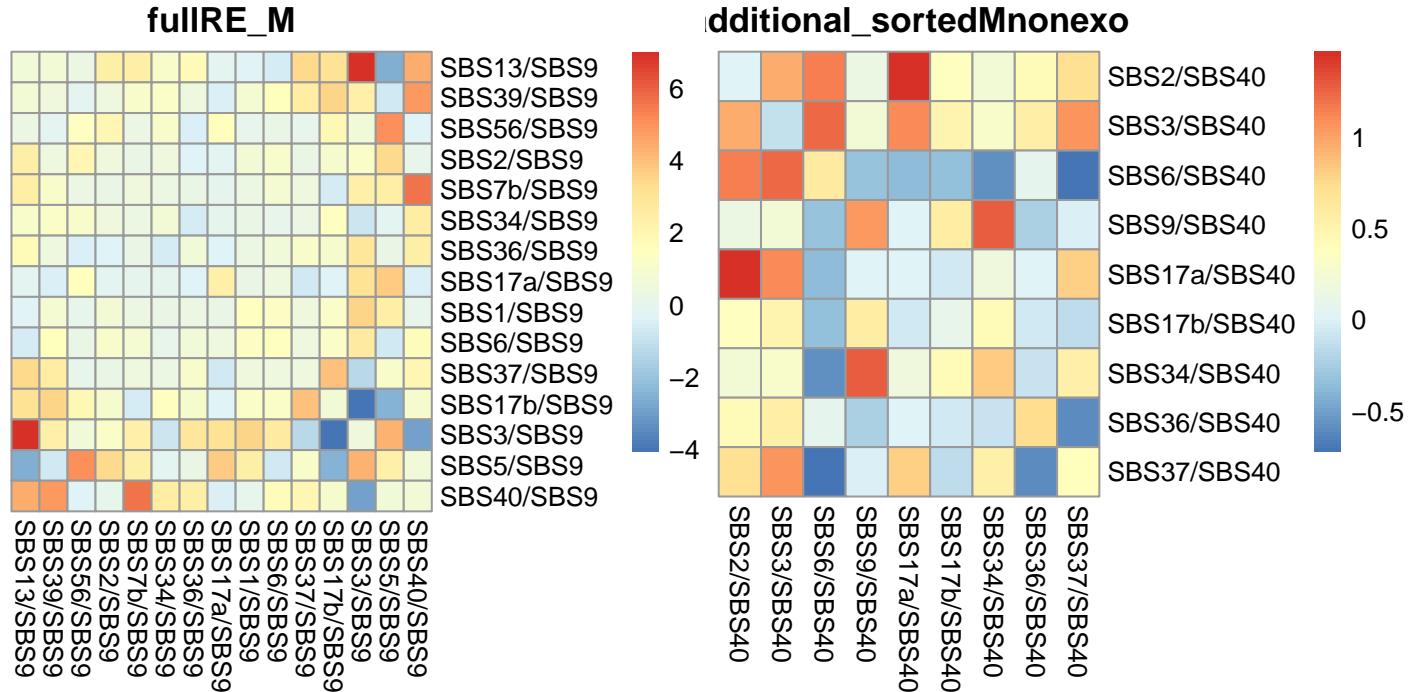
We use the results from the full RE single lambda DM with the subset of signatures (removing the two problematic ones) to test for differential abundance, giving a p-value of 9.5835037×10^{-7} .

Covariance matrices

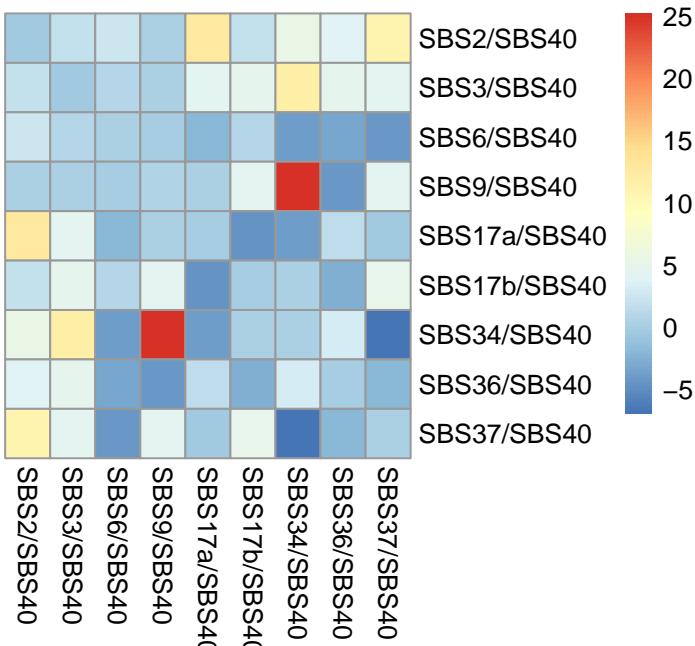
```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```



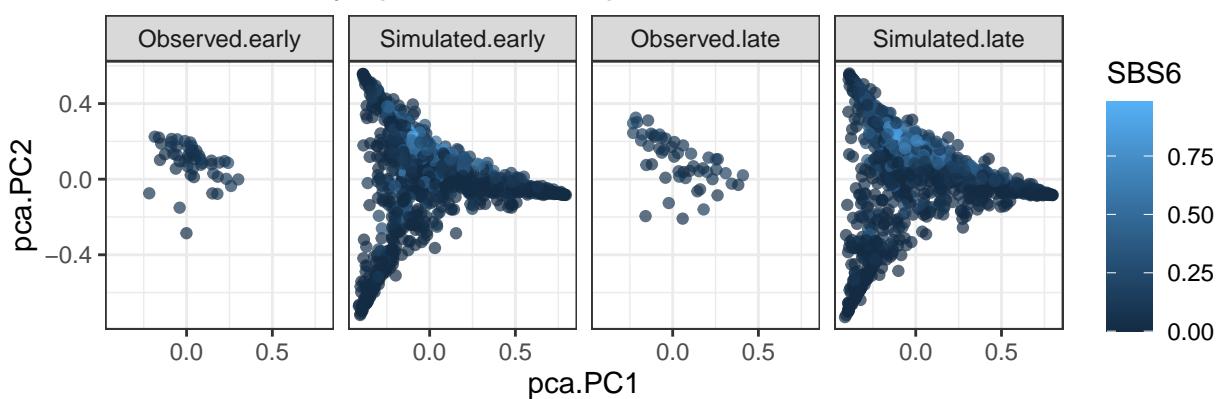
ditional_sortedDMSLnonexo



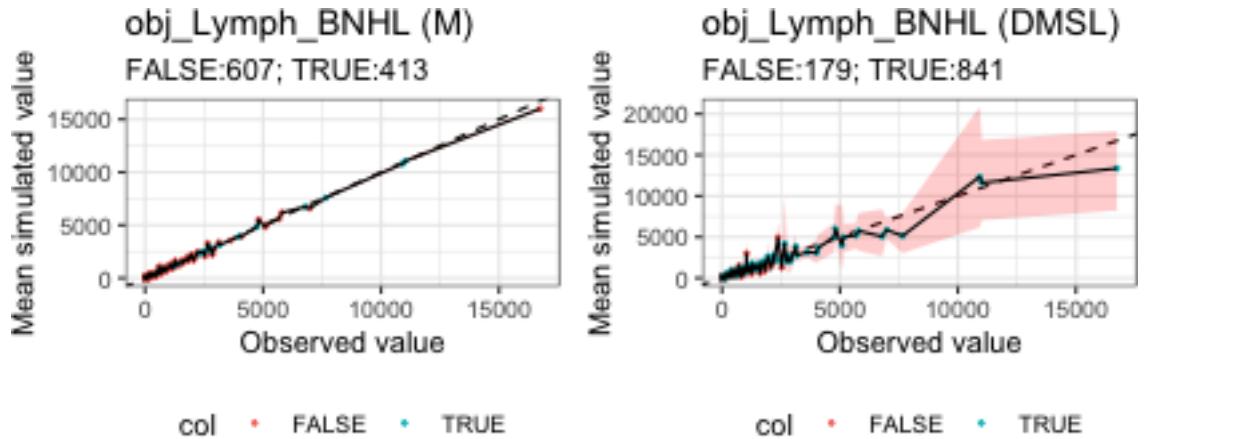
Simulation under inferred data

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
## Warning in mvtnorm::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite
```

Simulation of Lymph-BNHL samples



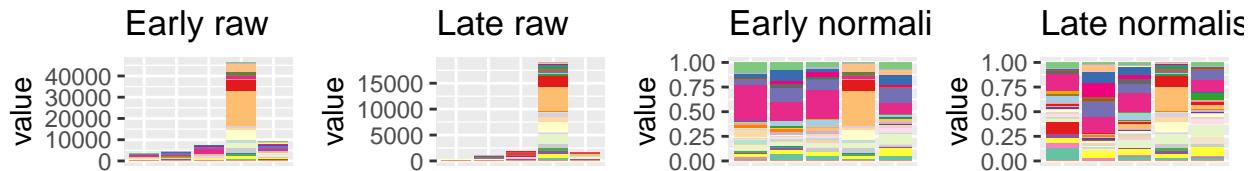
Ranked plot for coverage



Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

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

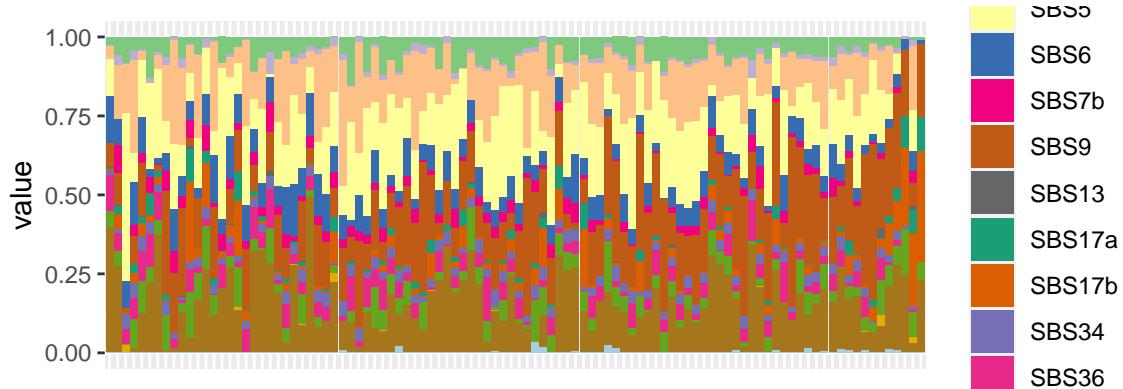


something must have gone wrong here. Dims of Y for mutsigextractor and normal signatures:

```
## [1] 10 53
```

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

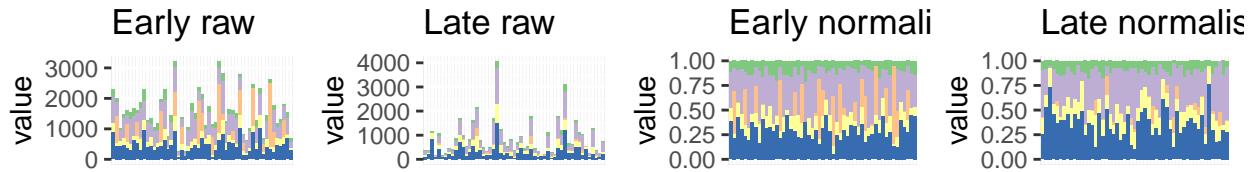
Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.



Lymph-CLL

Barplot and general statistics

```
## [1] 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)
```

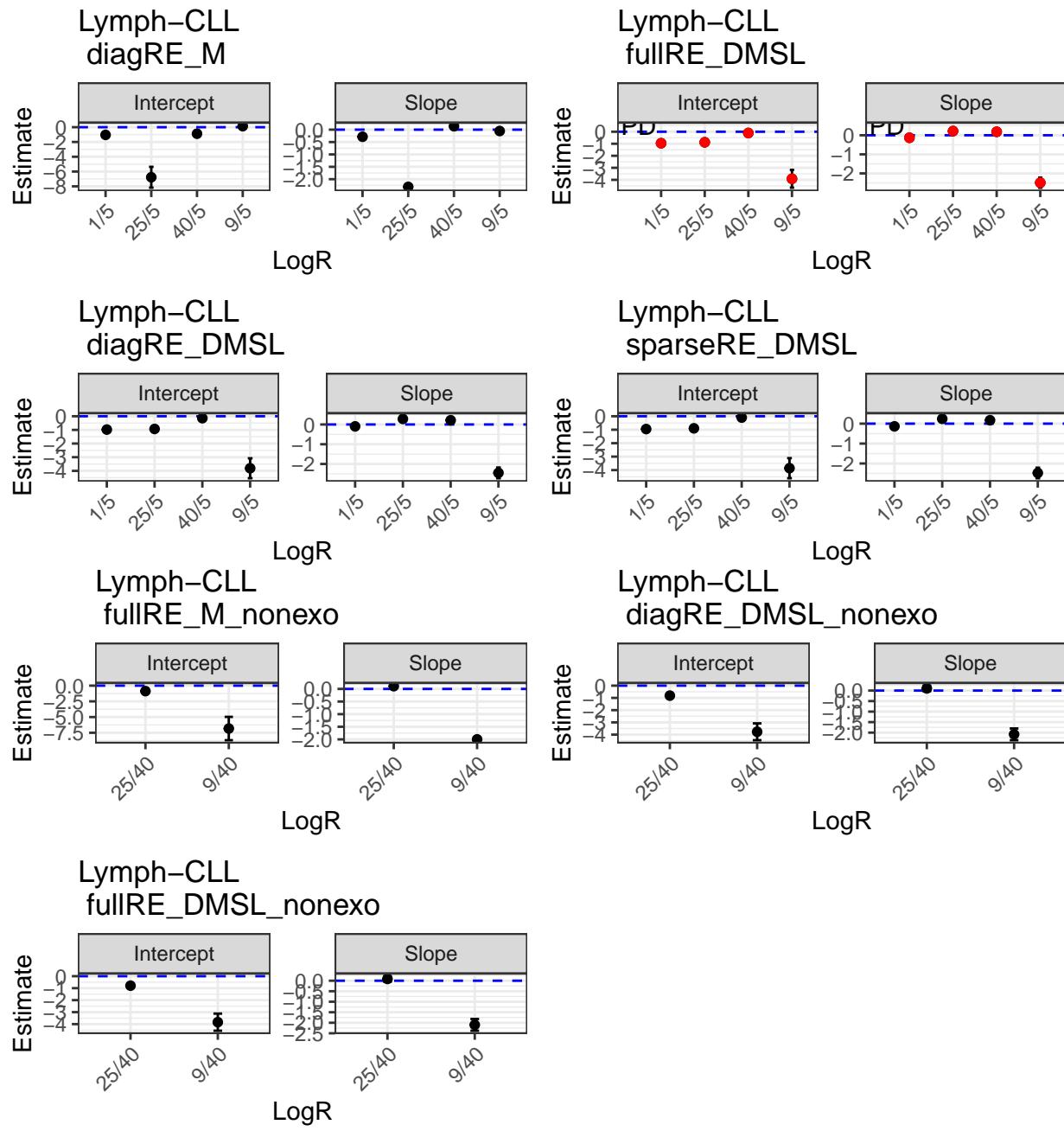
```
##      SBS1      SBS5      SBS9      SBS25      SBS40
## 0.000000000 0.028301887 0.613207547 0.009433962 0.000000000
```

```
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.



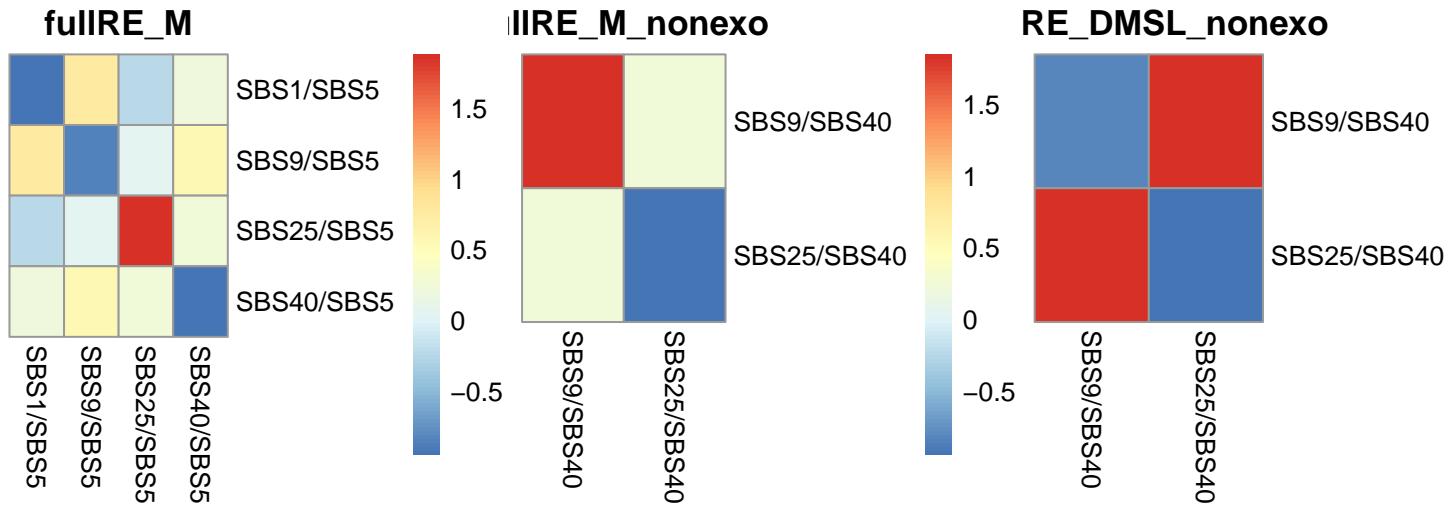
We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of $6.1779312 \times 10^{-14}$.

Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]])$par.fixed, : This function had been incorrect until now (30 july 2021)
```



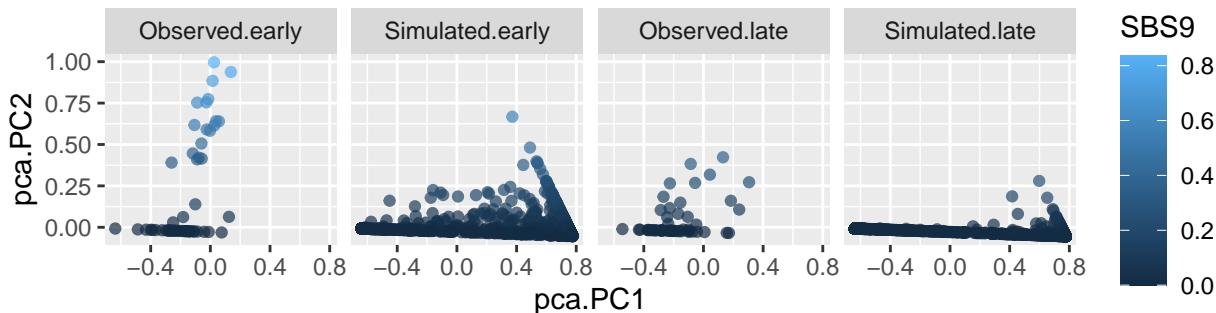
Simulation under inferred data

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)

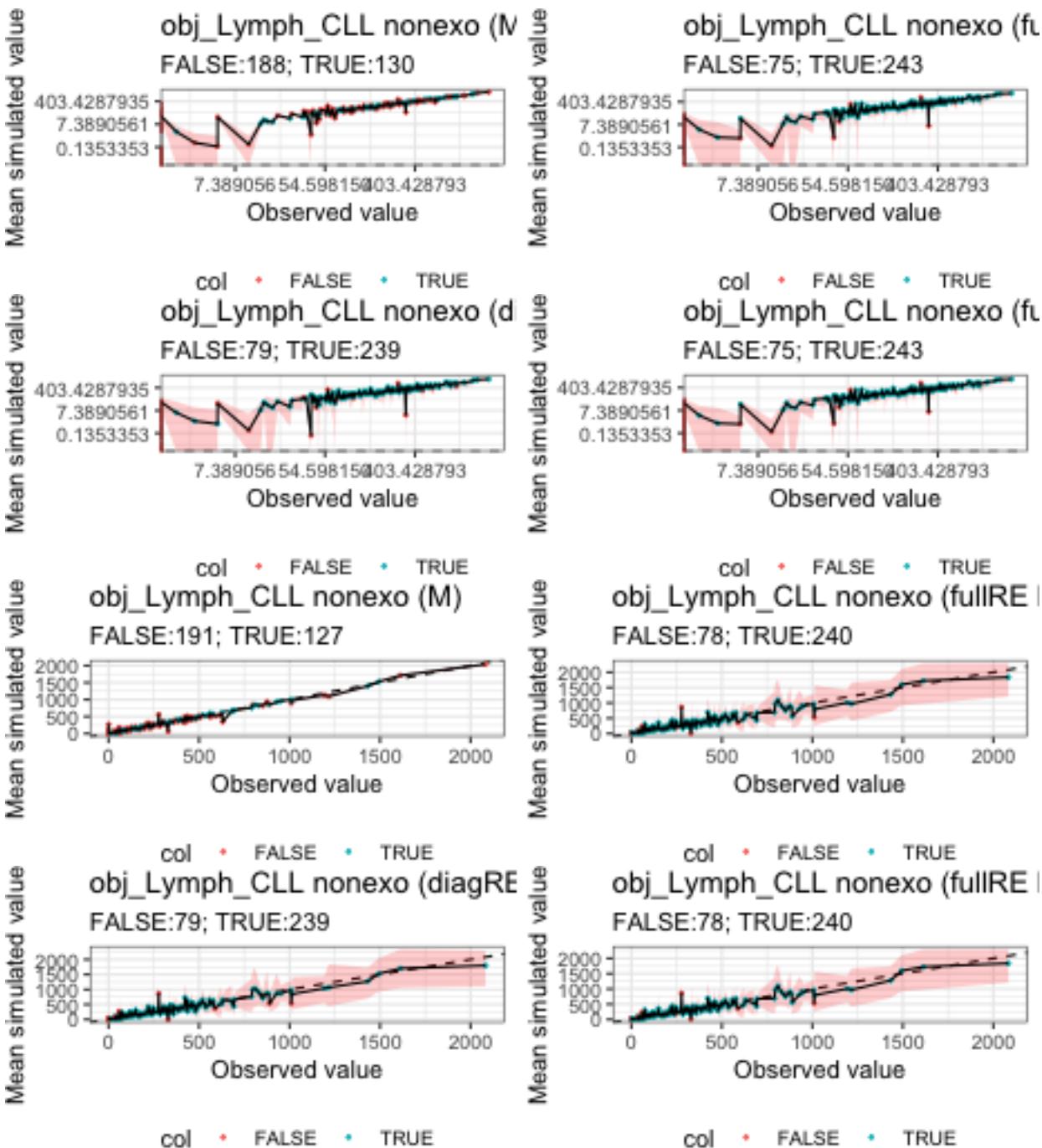
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)

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

Simulation of Lymph–CLL samples



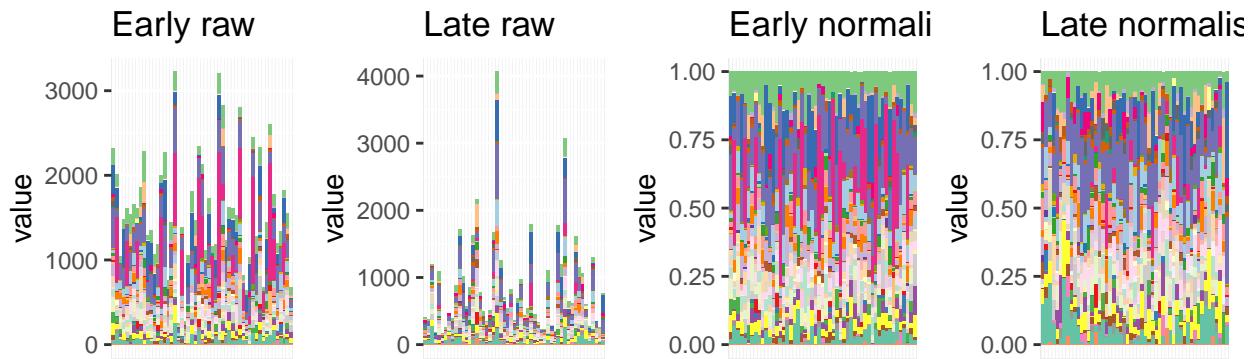
Ranked plot for coverage



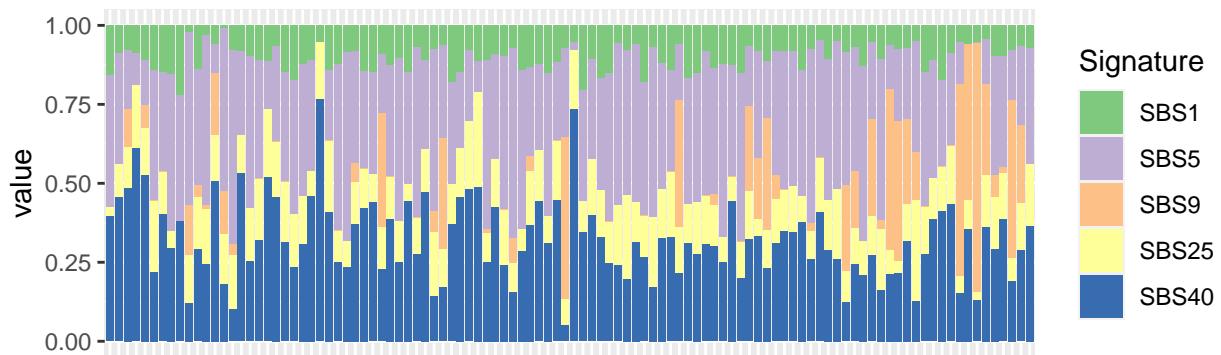
Signatures from mutSigExtractor

These are the signatures from mutSigExtractor:

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



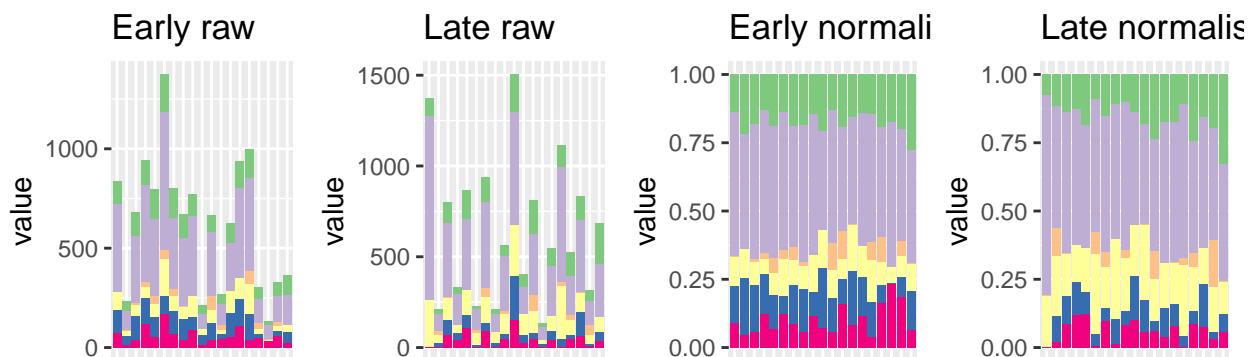
Exposures sorted by increasing number of mutations: SBS9 and SBS25 seem to be somewhat associated with samples with a high number of mutations.



Myeloid-MPN

Barplot and general statistics

```
## [1] 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_MPNS$Y == 0) / nrow(obj_Myeloid_MPNS$Y)
```

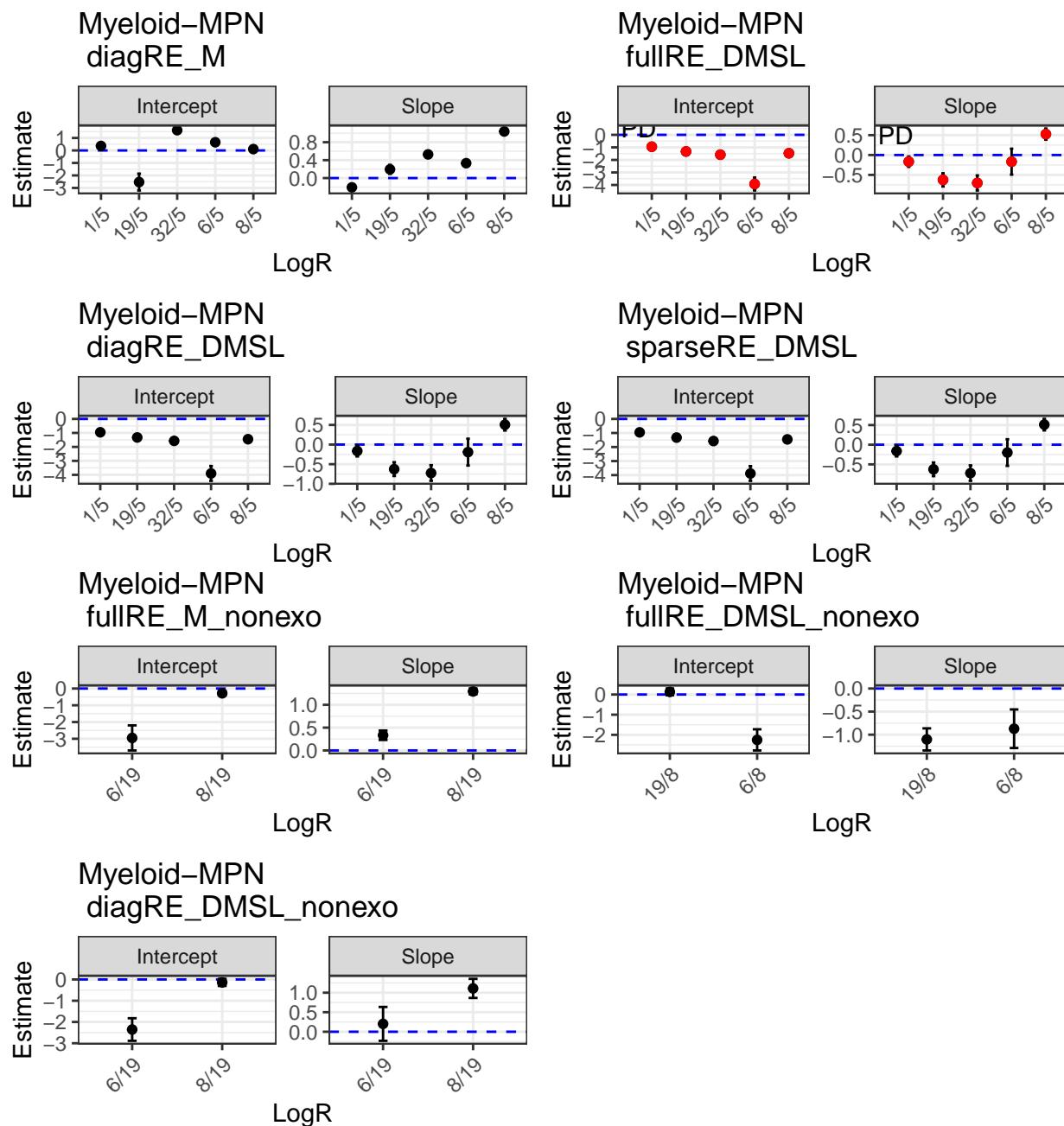
```
#> SBS1      SBS5      SBS6      SBS8      SBS19     SBS32
#> 0.00000000 0.00000000 0.50000000 0.00000000 0.05263158 0.05263158
```

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

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

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



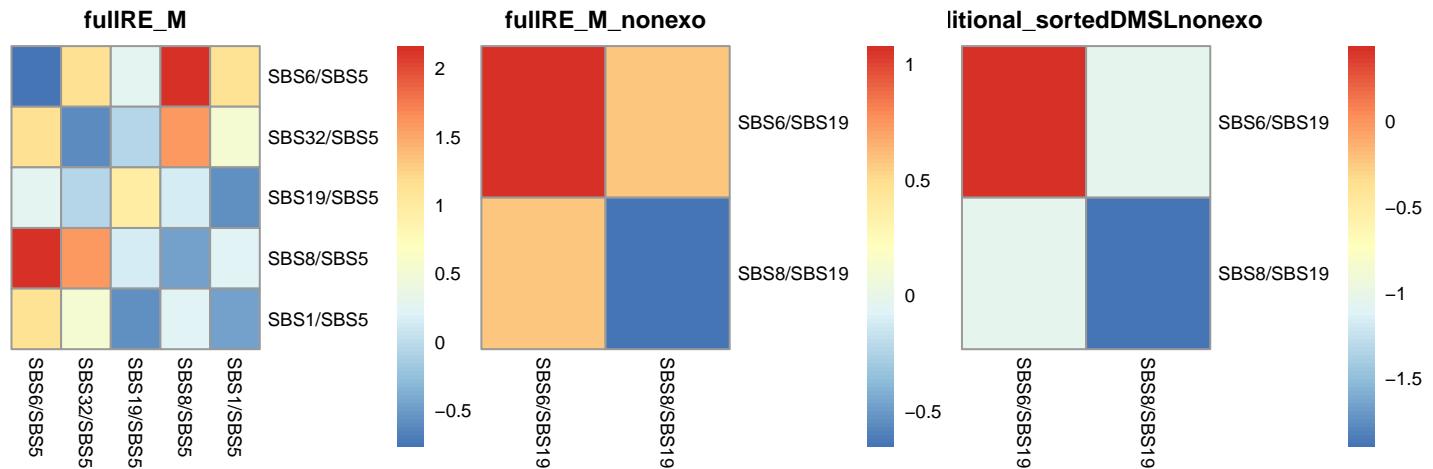
Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
```

```
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```



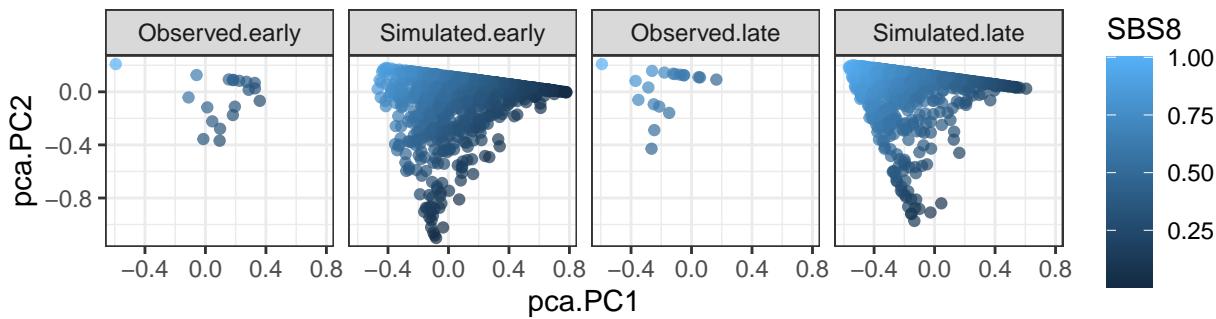
Simulation under inferred data

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
```

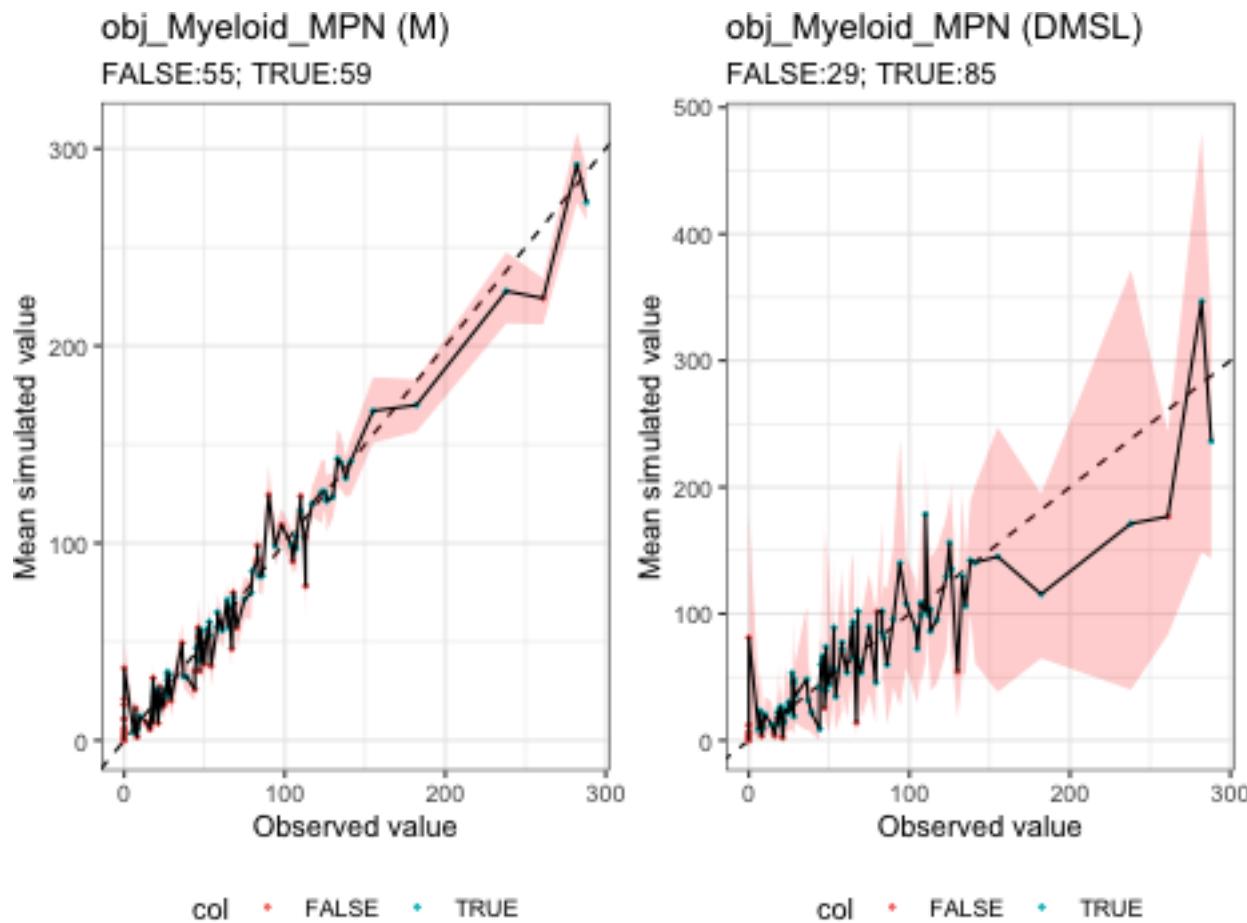
```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

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

Simulation of Myeloid–MPN samples



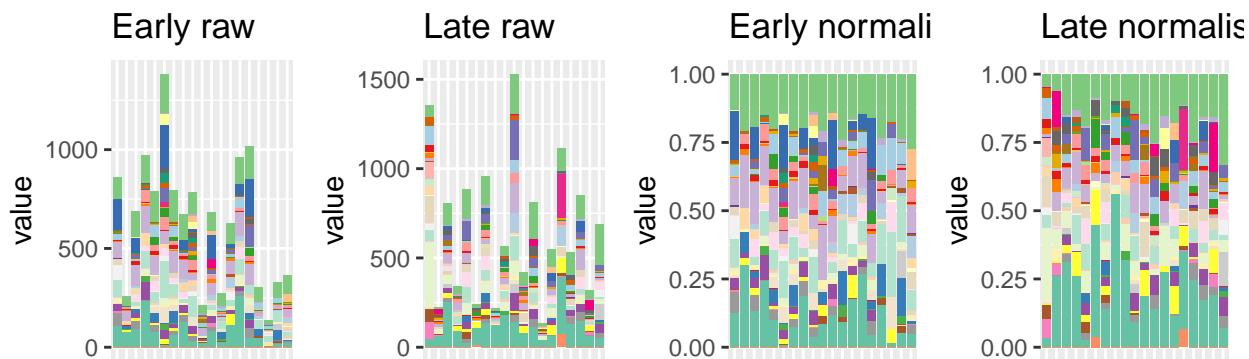
Ranked plot for coverage



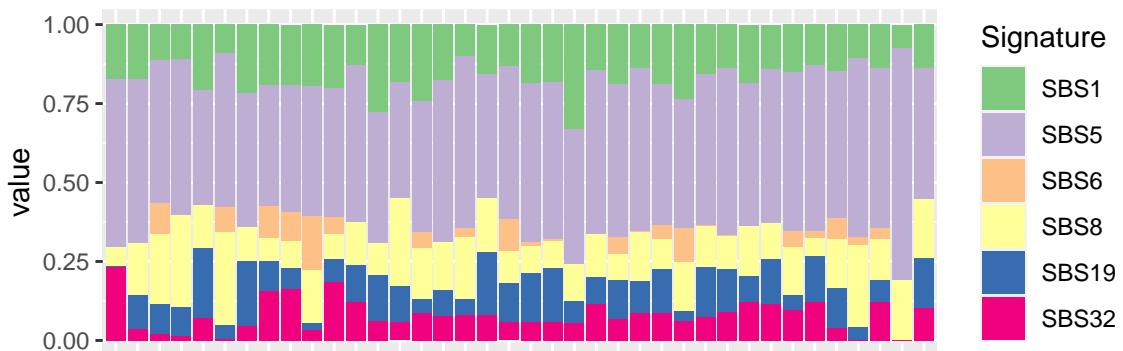
Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

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



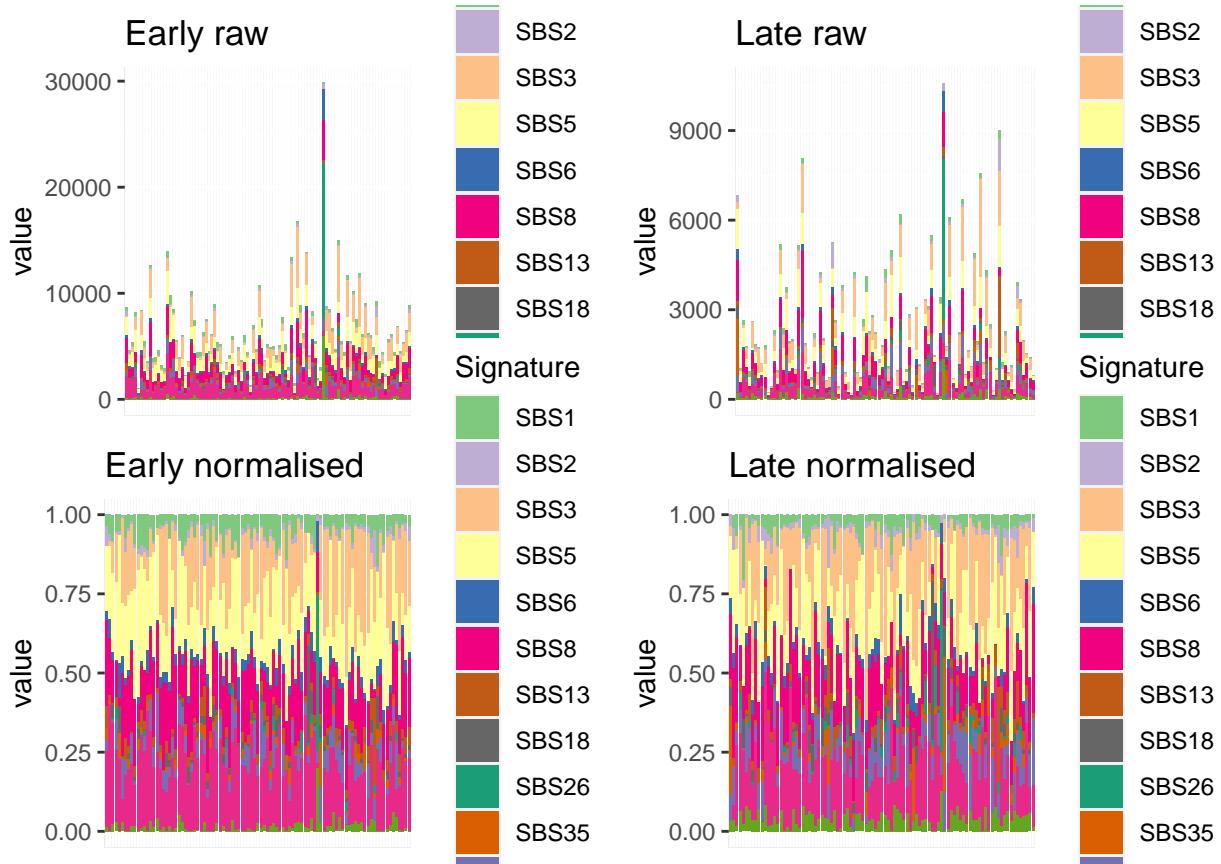
Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.



Ovary-AdenoCA

Barplot and general statistics

```
## [1] 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.

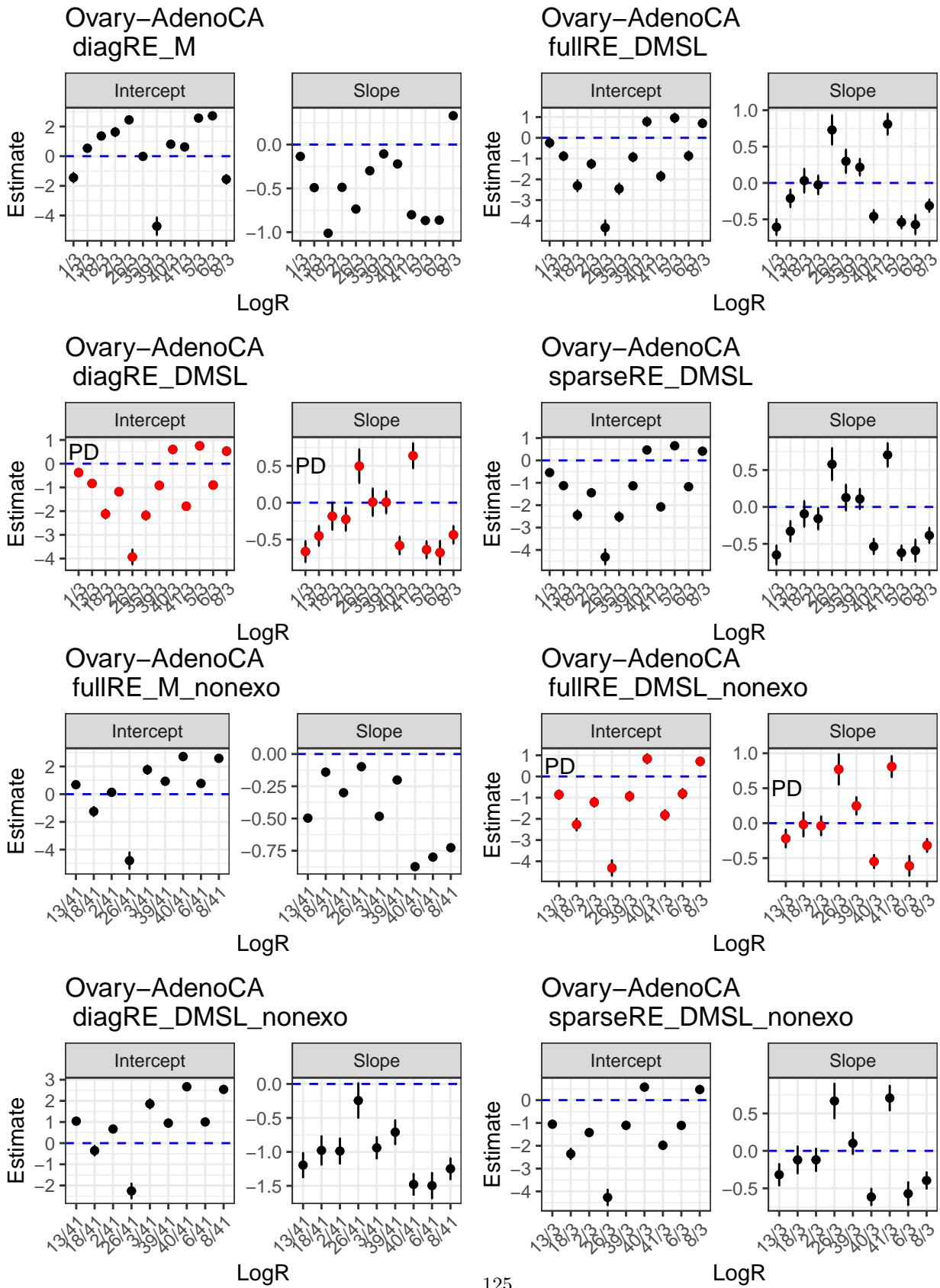
```
colSums(obj_Ovary_AdenoCA$Y == 0) / nrow(obj_Ovary_AdenoCA$Y)

##      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

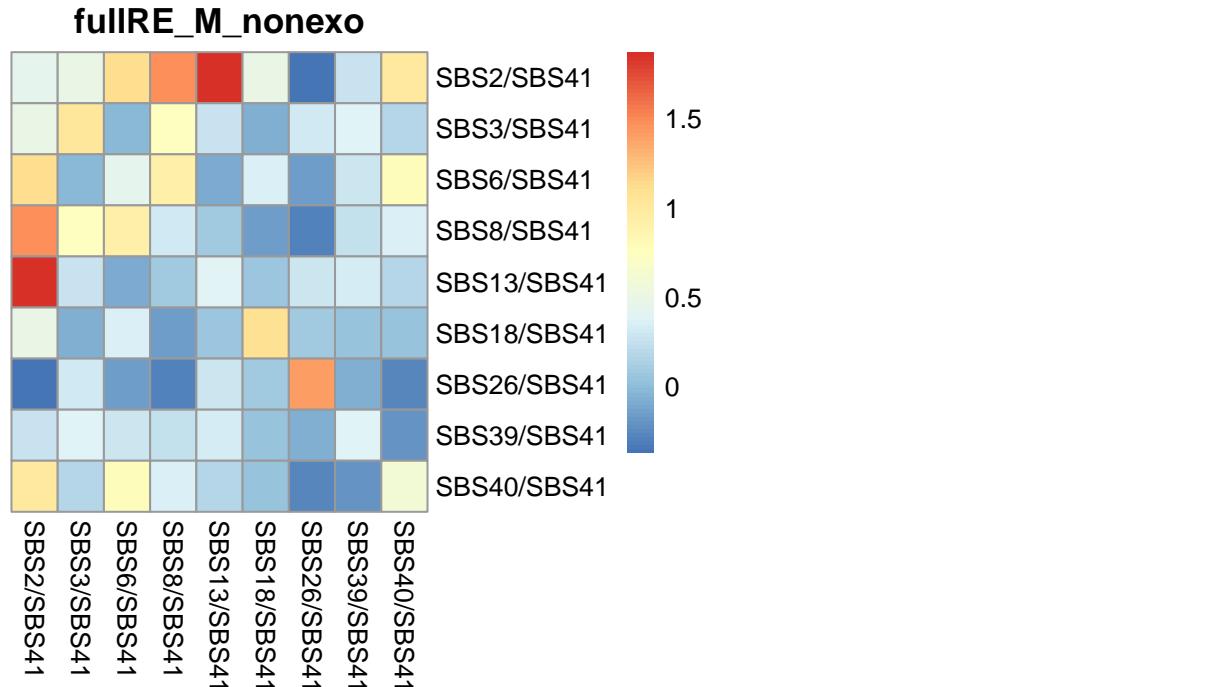


We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of $2.6852565 \times 10^{-28}$.

Covariance matrices

Keep in mind that fullRE DMSL nonexo has not converged.

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```



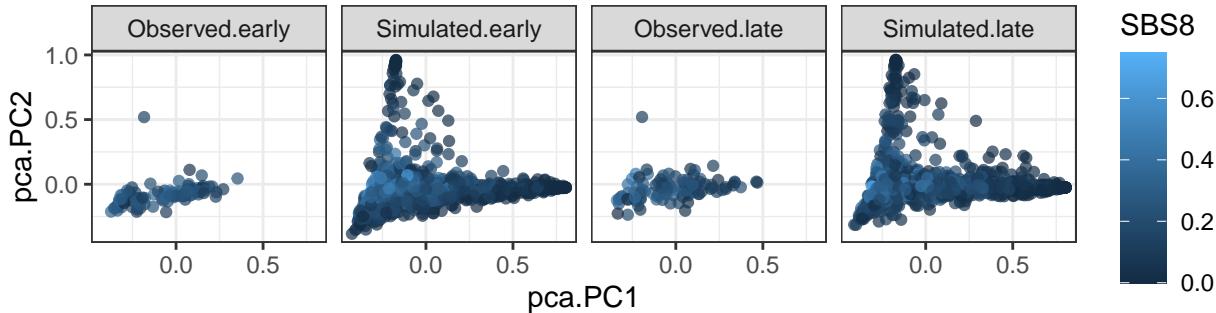
Simulation under inferred data

Using diagRE DMSL nonexo.

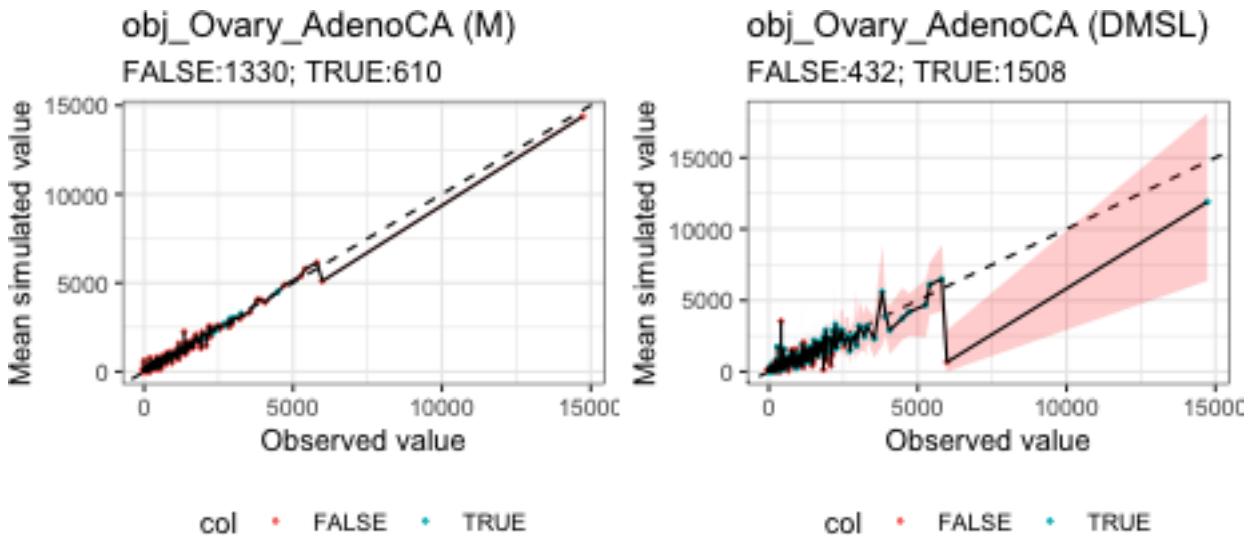
```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

Simulation of Ovary–AdenoCA samples



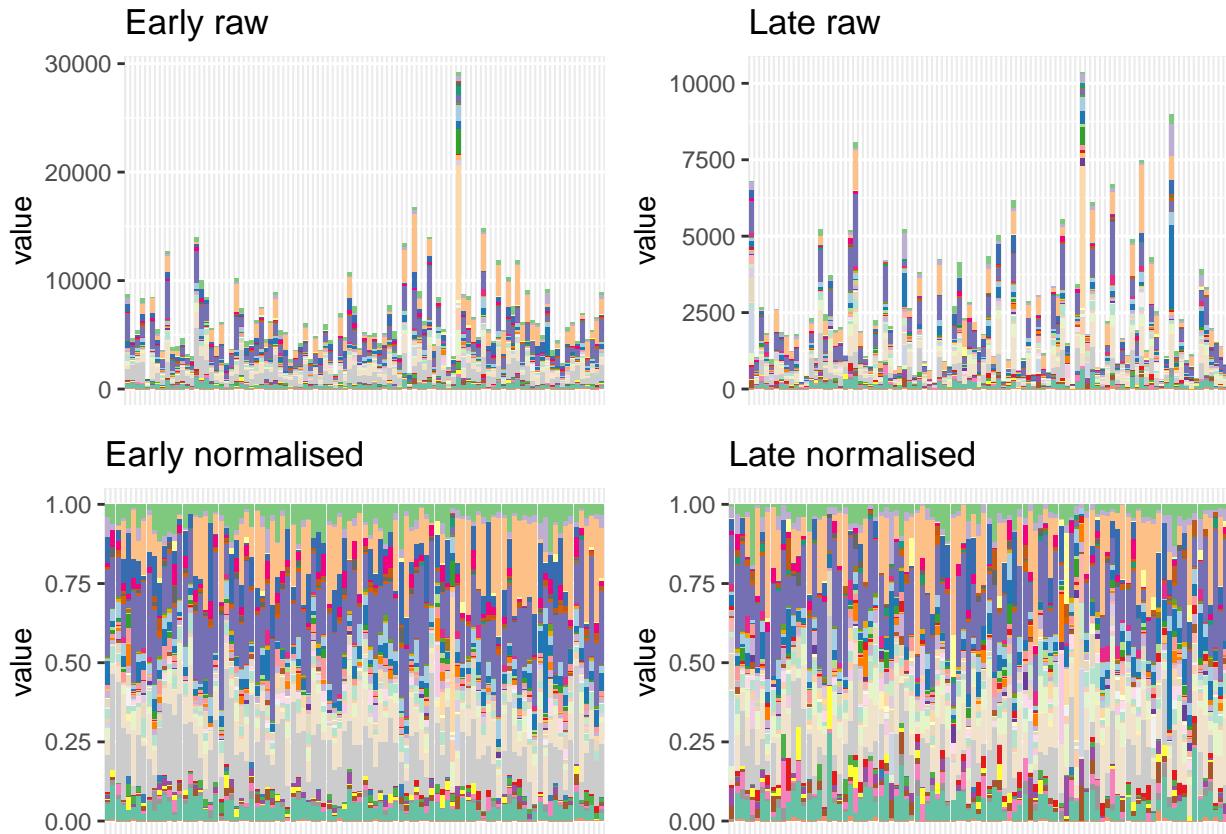
Ranked plot for coverage



Signatures from mutSigExtractor

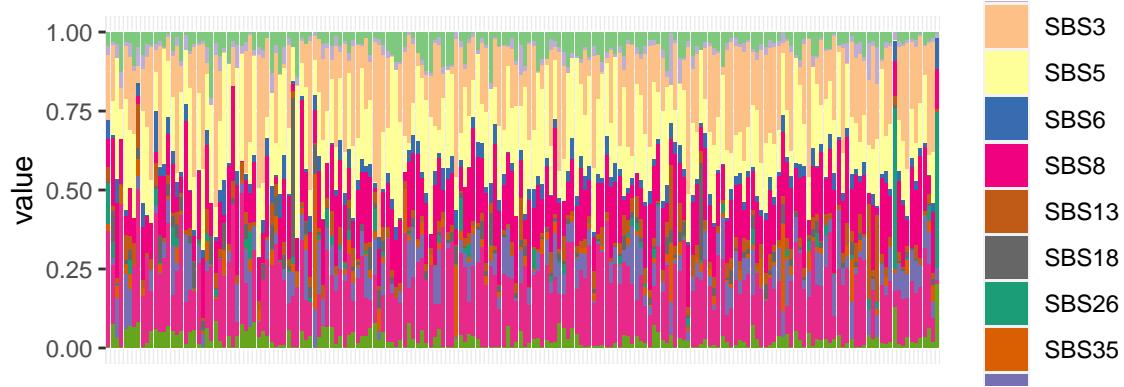
The signatures from mutSigExtractor are as follows:

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



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

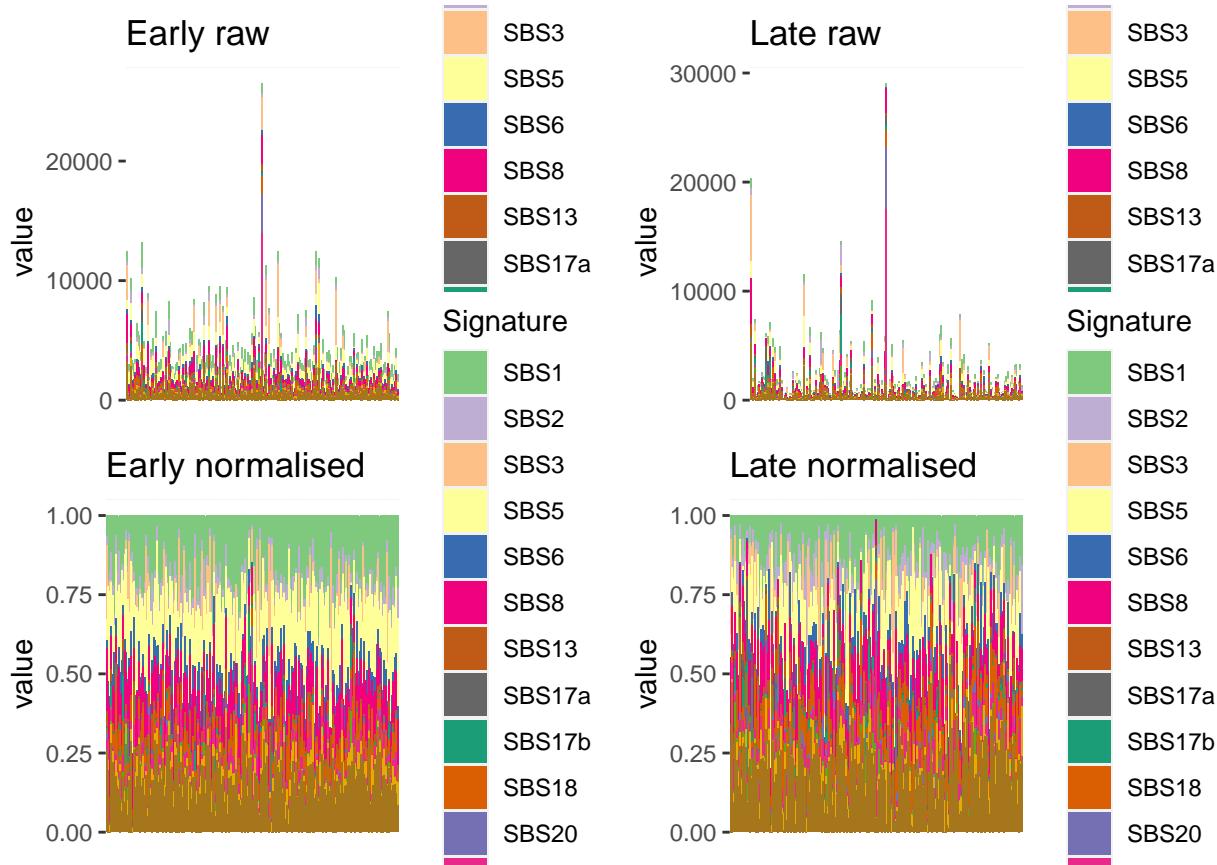
number of mutations.



Panc-AdenoCA

Barplot and general statistics

```
## [1] 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.

| | 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

```

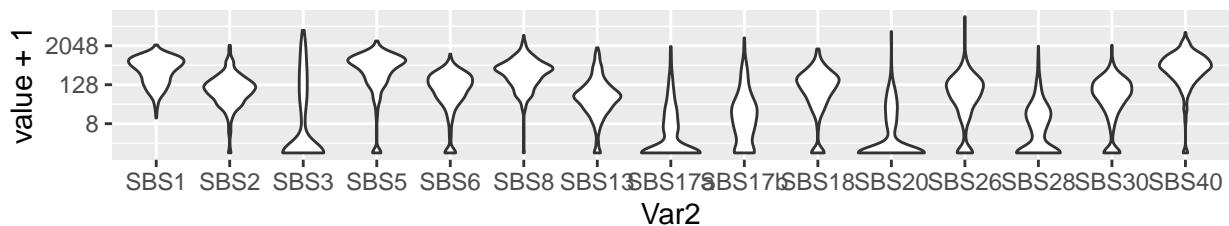
```
colSums(obj_Panc_AdenoCA$Y) / sum(obj_Panc_AdenoCA$Y)
```

```

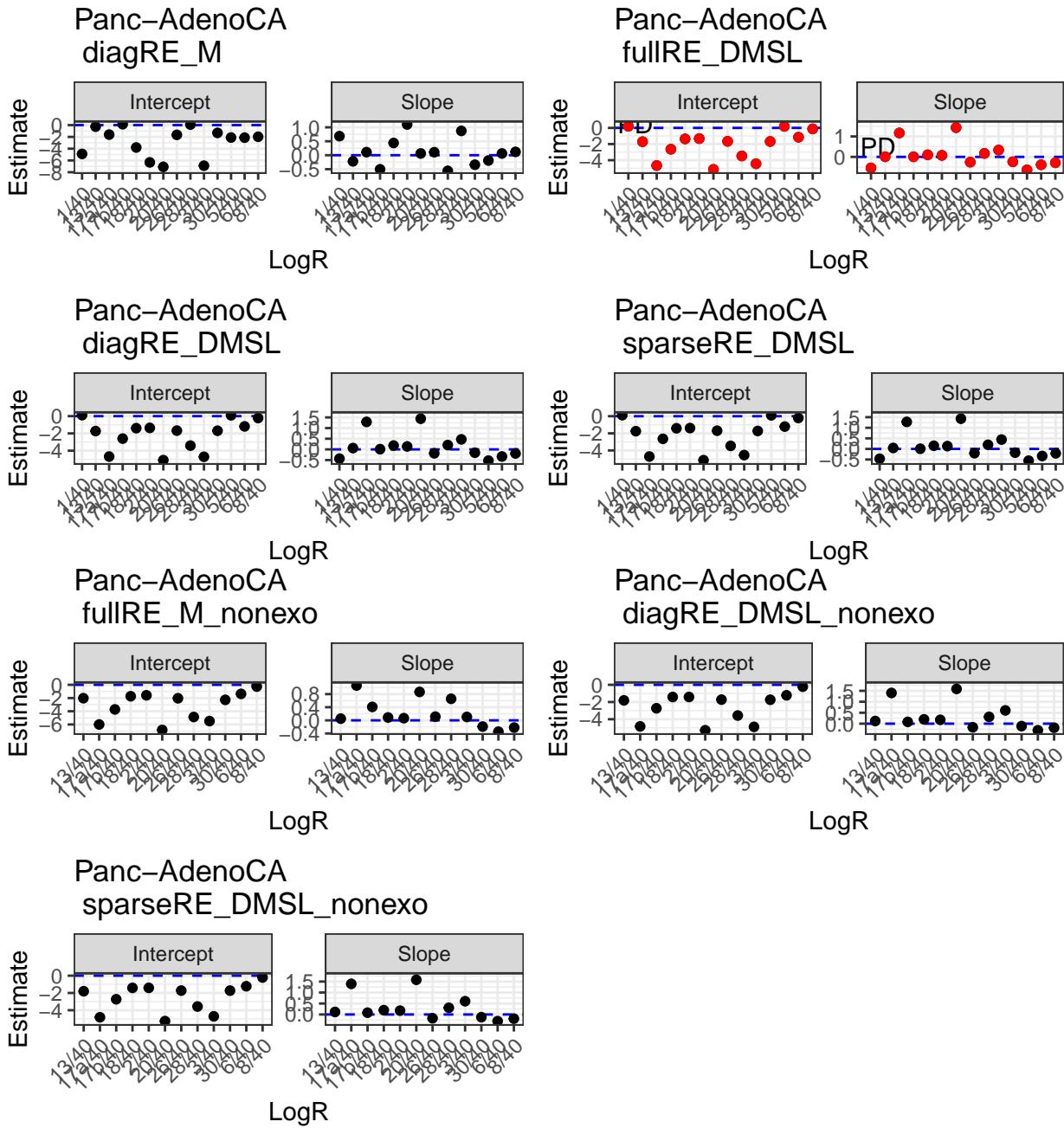
##      SBS1      SBS2      SBS3      SBS5      SBS6      SBS8
## 0.146510755 0.044043854 0.068370611 0.164694624 0.043276473 0.126954041
##      SBS13     SBS17a     SBS17b     SBS18     SBS20     SBS26
## 0.035397768 0.009365890 0.021818955 0.052439007 0.011446261 0.054377412
##      SBS28     SBS30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

```

From the violin plot, none seem too problematic.



Betas



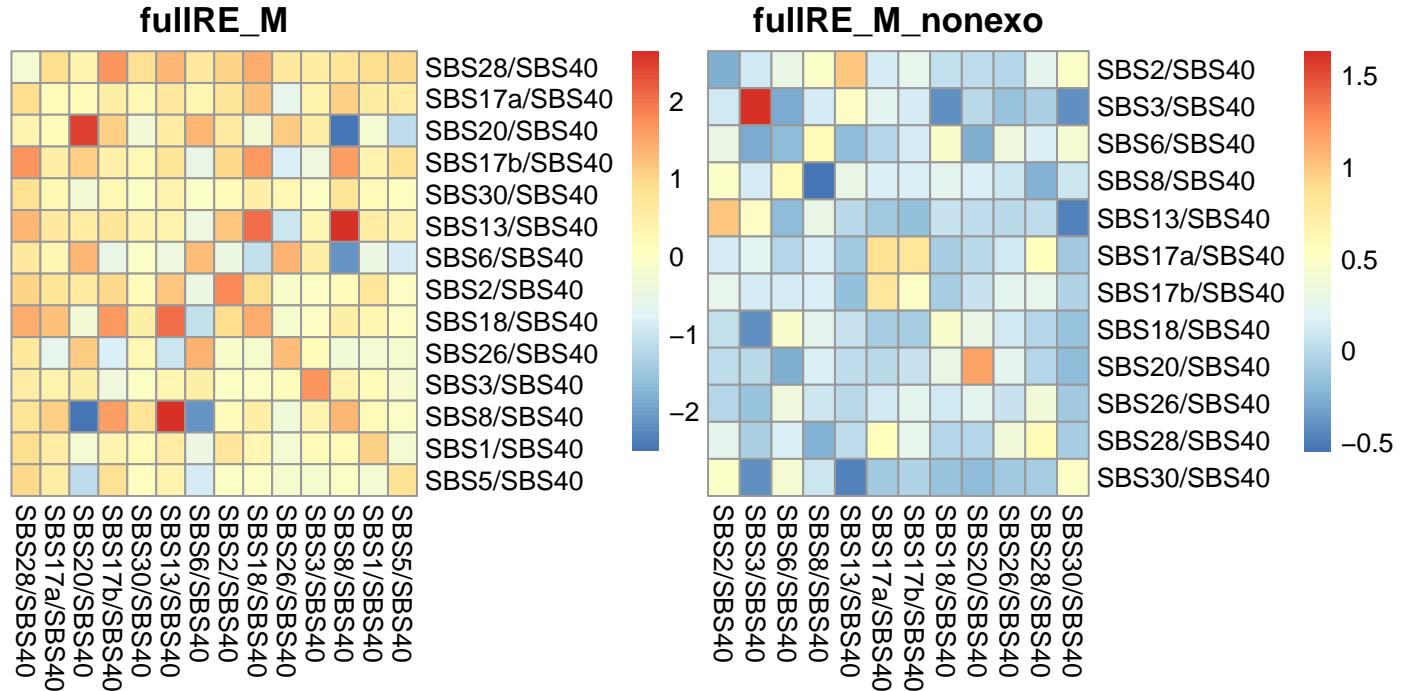
We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of

$6.8710408 \times 10^{-46}$.

Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

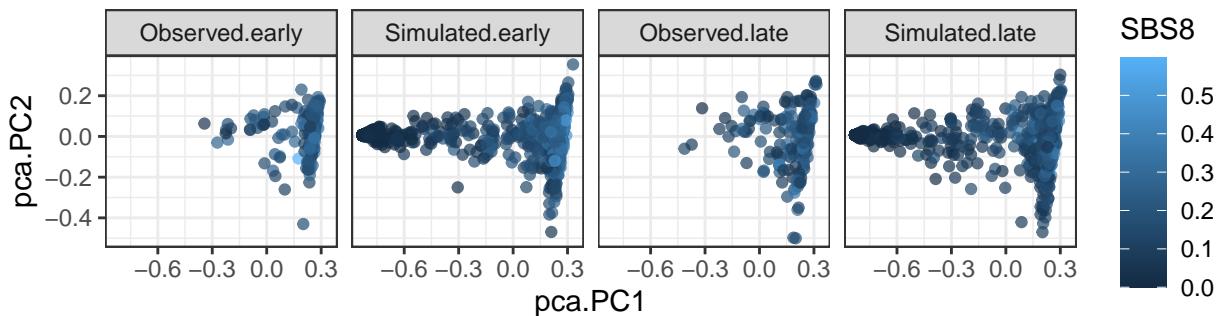


Simulation under inferred data

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

Simulation of Panc–AdenoCA samples



Multinomial:

```

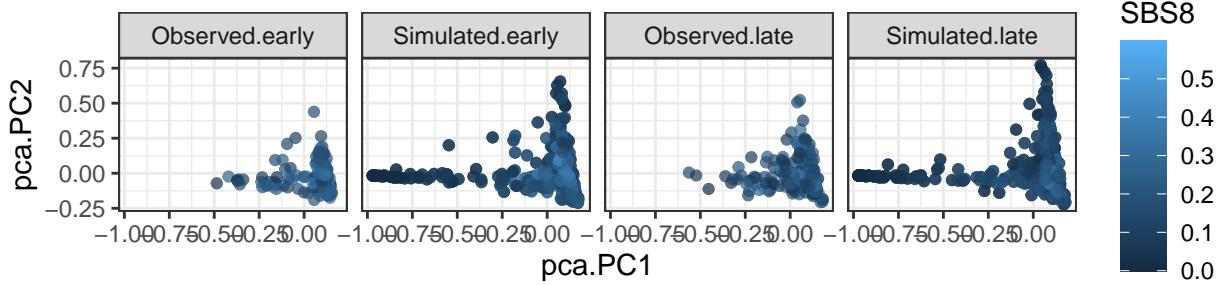
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)

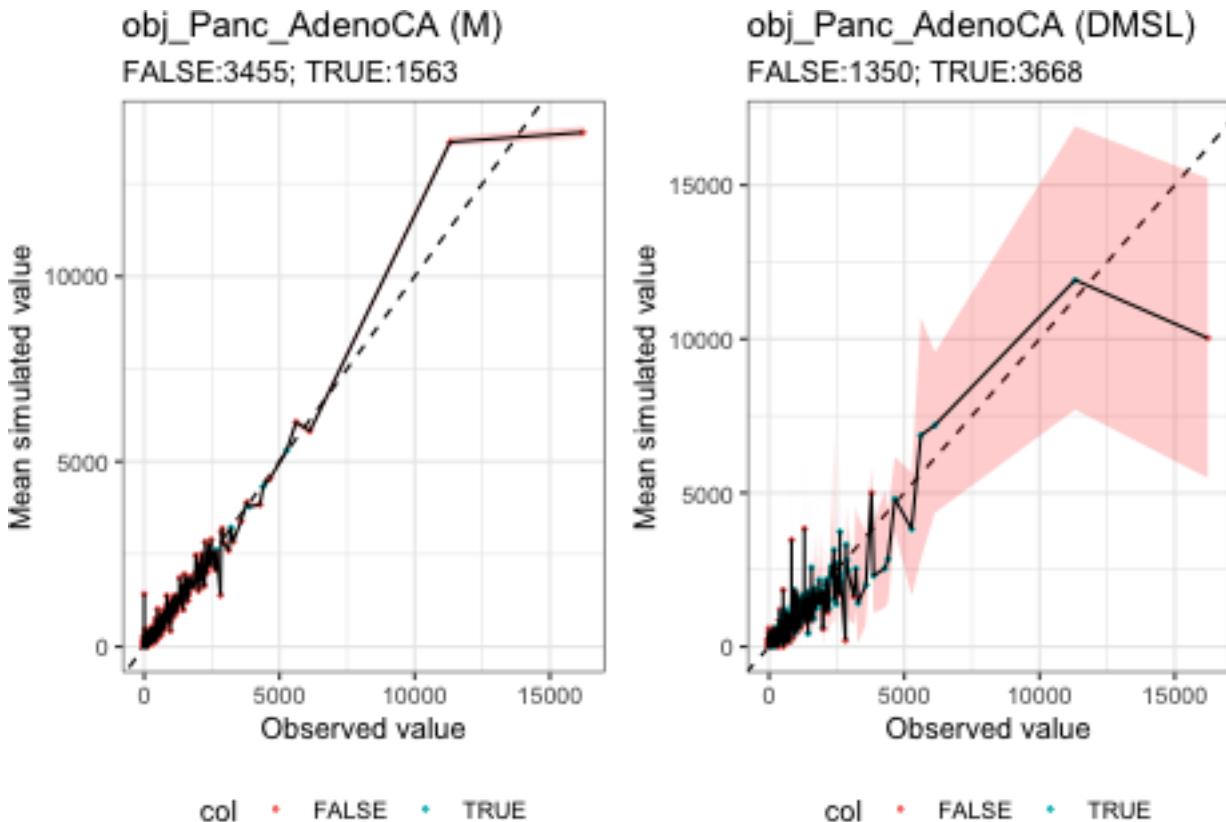
## Warning in mvtnorm:::rmvnorm(n = n_sim, mean = rep(0, dmin1), sigma = cov_mat):
## sigma is numerically not positive semidefinite

```

Simulation of Panc–AdenoCA samples Using multinomial



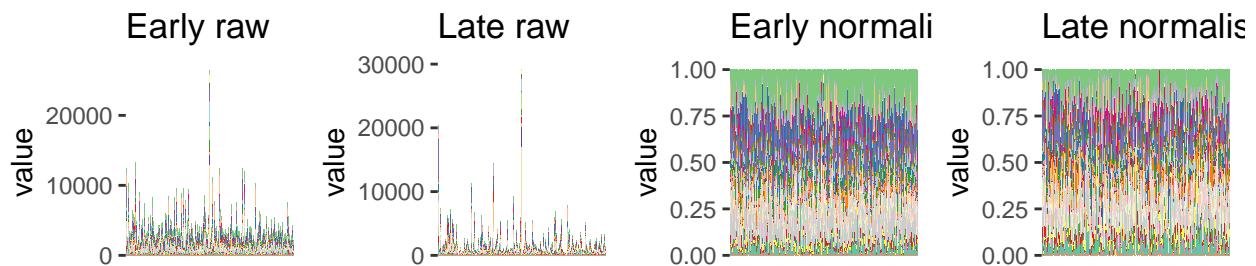
Ranked plot for coverage



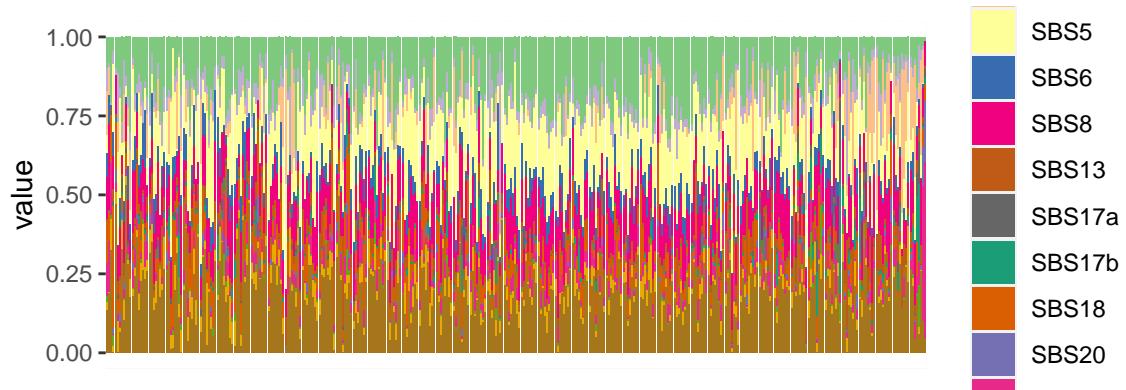
Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

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



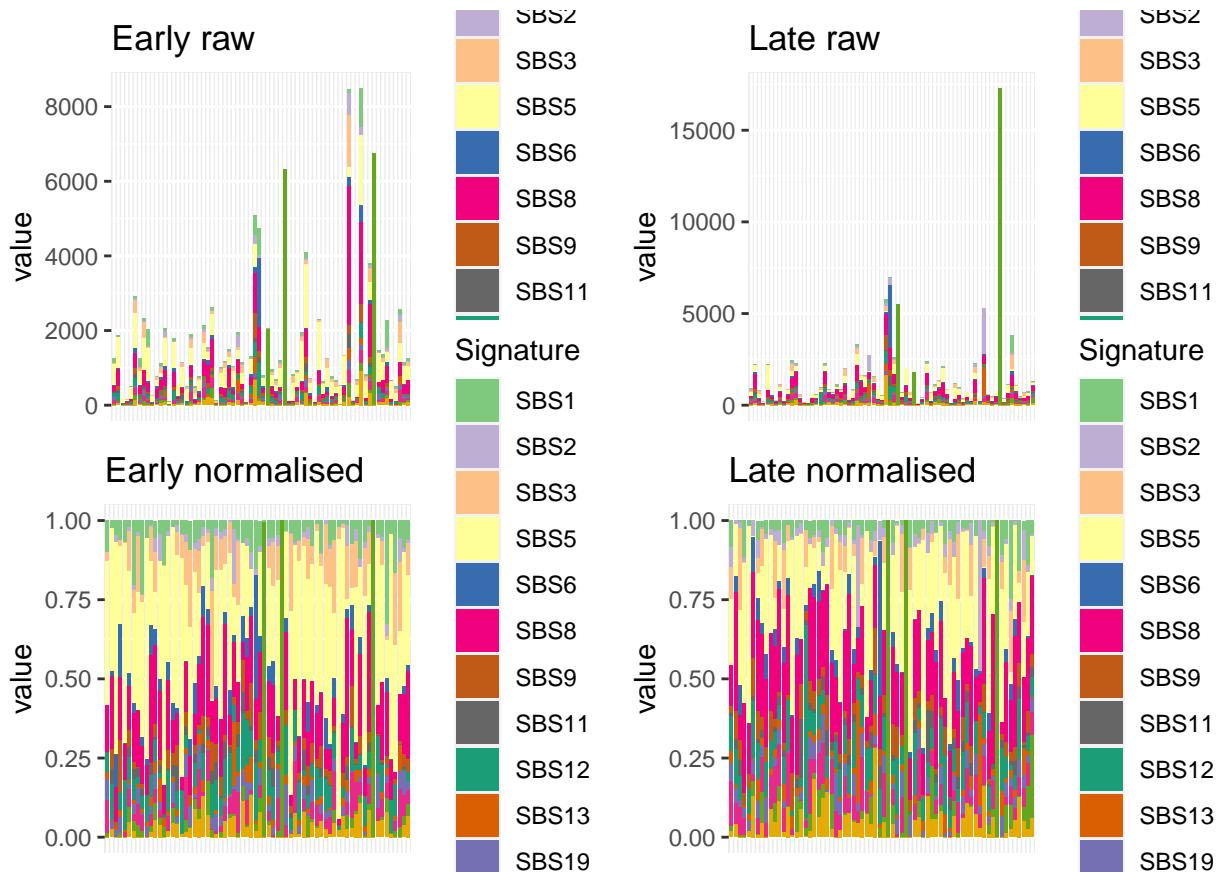
Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.



Panc-Endocrine

Barplot and general statistics

```
## [1] 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.

| | | 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

```

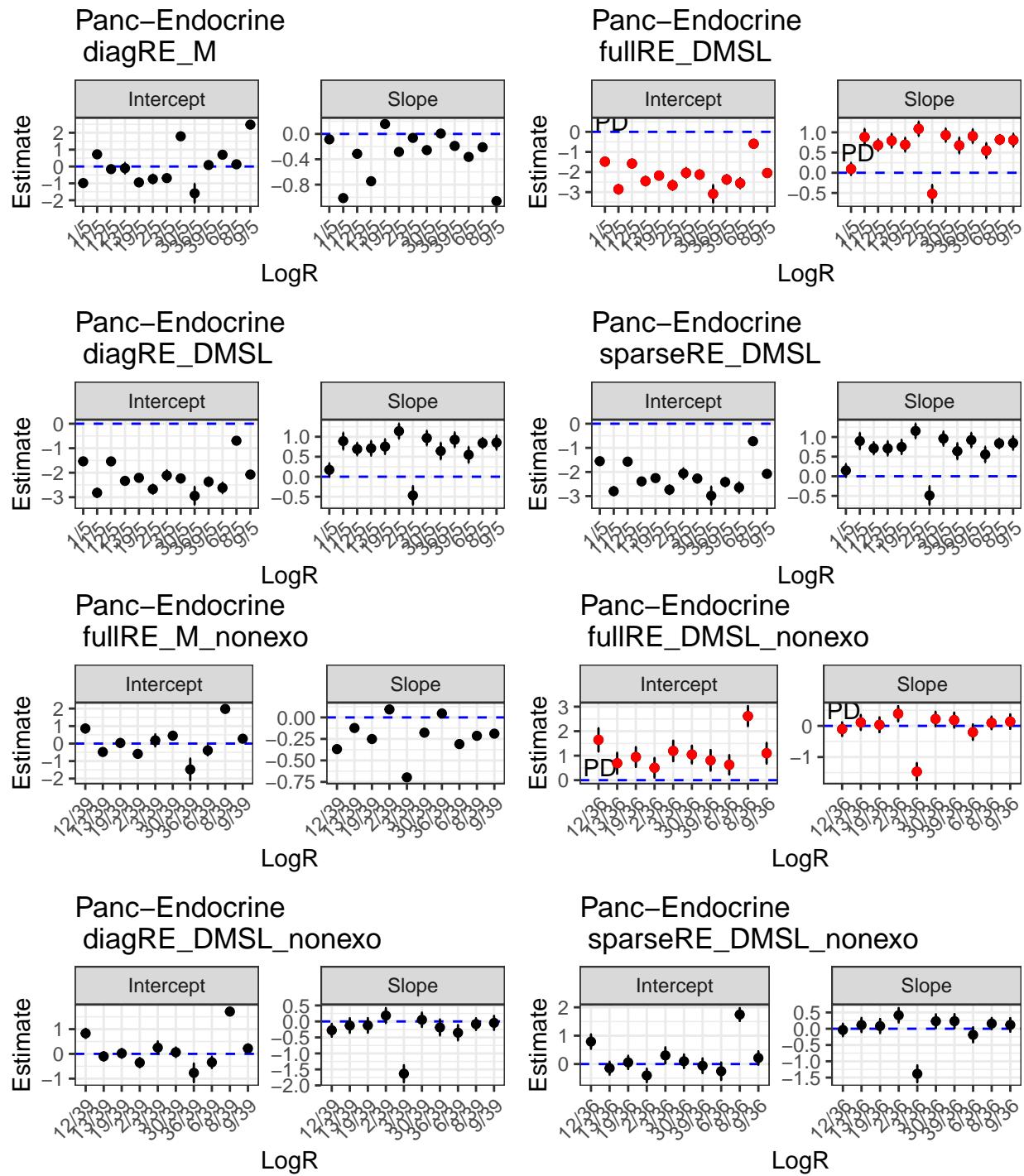
```
colSums(obj_Panc_Endocrine$Y) / sum(obj_Panc_Endocrine$Y)
```

```

##      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

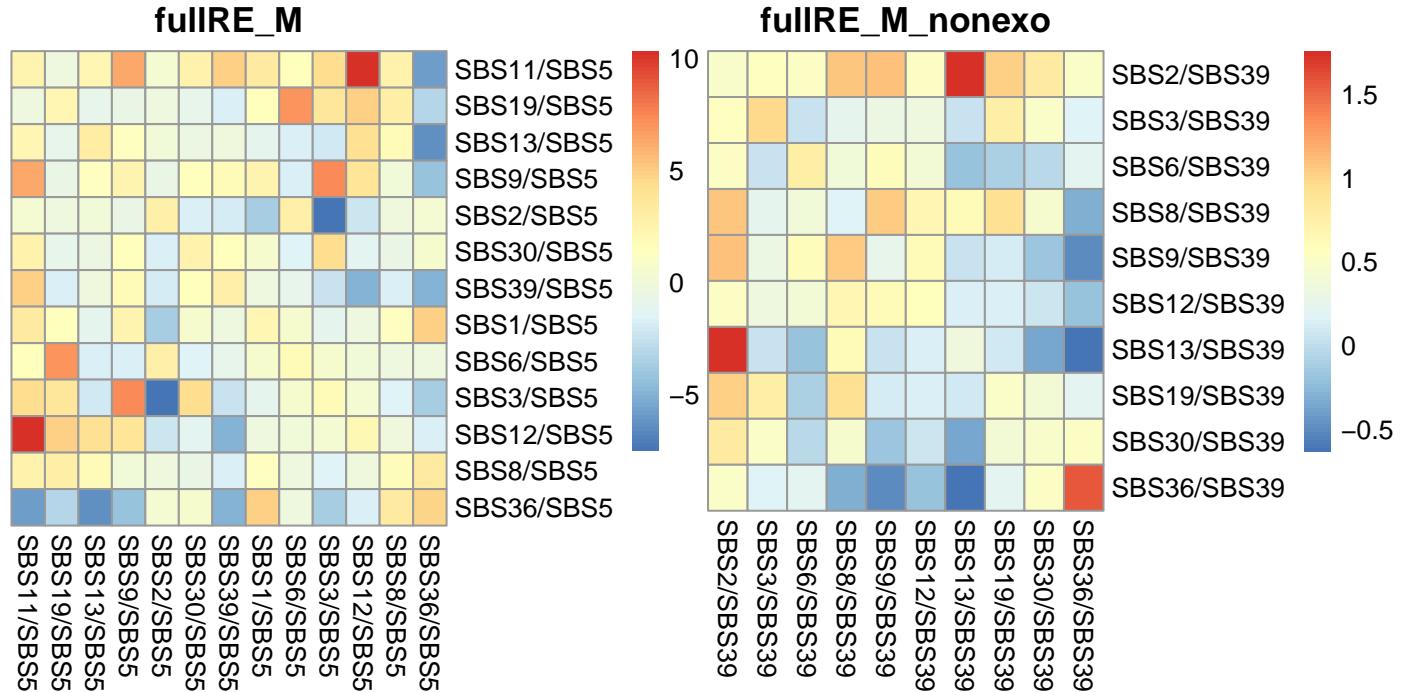


We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of 1.9645842×10^{-9} .

Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

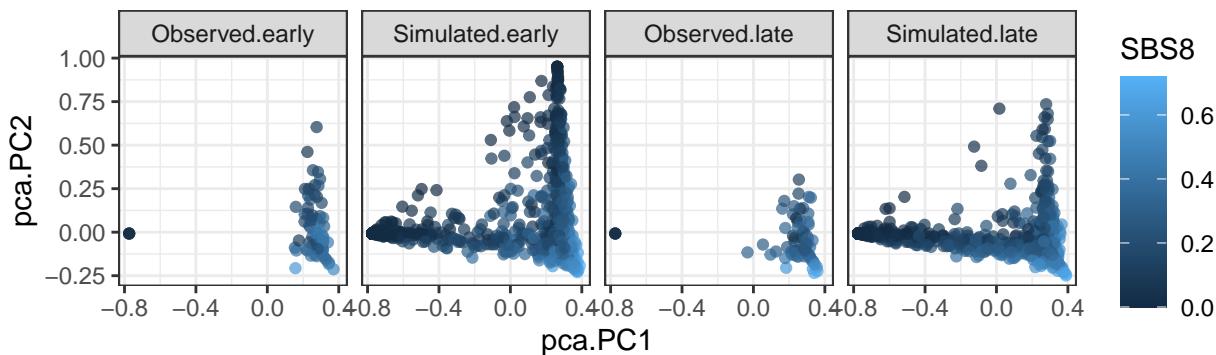


Simulation under inferred data

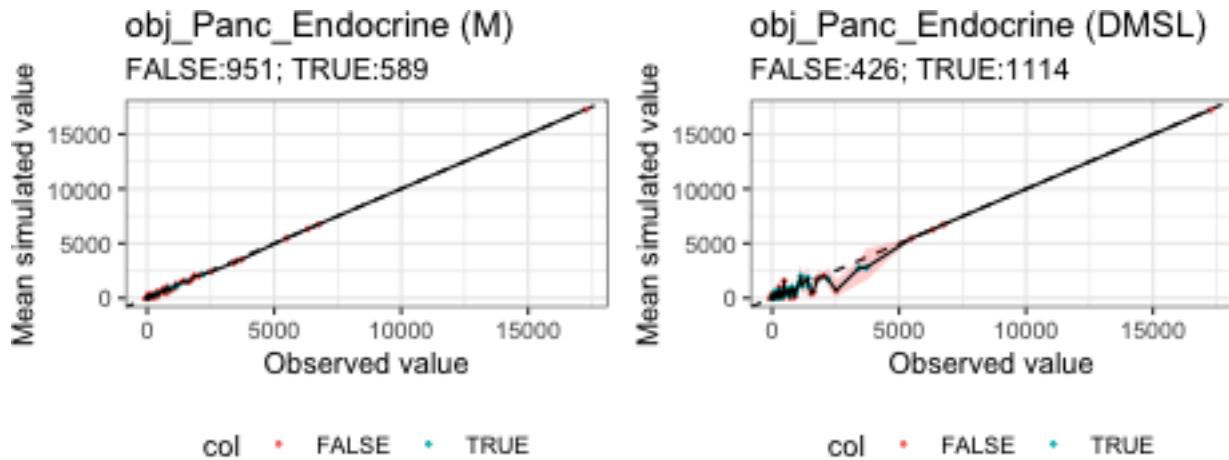
```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

Simulation of Panc–Endocrine samples



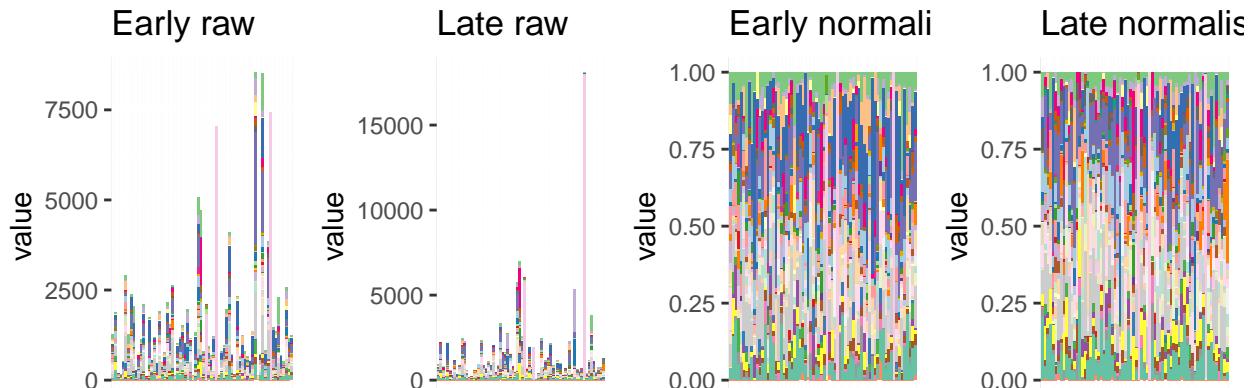
Ranked plot for coverage



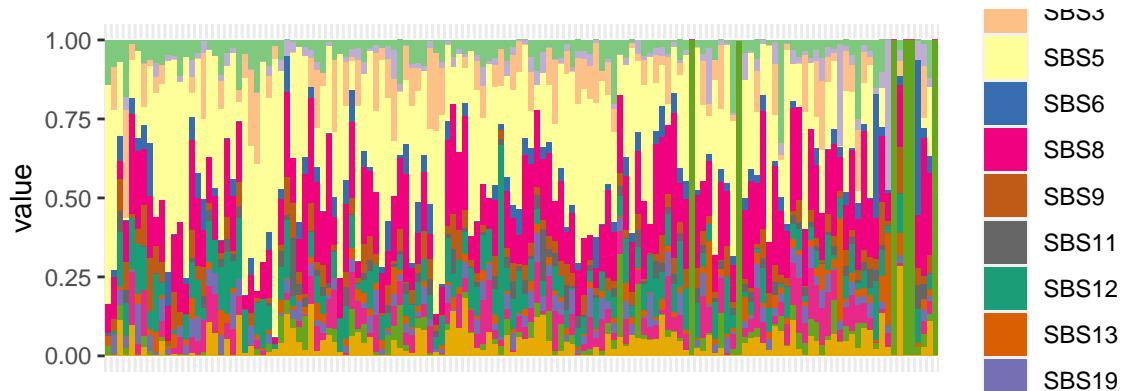
Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

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



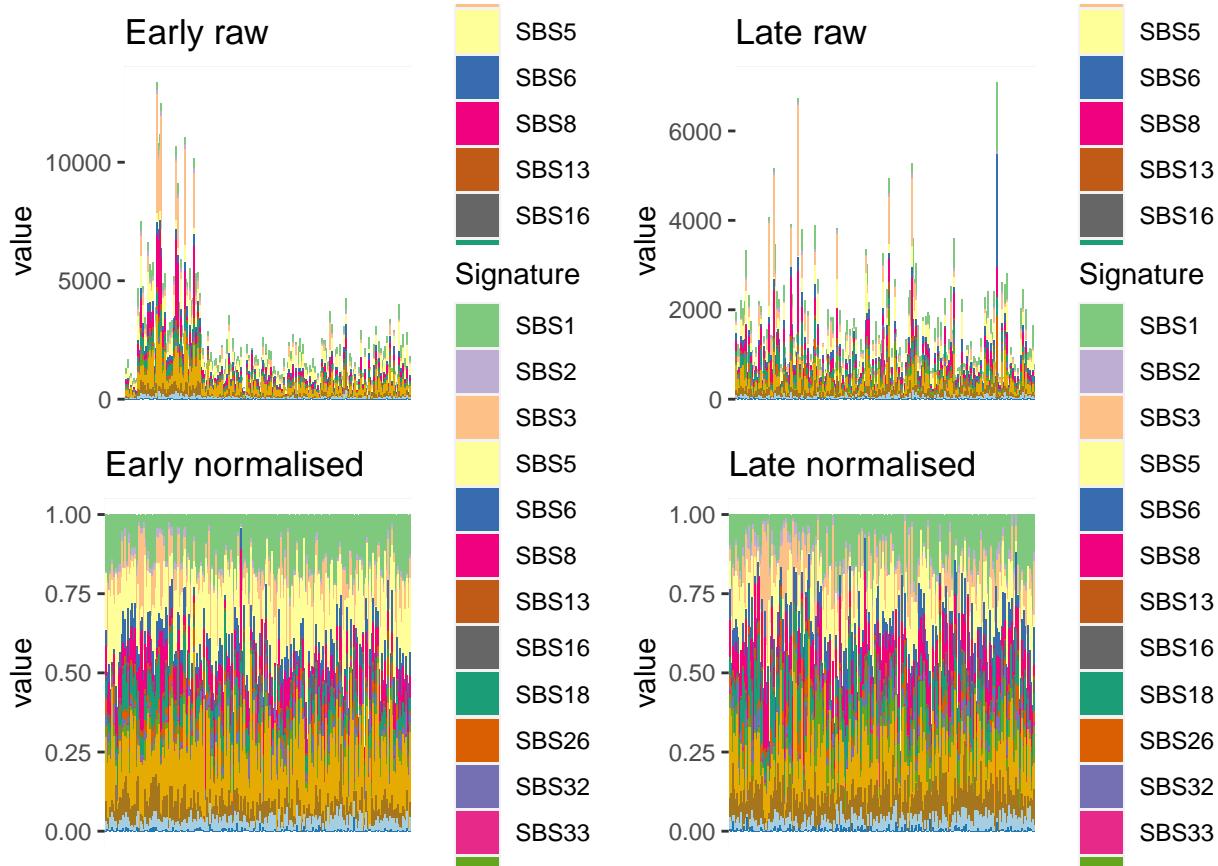
Exposures sorted by increasing number of mutations: there is a trend with one signature only being present, and in very large amounts, in hypermutated samples.



Prost-AdenoCA

Barplot and general statistics

```
## [1] 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

```

```

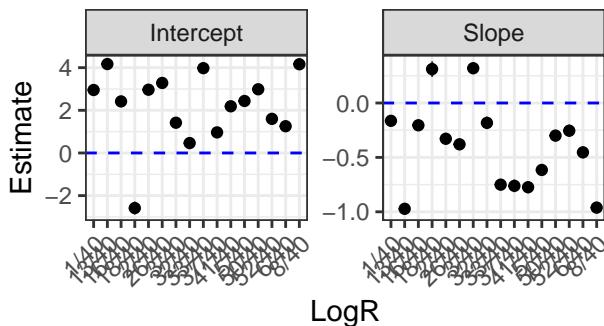
colSums(obj_Prost_AdenoCA$Y) / sum(obj_Prost_AdenoCA$Y)

##      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

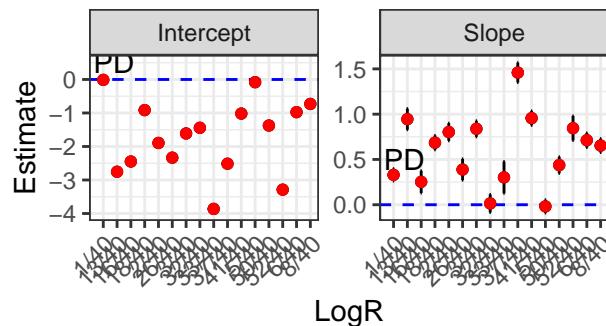
```

Betas

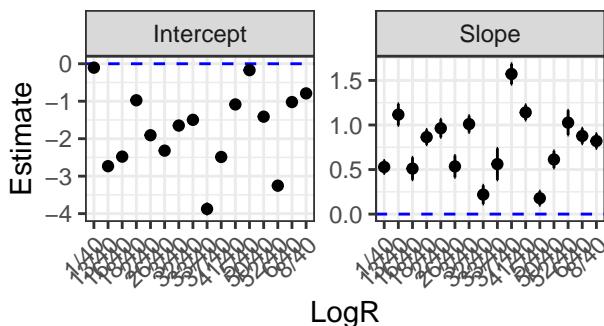
Prost-AdenoCA
diagRE_M



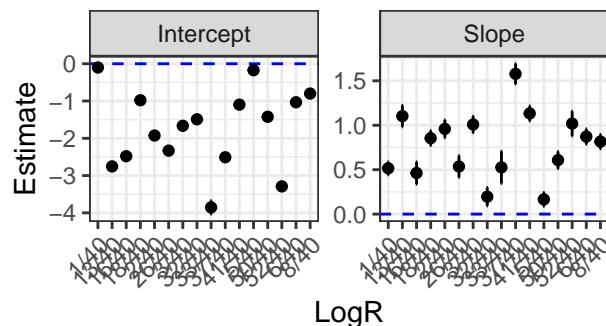
Prost-AdenoCA
fullRE_DMSL



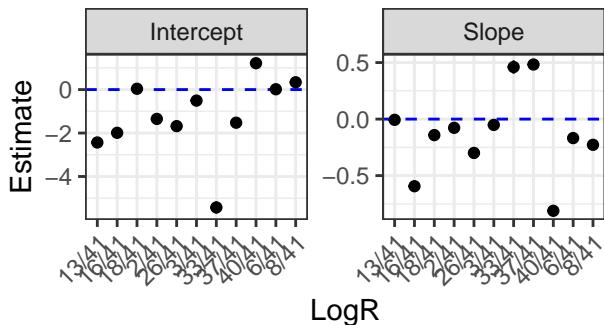
Prost-AdenoCA
diagRE_DMSL



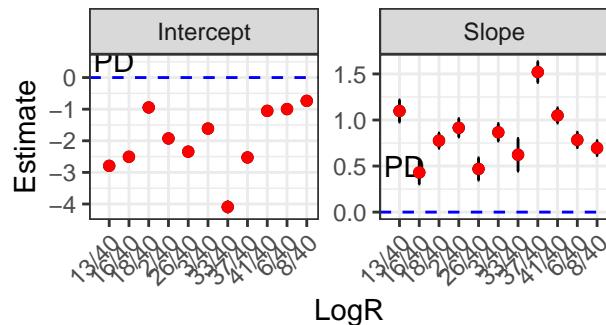
Prost-AdenoCA
sparseRE_DMSL



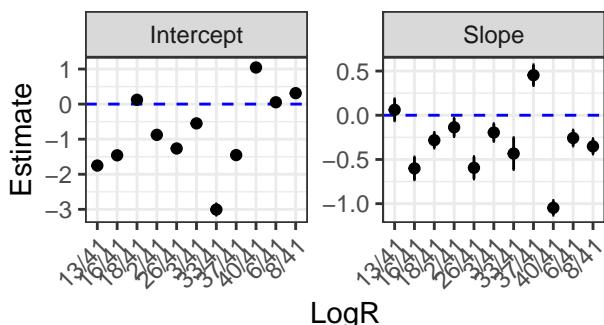
Prost-AdenoCA
fullRE_M_nonexo



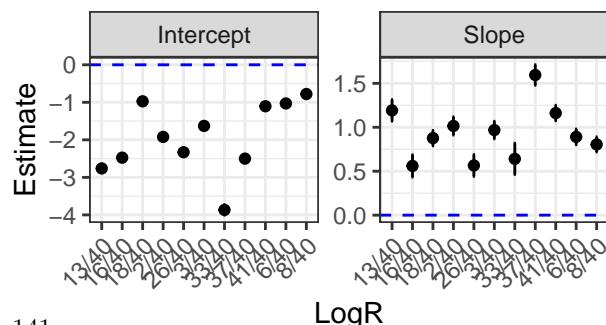
Prost-AdenoCA
fullRE_DMSL_nonexo



Prost-AdenoCA
diagRE_DMSL_nonexo



Prost-AdenoCA
sparseRE_DMSL_nonexo

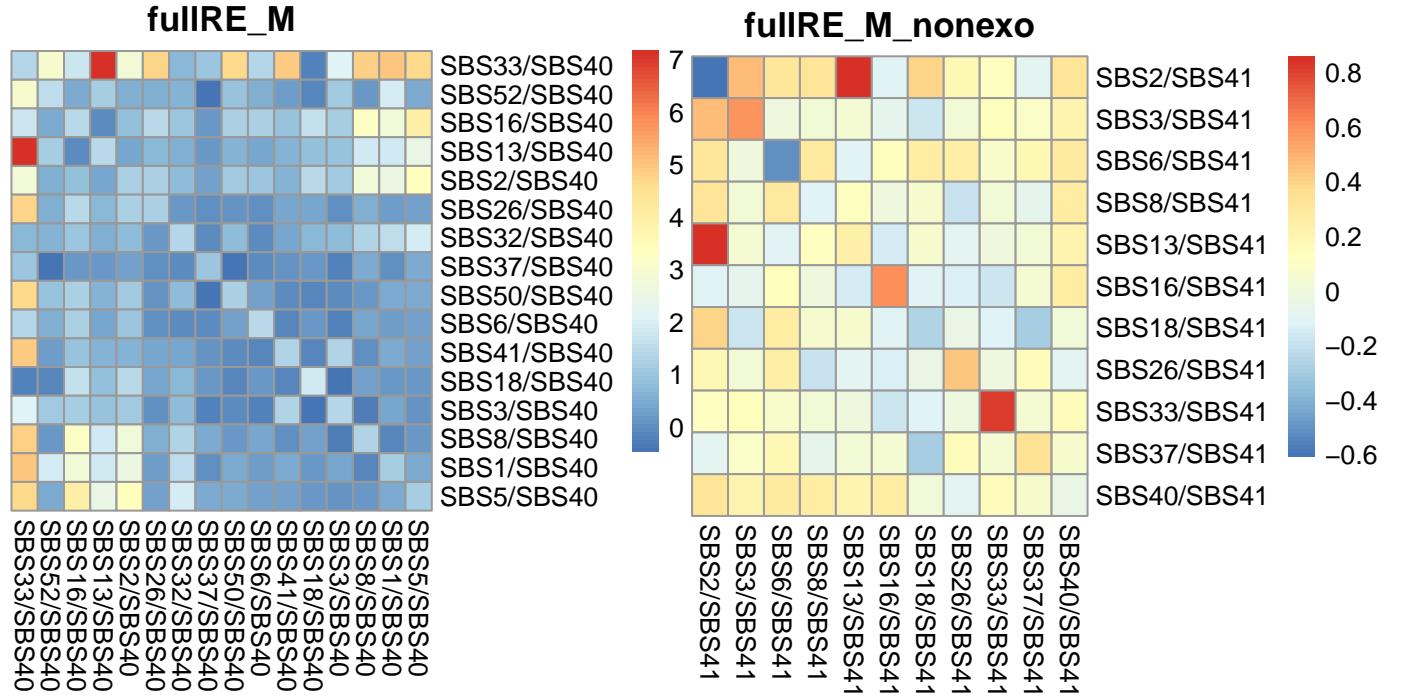


We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of 5.142907×10^{-58} .

Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

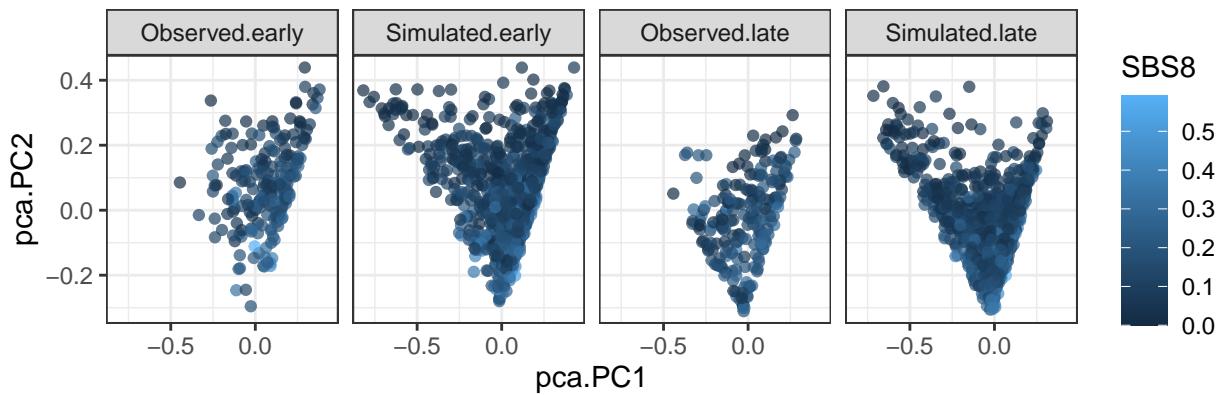


Simulation under inferred data

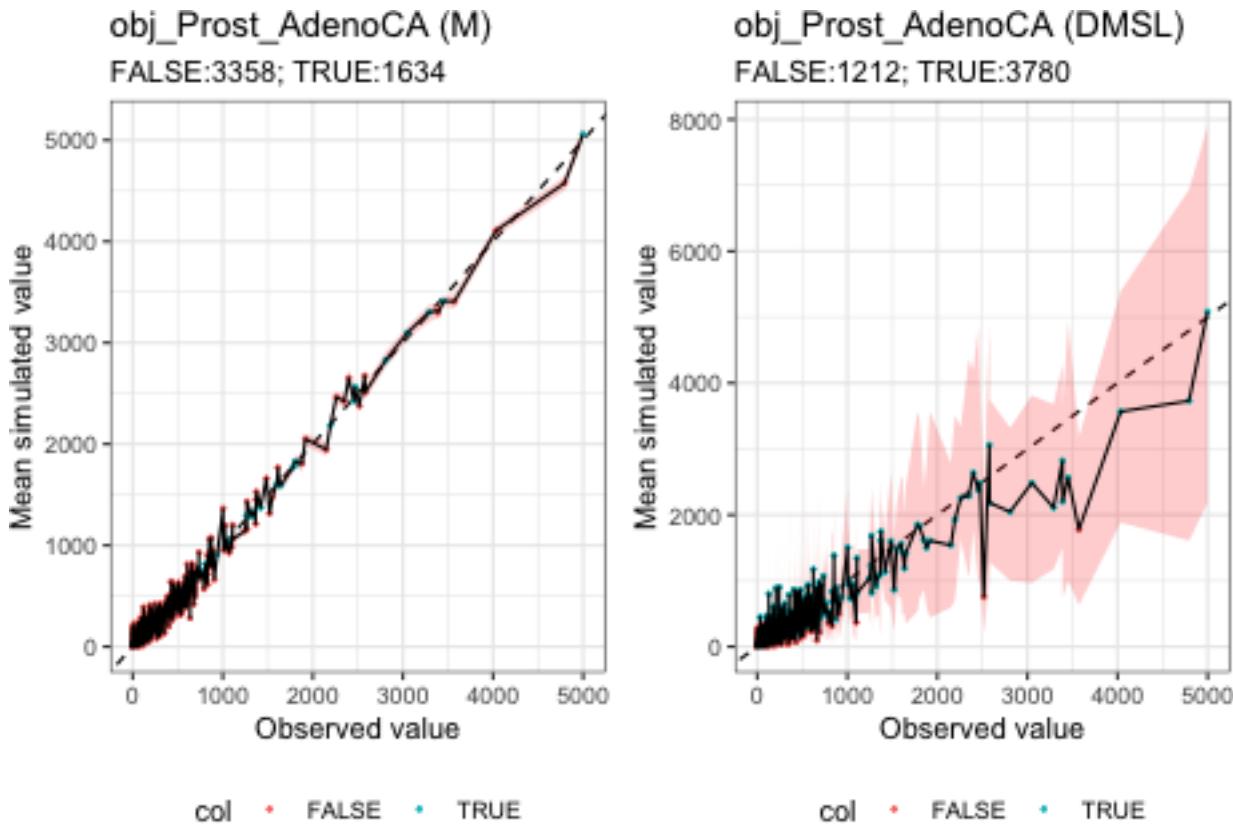
```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

Simulation of Prost–AdenoCA samples



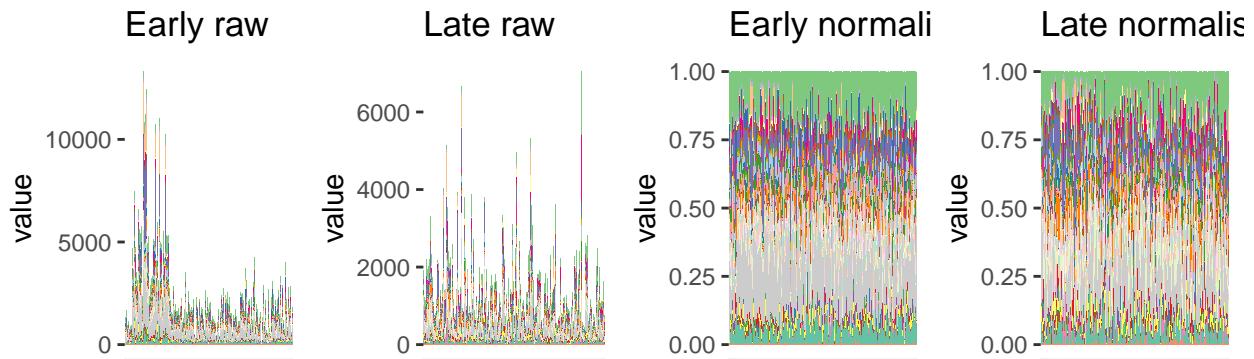
Ranked plot for coverage



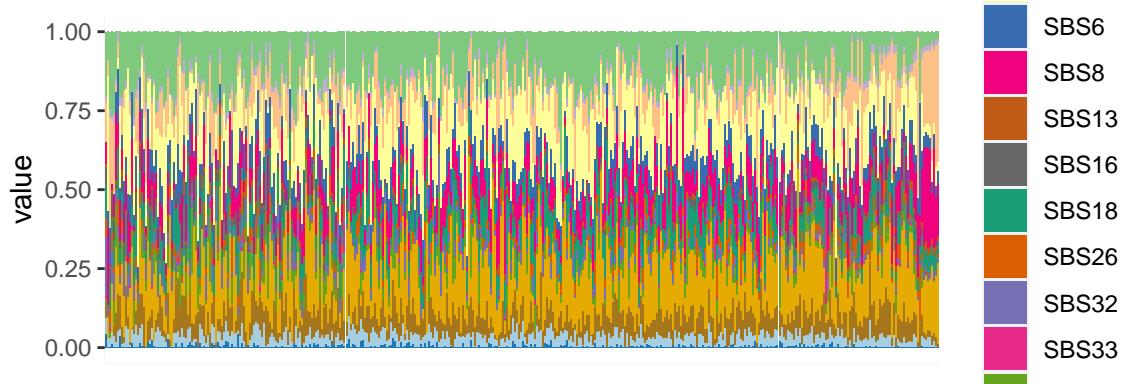
Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

```
## [1] 208
```



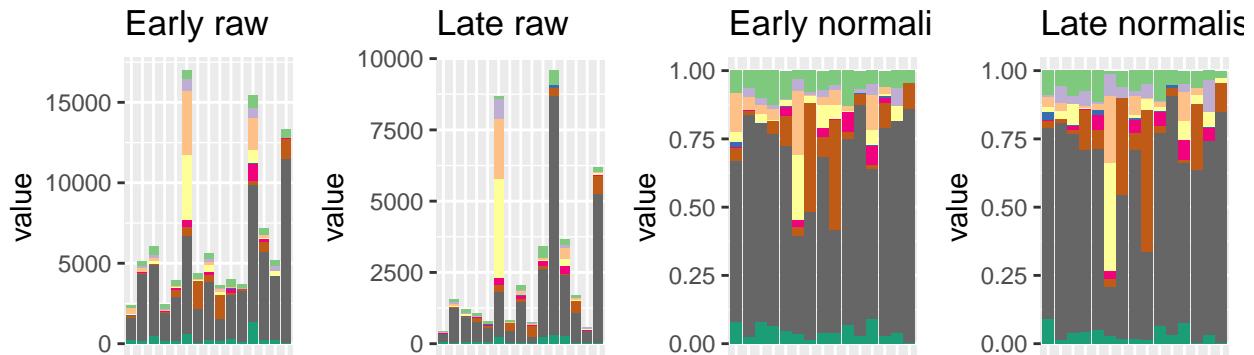
Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations, except perhaps SBS3 in the hypermutated ones.



Skin-Melanoma.acral

Barplot and general statistics

```
## [1] 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

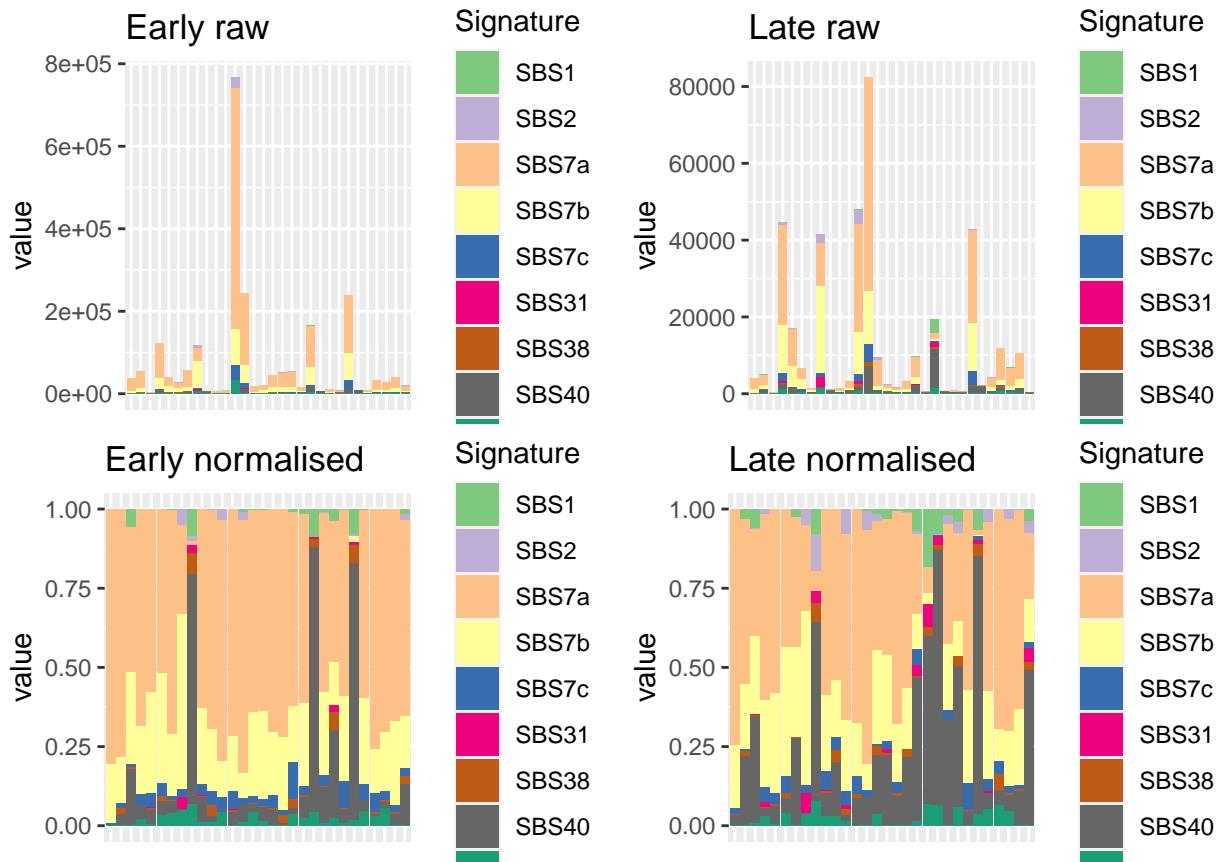
These are the results for the convergence of models fits. They have converged even though very clearly we have very few observations and too many parameters. I thought I would have excluded this cancer type? In CT_sufficient_samples.txt it does appear but shouldn't - I don't continue the analyses for 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
##           value          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
```



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

```

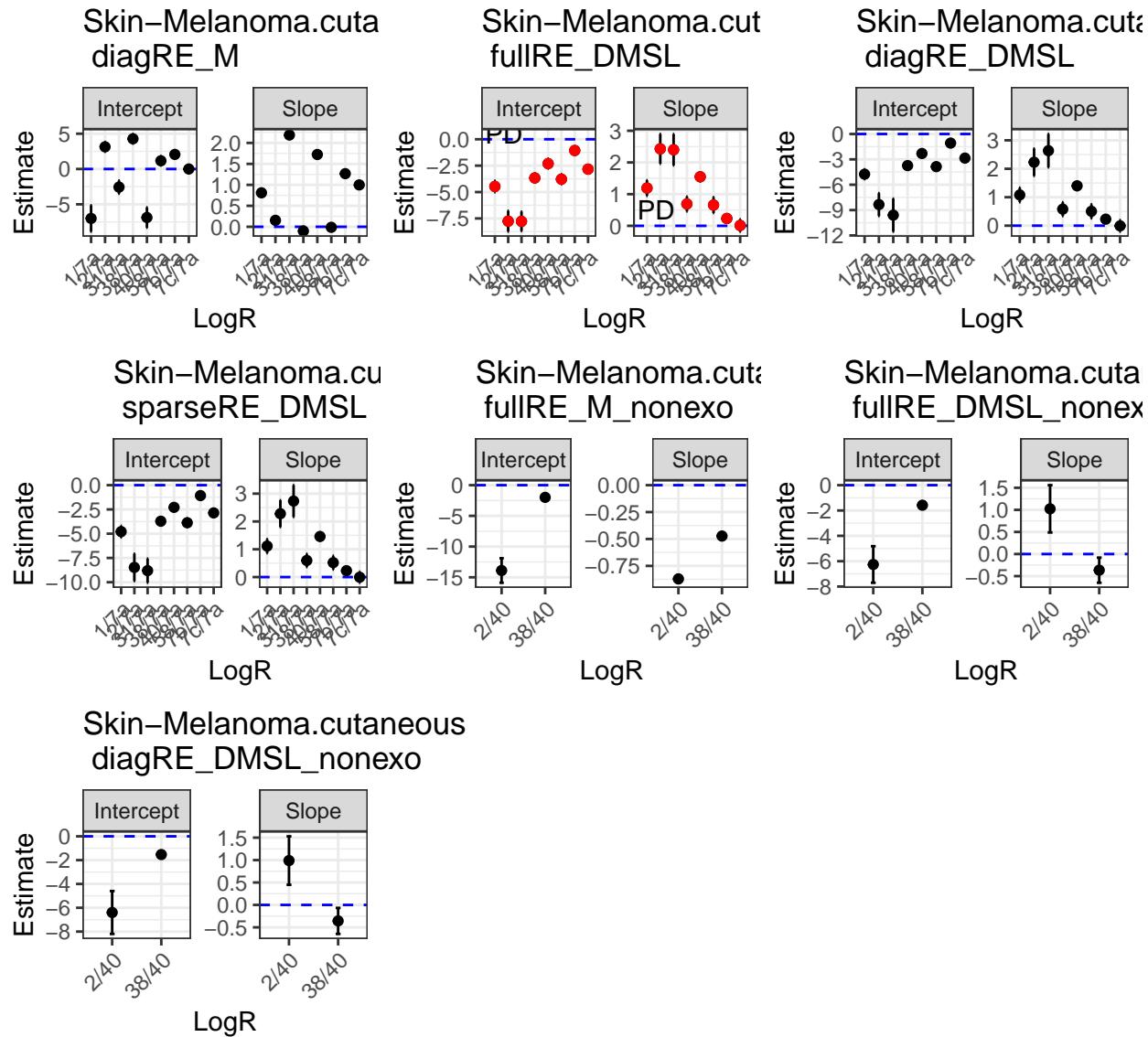
```
colSums(obj_Skin_Melanomacutaneous$Y) / sum(obj_Skin_Melanomacutaneous$Y)
```

```

##      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



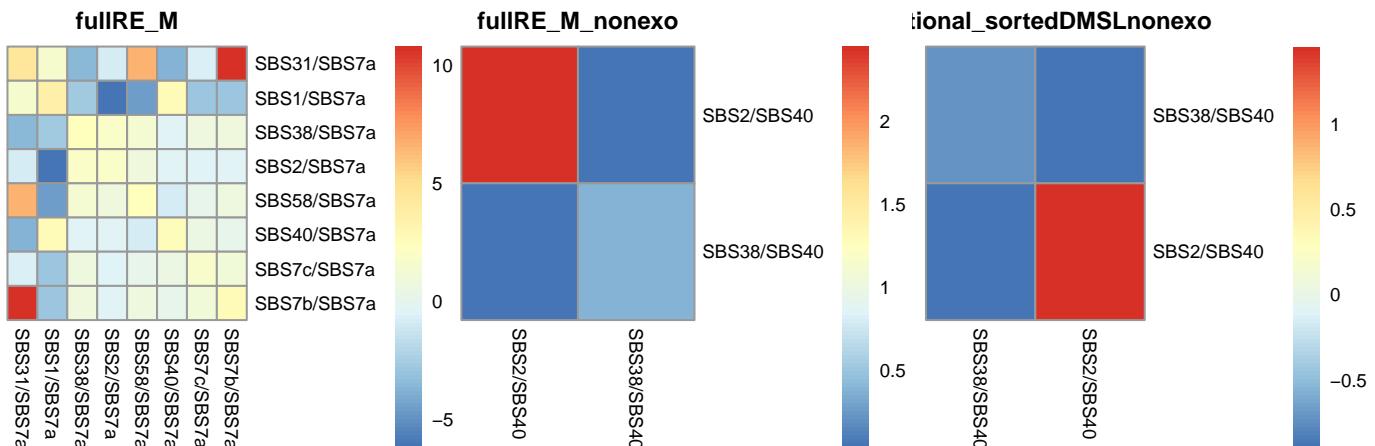
We use the results from the full RE single lambda DM to test for differential abundance, giving a p-value of 0.0628799.

Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

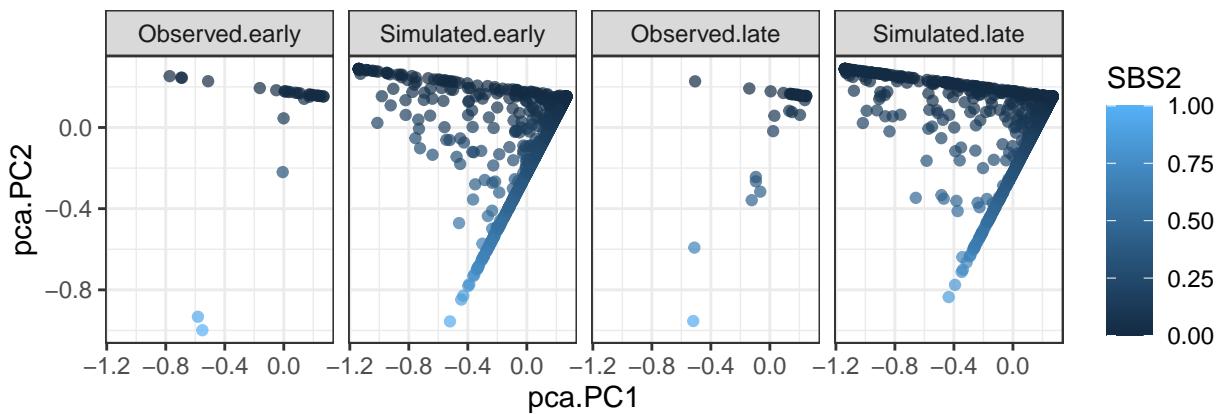
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```



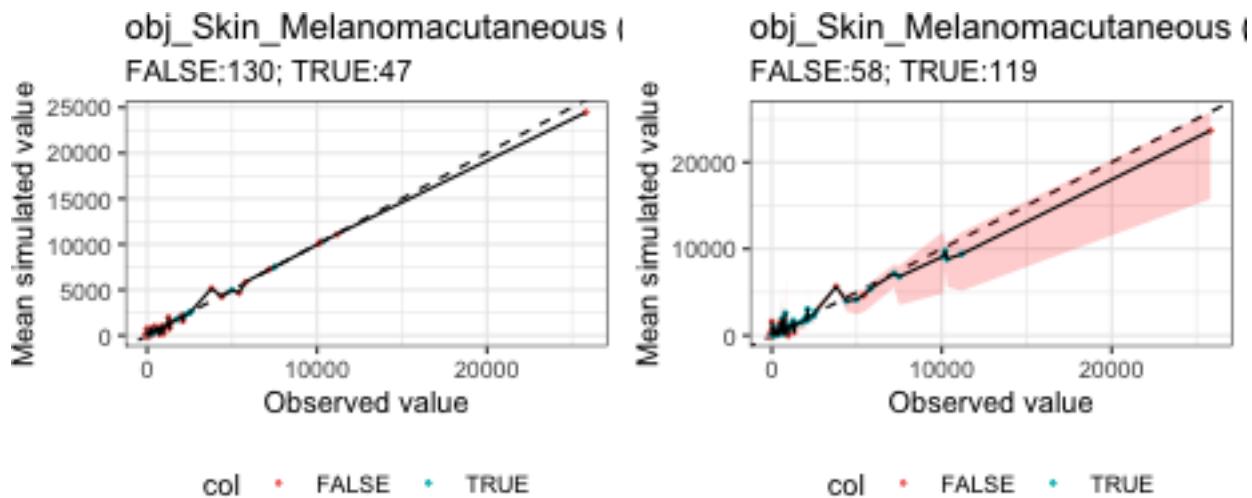
Simulation under inferred data

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

Simulation of Skin–Melanoma.cutaneous samples



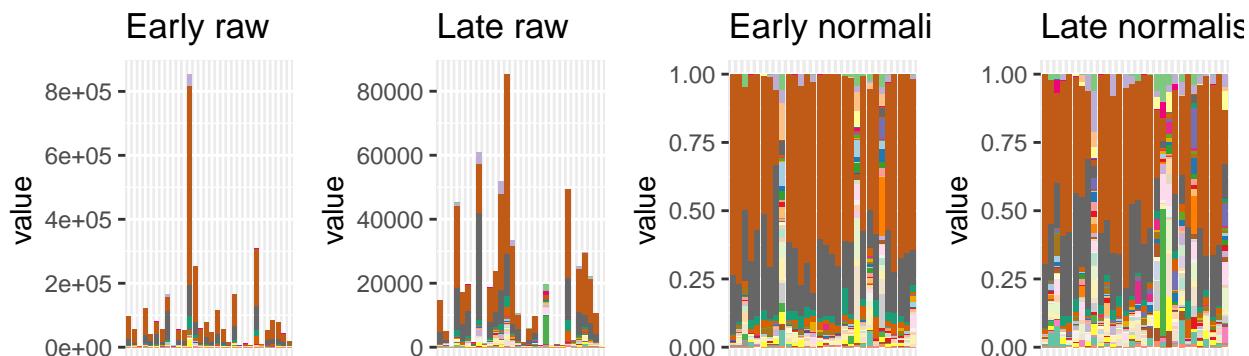
Ranked plot for coverage



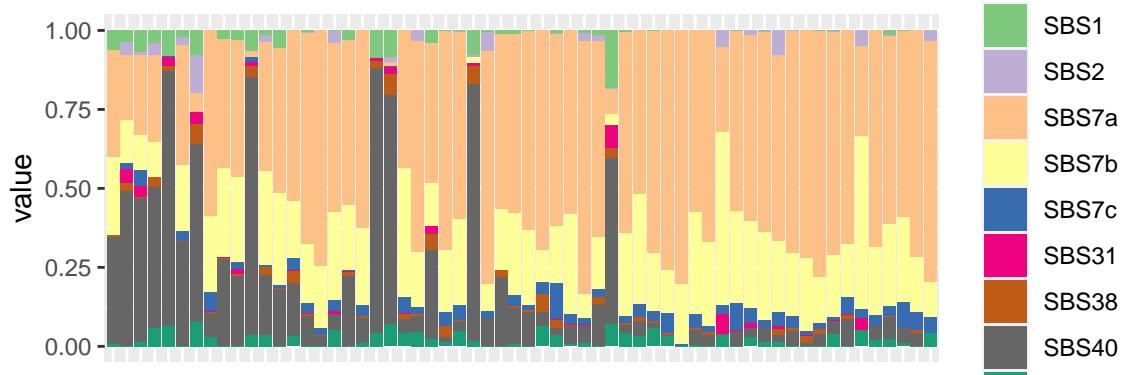
Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

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



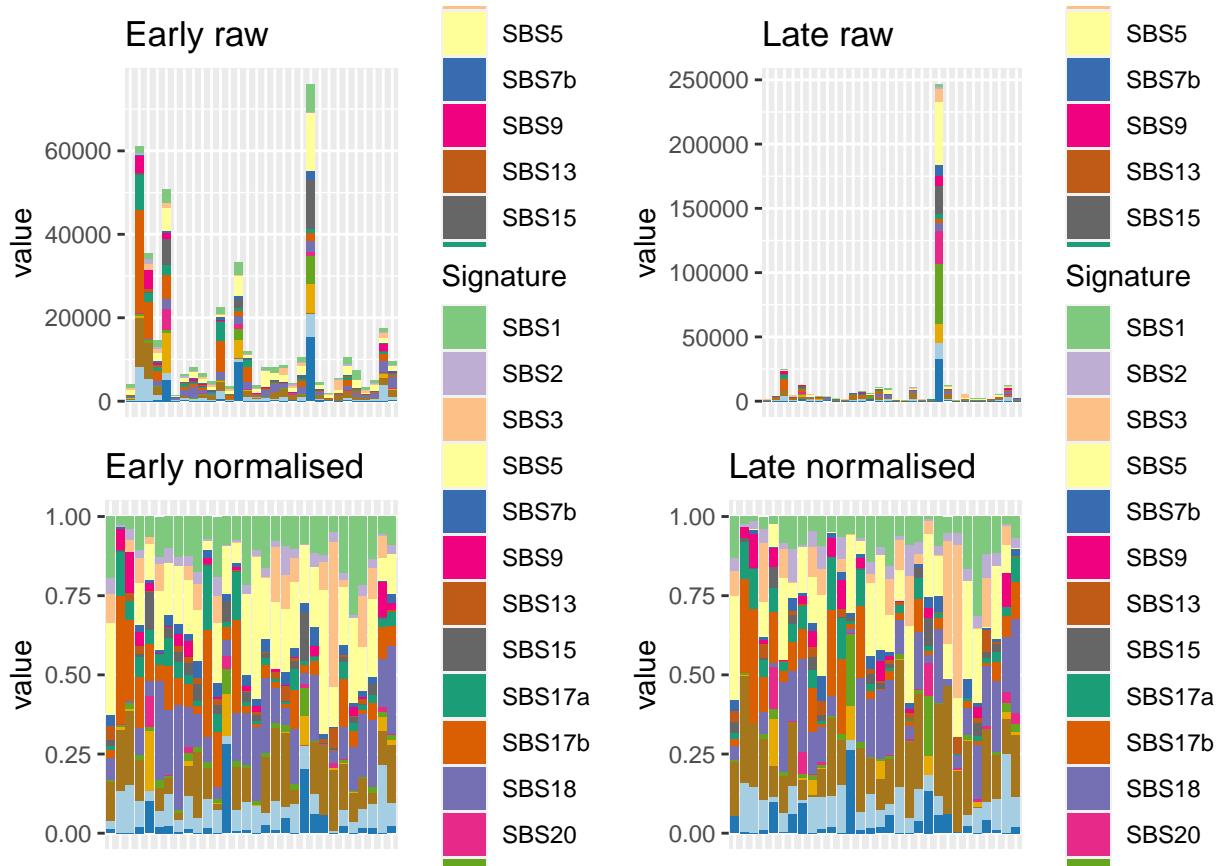
Exposures sorted by increasing number of mutations: SBS40 is clearly prevalent in samples with few mutations.



Stomach-AdenoCA

Barplot and general statistics

```
## [1] 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

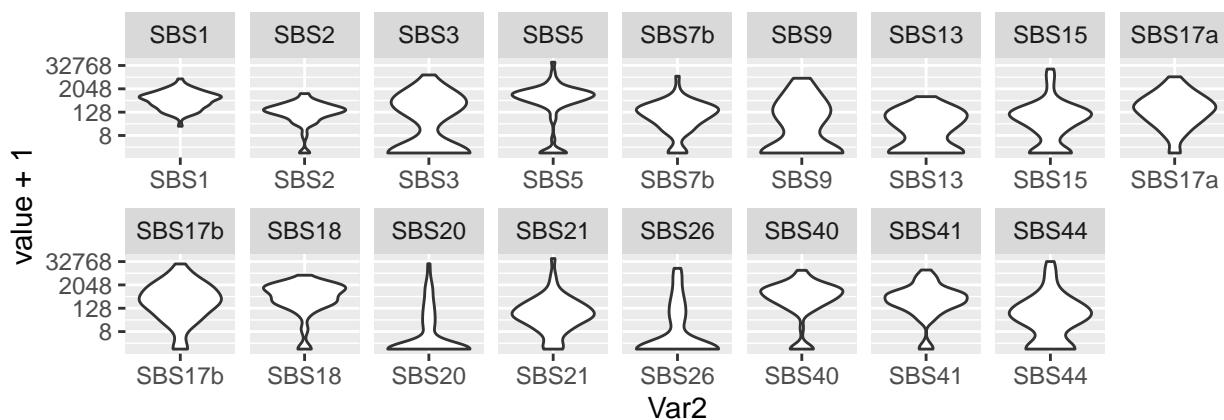
```

```
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

```

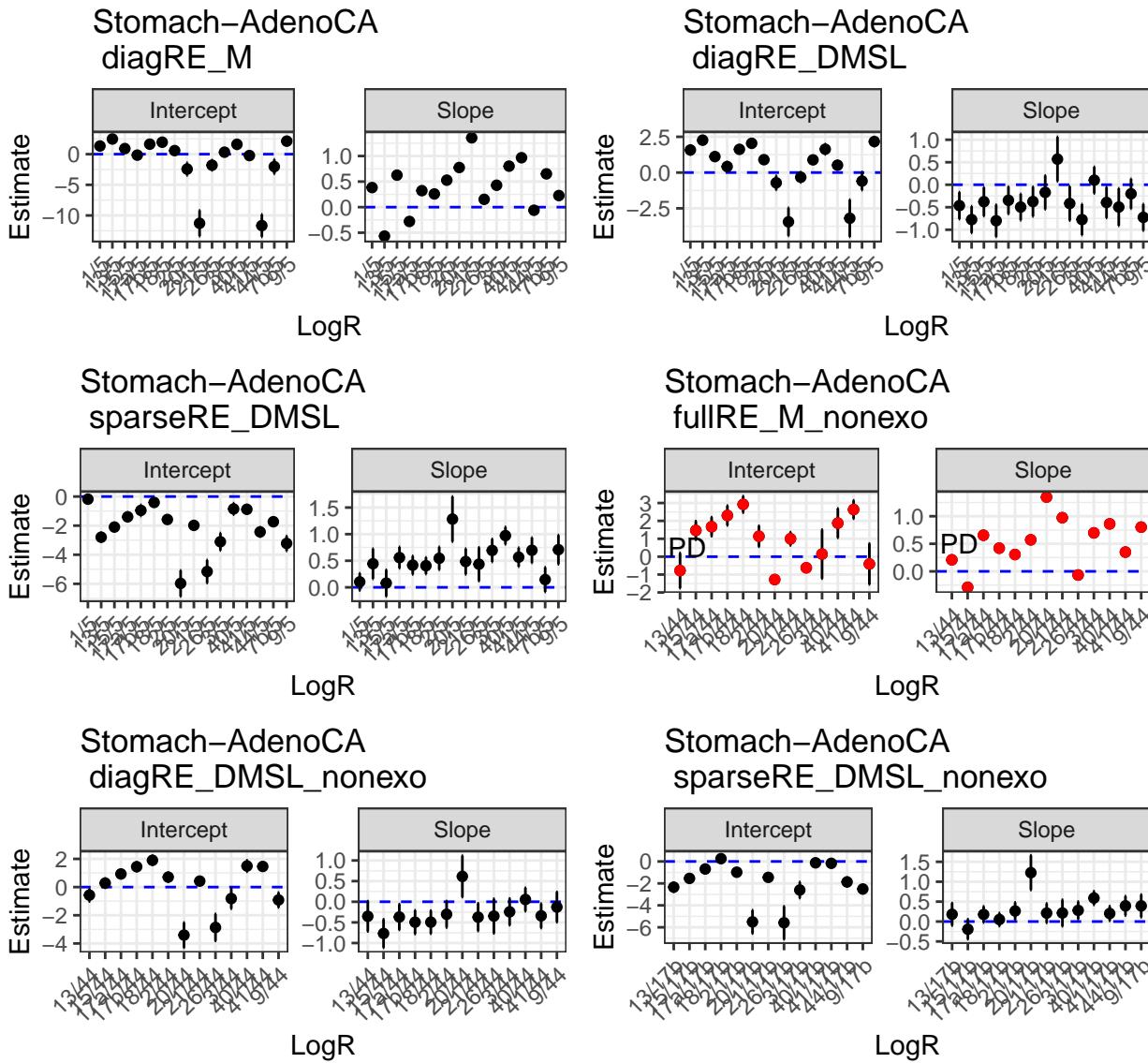


- Removing SBS20, SBS26, fullM still hasn't converged

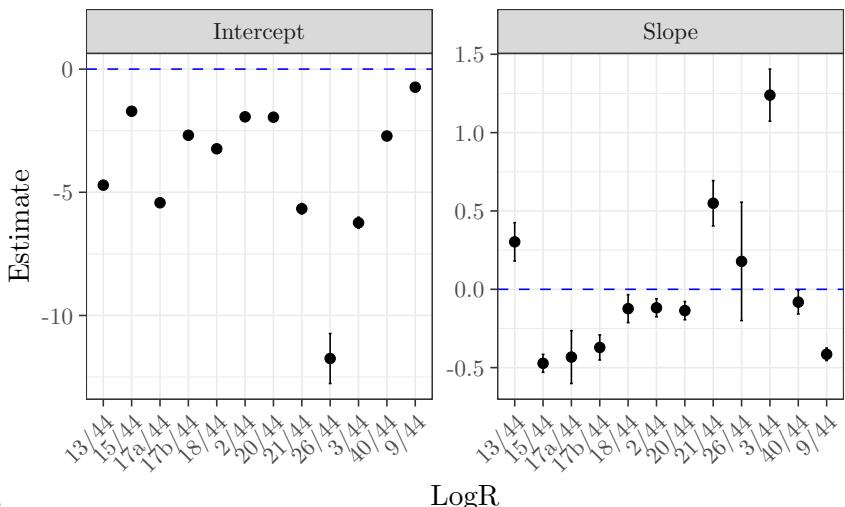
- Removing SBS20, SBS26, SBS9 fullM still hasn't converged
- Removing SBS20, SBS26, SBS9, SBS13 fullM still hasn't converged
- Removing SBS20, SBS26, SBS9, SBS13, SBS44 fullM still hasn't converged

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

Betas



Stomach-AdenoCA diagRE DMSL non-exogenous



Difficult to see the labels, so I replot it here

We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of 0.047603.

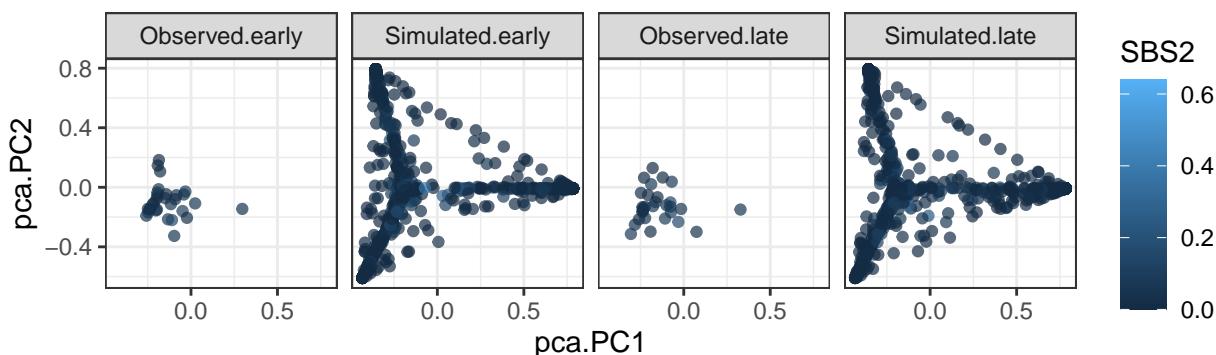
Covariance matrices

I do not include this section as I have had to use only diagonal matrices.

Simulation under inferred data

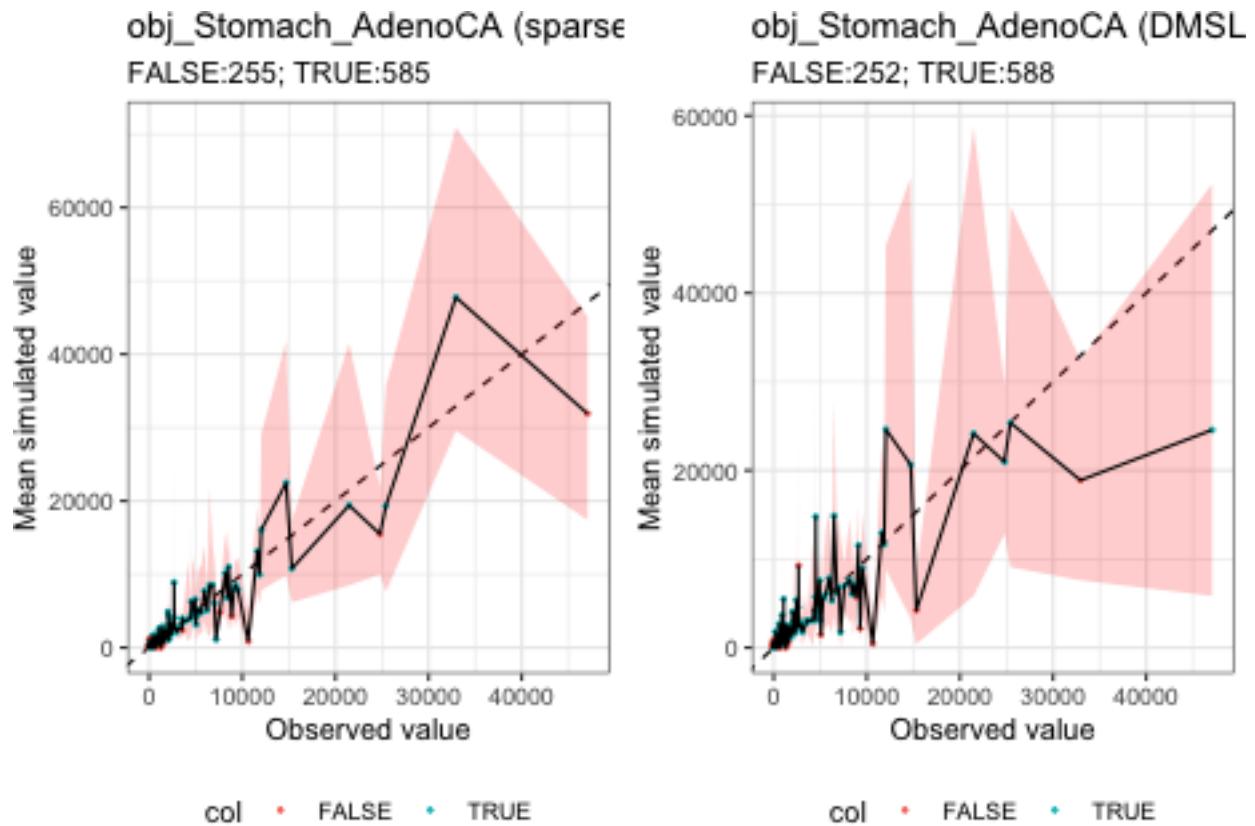
```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

Simulation of Stomach–AdenoCA samples



Ranked plot for coverage

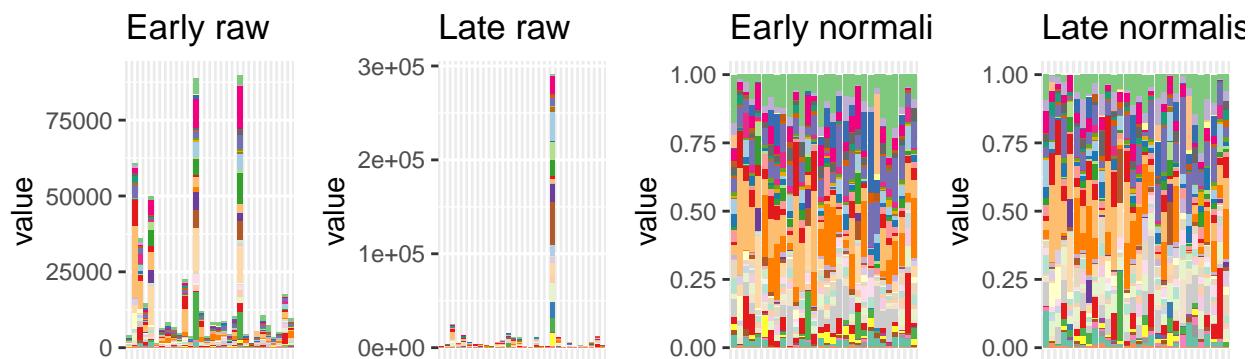
Comparing for now only diagRE_DMSL_nonexo and sparse for nonexo. The blue/red dots seem to behave incorrectly.



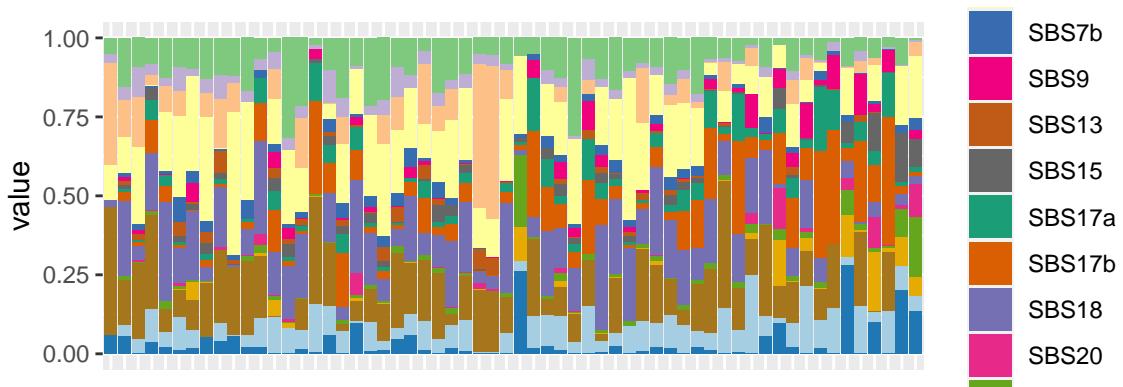
Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

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



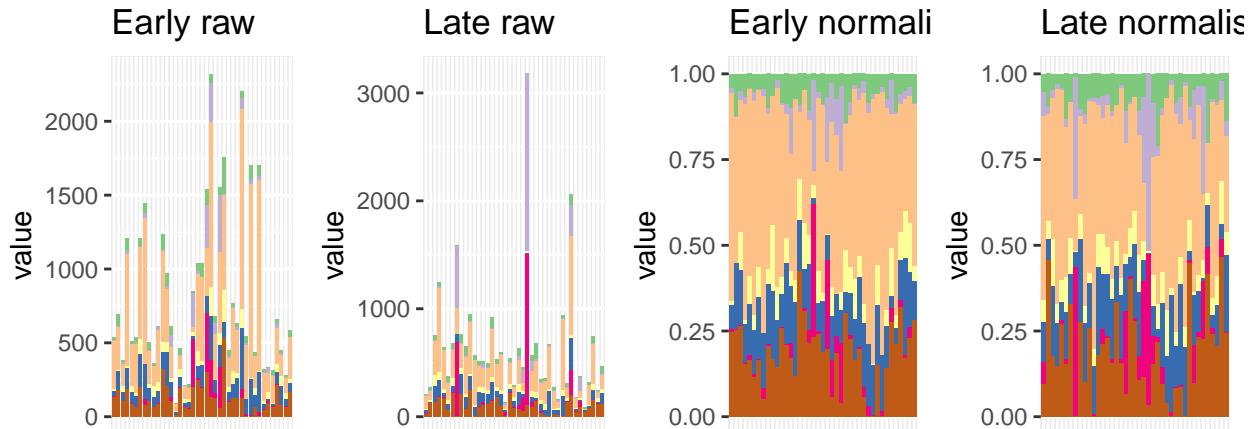
Exposures sorted by increasing number of mutations: there is no clear trend of signatures being associated with the number of mutations.



Thy-AdenoCA

Barplot and general statistics

```
## [1] 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.

| | | 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)
```

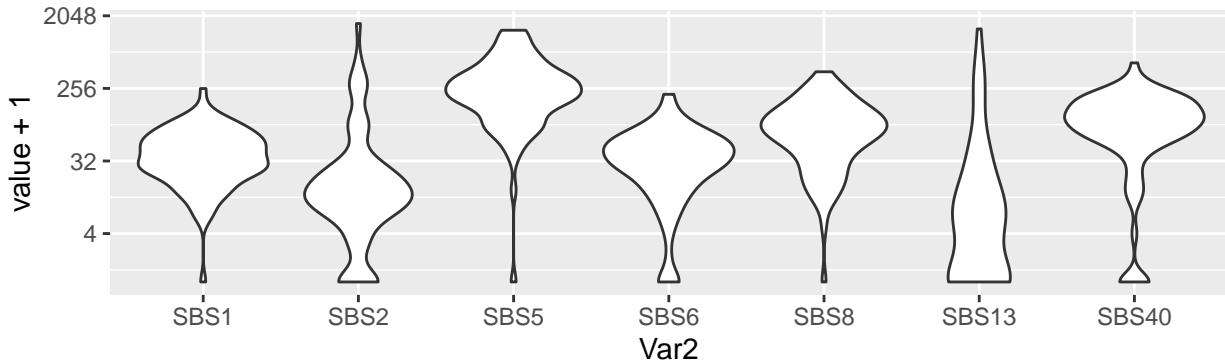
```
##      SBS1      SBS2      SBS5      SBS6      SBS8      SBS13     SBS40
```

```
## 0.01219512 0.12195122 0.01219512 0.06097561 0.01219512 0.35365854 0.07317073
```

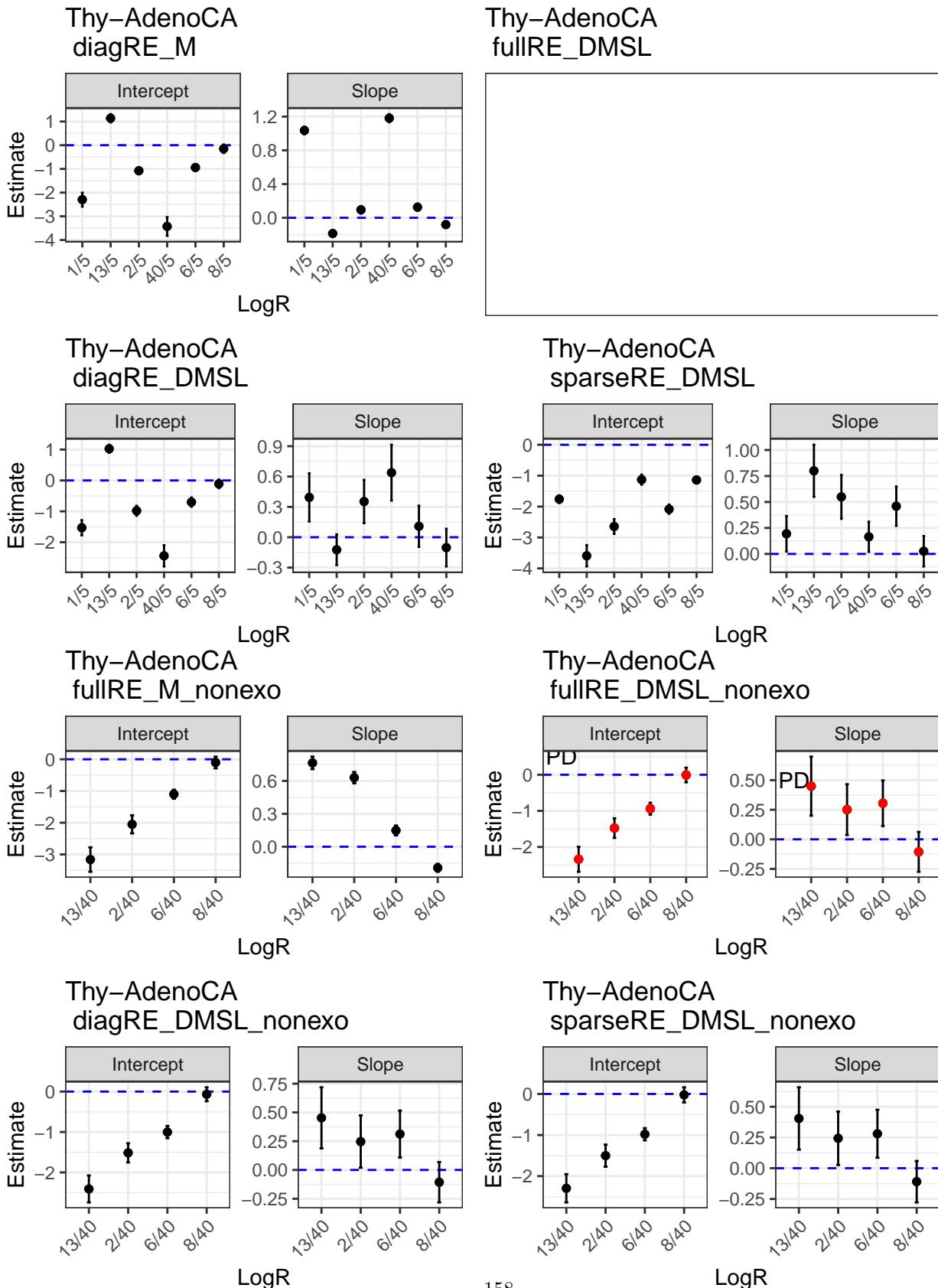
```
colSums(obj_Thy_AdenoCA$Y) / sum(obj_Thy_AdenoCA$Y)
```

```
##      SBS1      SBS2      SBS5      SBS6      SBS8      SBS13     SBS40
```

```
## 0.06120959 0.08303459 0.44489809 0.05581557 0.12930691 0.07239594 0.15333931
```



Betas



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

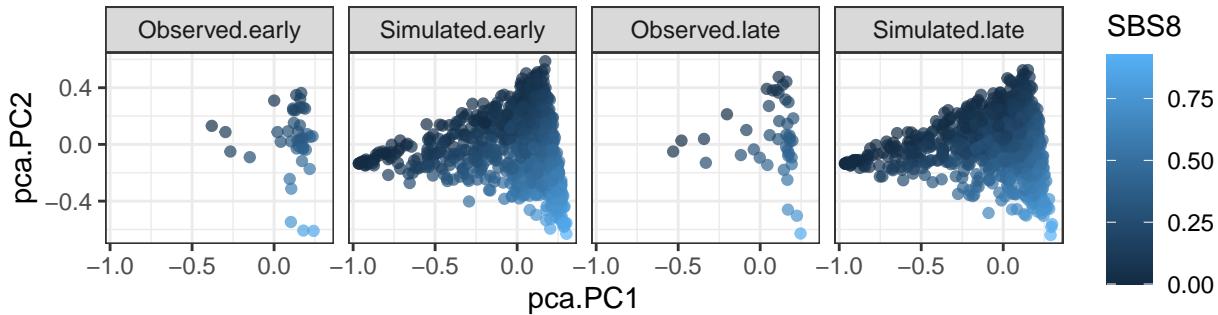
I do not include those.

Simulation under inferred data

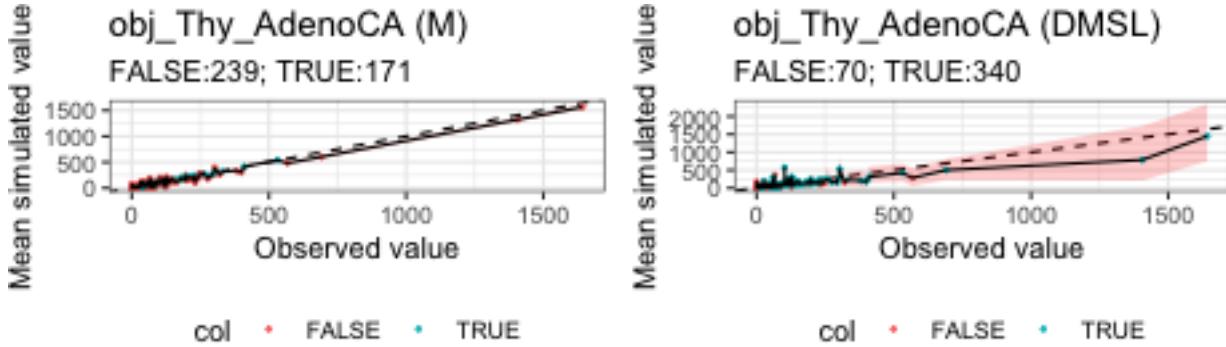
```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

Simulation of Thy–AdenoCA samples



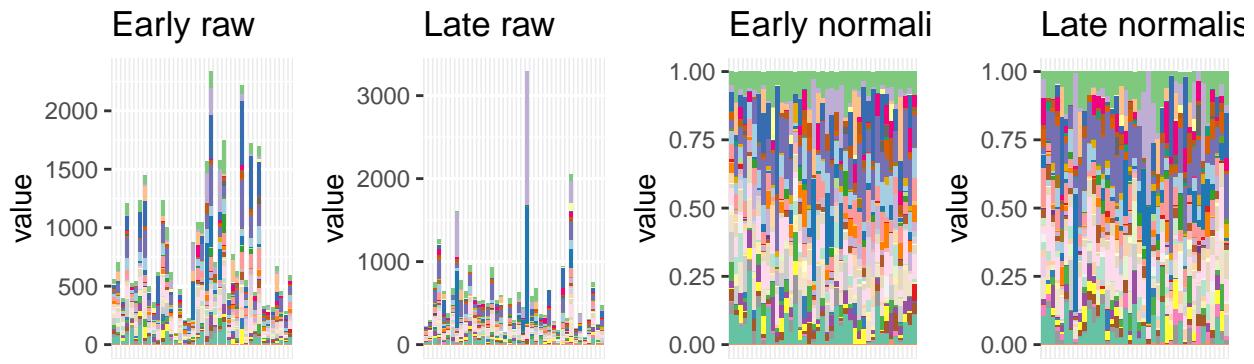
Ranked plot for coverage



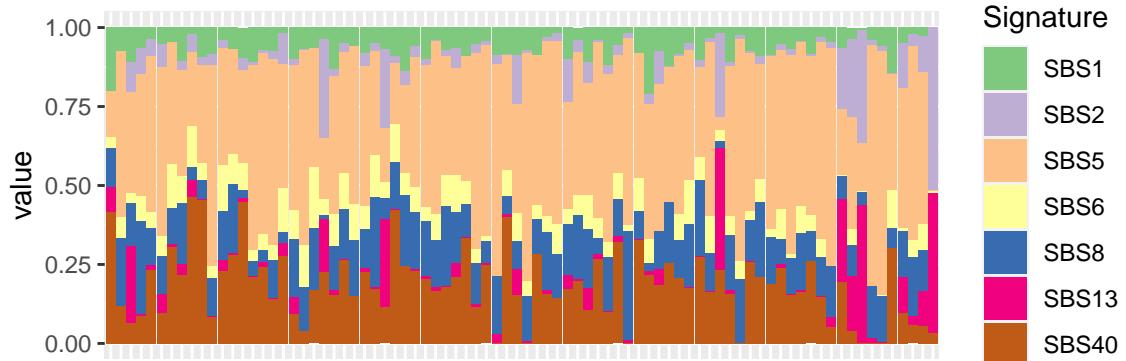
Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

```
## [1] 41
```



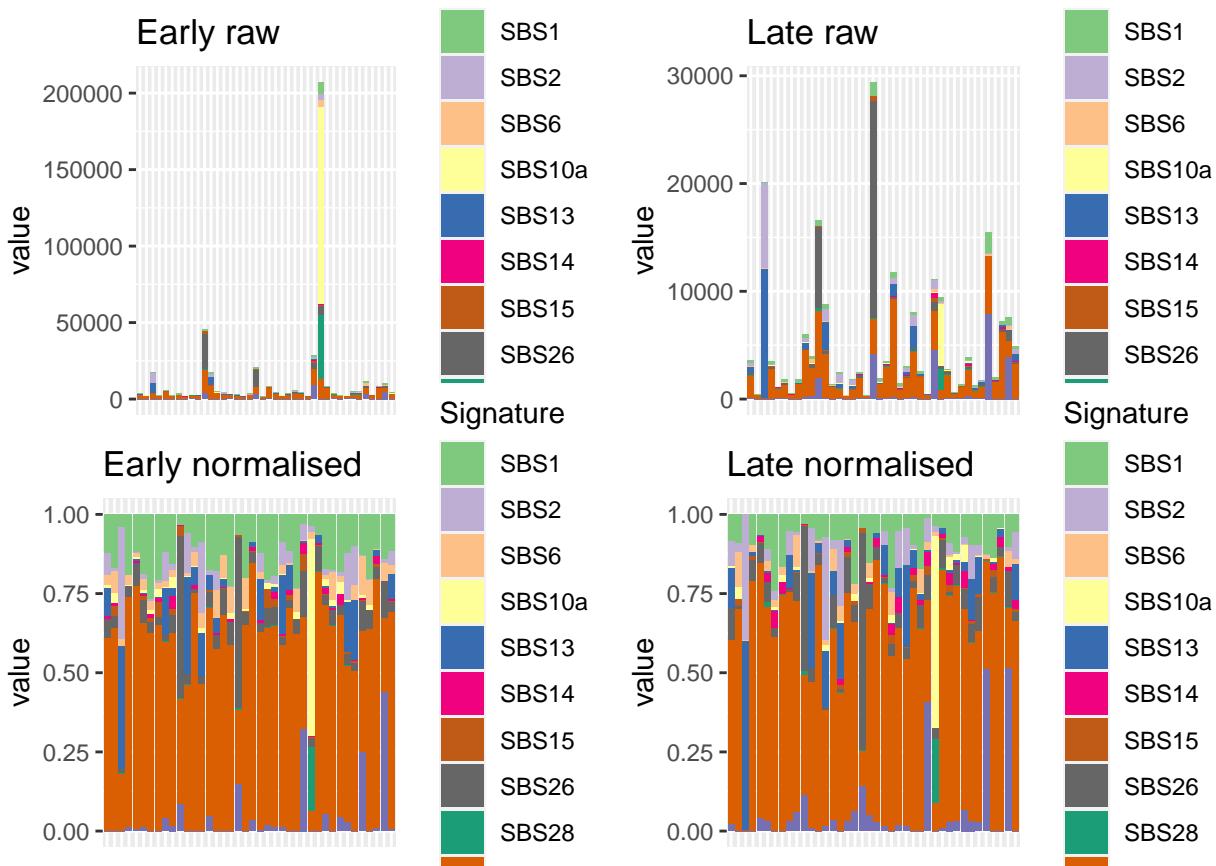
Exposures sorted by increasing number of mutations: there is no trend of signatures being associated with the number of mutations.



Uterus-AdenoCA

Barplot and general statistics

```
## [1] 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:

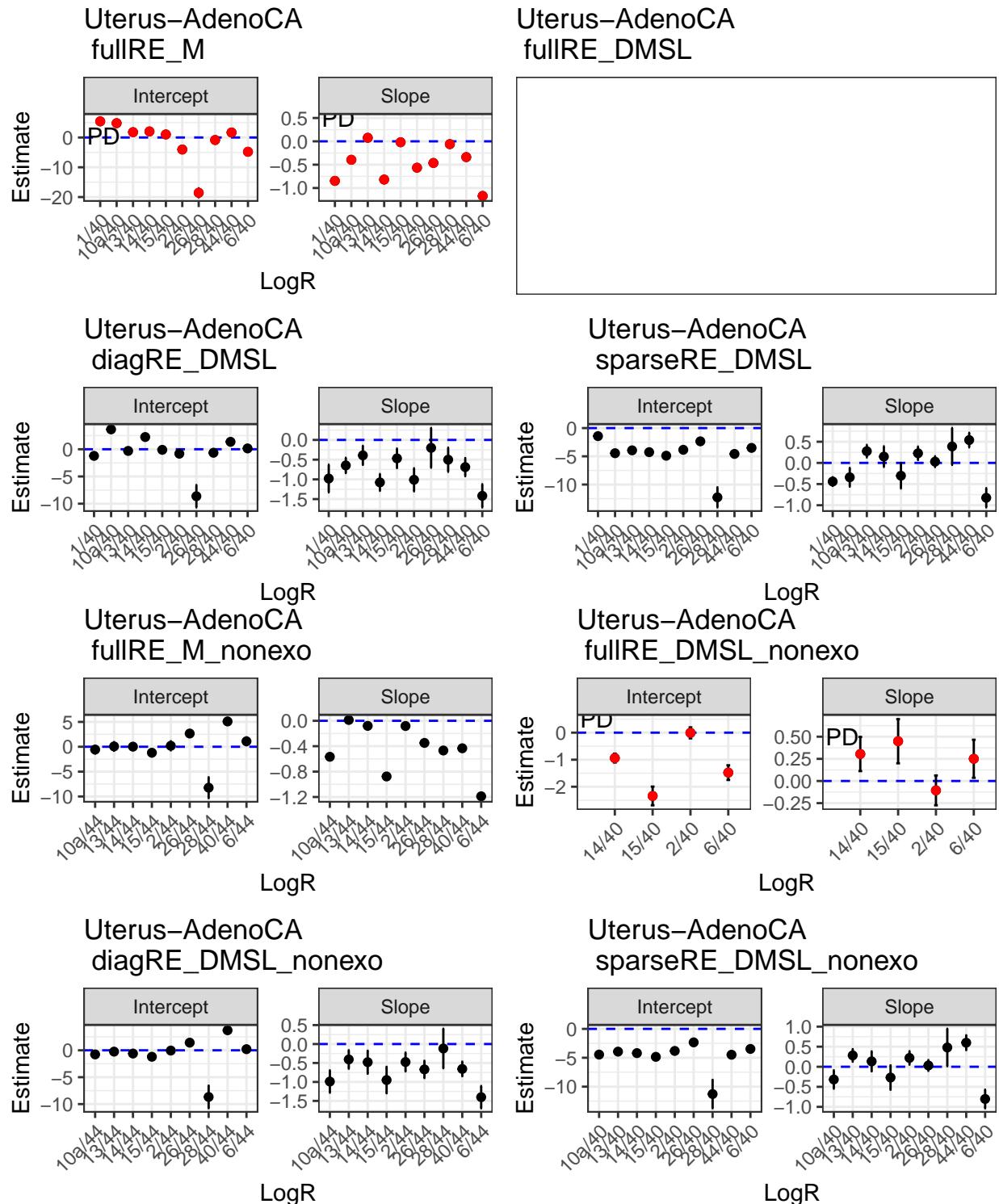
```
colSums(obj_Uterus_AdenoCA$Y == 0)/nrow(obj_Uterus_AdenoCA$Y)
```

```
##      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

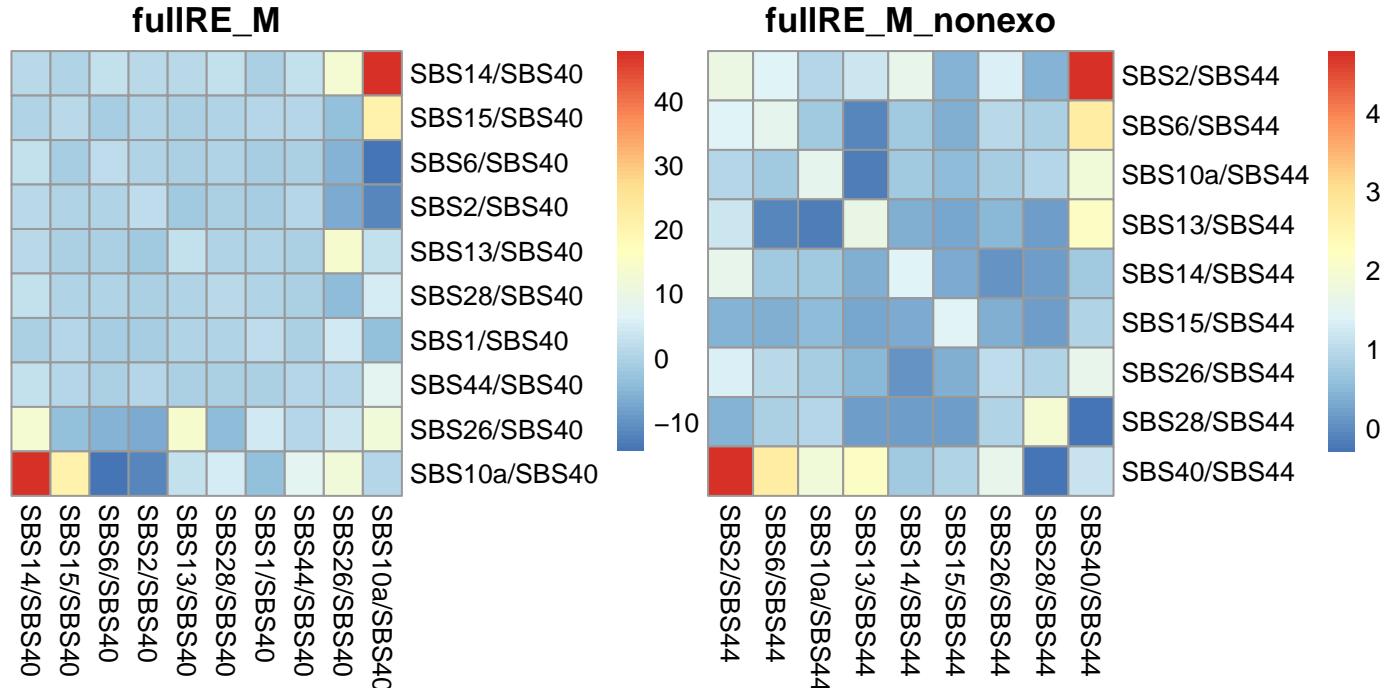


We use the results from the diag RE single lambda DM to test for differential abundance, giving a p-value of 1.4837739×10^{-4} .

Covariance matrices

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)
```

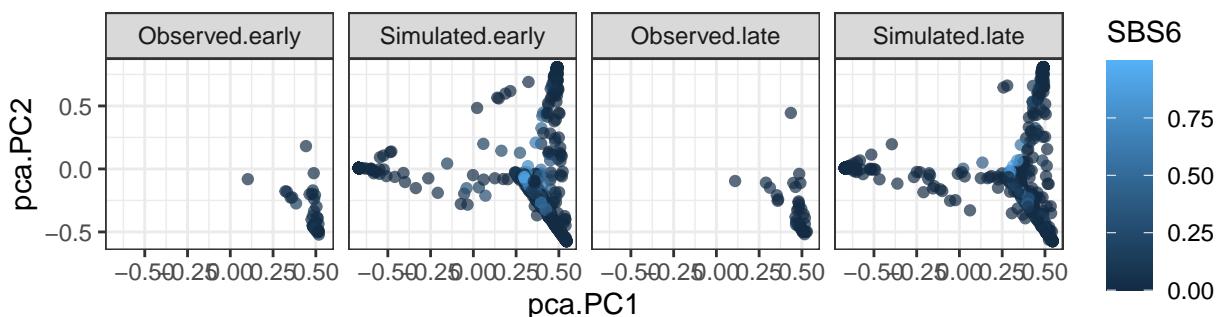


Simulation under inferred data

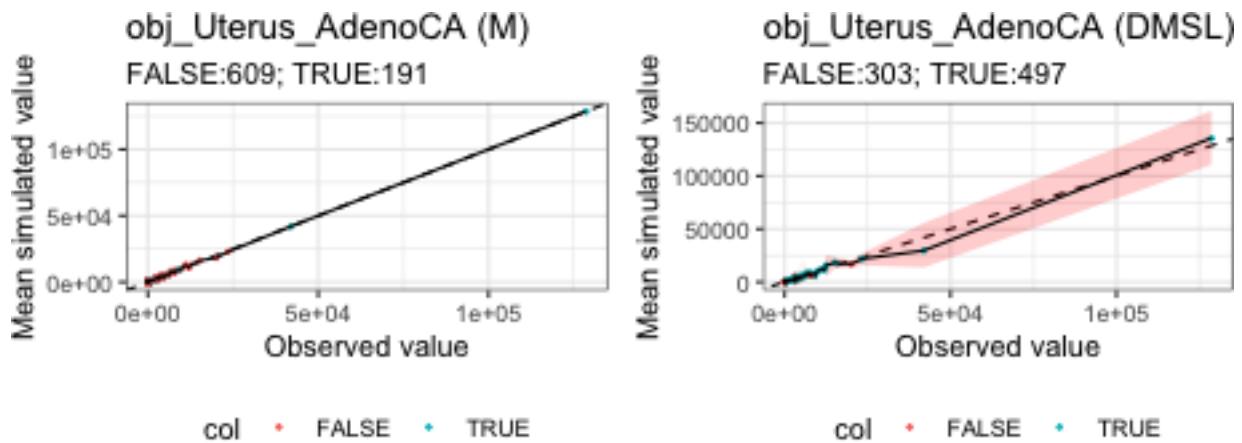
```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec, :
## This function had been incorrect until now (30 july 2021)
```

```
## Warning in fill_covariance_matrix(arg_d = dmin1, arg_entries_var = var_vec_v2, :
## This function had been incorrect until now (30 july 2021)
```

Simulation of Uterus-AdenoCA samples



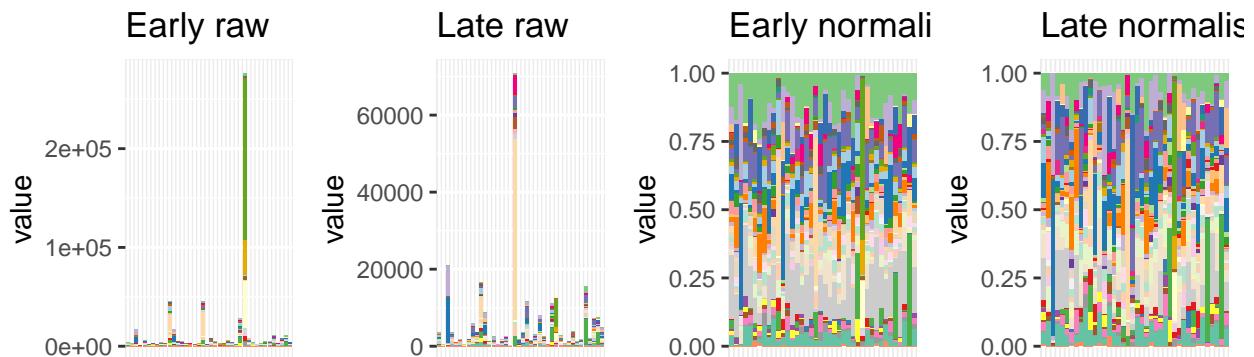
Ranked plot for coverage



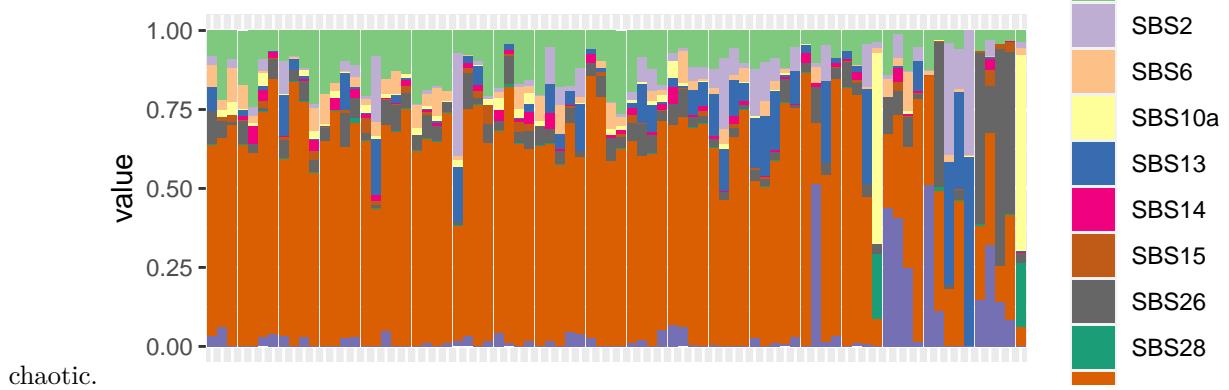
Signatures from mutSigExtractor

The signatures from mutSigExtractor are as follows:

```
## [1] 40
```



Exposures sorted by increasing number of mutations: there is a trend of hypermutated samples being very



All p-values for non-exogenous signatures

% latex table generated in R 4.0.3 by xtable 1.8-4 package % Thu Jul 15 14:31:19 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-GBM | 0.00 | fullRE_DMSL_nonexo |
| 5 | CNS-Medullo | 0.07 | fullRE_DMSL_nonexo |
| 6 | CNS-Oligo | 0.52 | fullRE_DMSL_nonexo |
| 7 | CNS-PiloAstro | 0.26 | fullRE_DMSL_nonexo |
| 8 | ColoRect-AdenoCA | 0.00 | diagRE_DMSL_nonexo |
| 9 | Eso-AdenoCA | 0.00 | diagRE_DMSL_nonexo |
| 10 | Head-SCC | 0.00 | fullRE_DMSL_nonexo |
| 11 | Kidney-ChRCC | 0.27 | fullRE_DMSL_nonexo |
| 12 | Kidney-RCC.clearcell | 0.00 | fullRE_DMSL_nonexo |
| 13 | Kidney-RCC.papillary | 0.00 | fullRE_DMSL_nonexo |
| 14 | Liver-HCC | 0.00 | fullRE_DMSL_nonexo |
| 15 | Lung-AdenoCA | 0.00 | diagRE_DMSL_nonexo |
| 16 | Lung-SCC | 0.03 | diagRE_DMSL_nonexo |
| 17 | Lymph-BNHL | 0.00 | fullRE_DMSL_nonexo |
| 18 | Lymph-CLL | 0.00 | fullRE_DMSL_nonexo |
| 19 | Myeloid-MPN | 0.00 | fullRE_DMSL_nonexo |
| 20 | Ovary-AdenoCA | 0.00 | diagRE_DMSL_nonexo |
| 21 | Panc-AdenoCA | 0.00 | diagRE_DMSL_nonexo |
| 22 | Panc-Endocrine | 0.00 | diagRE_DMSL_nonexo |
| 23 | Prost-AdenoCA | 0.00 | diagRE_DMSL_nonexo |
| 24 | Skin-Melanoma.acral | | |
| 25 | Skin-Melanoma.cutaneous | 0.06 | fullRE_DMSL_nonexo |
| 26 | Stomach-AdenoCA | 0.05 | diagRE_DMSL_nonexo |
| 27 | Thy-AdenoCA | 0.11 | diagRE_DMSL_nonexo |
| 28 | Uterus-AdenoCA | 0.00 | diagRE_DMSL_nonexo |

All p-values

% latex table generated in R 4.0.3 by xtable 1.8-4 package % Thu Jul 15 14:13:08 2021

Correlation between p-values and number of samples

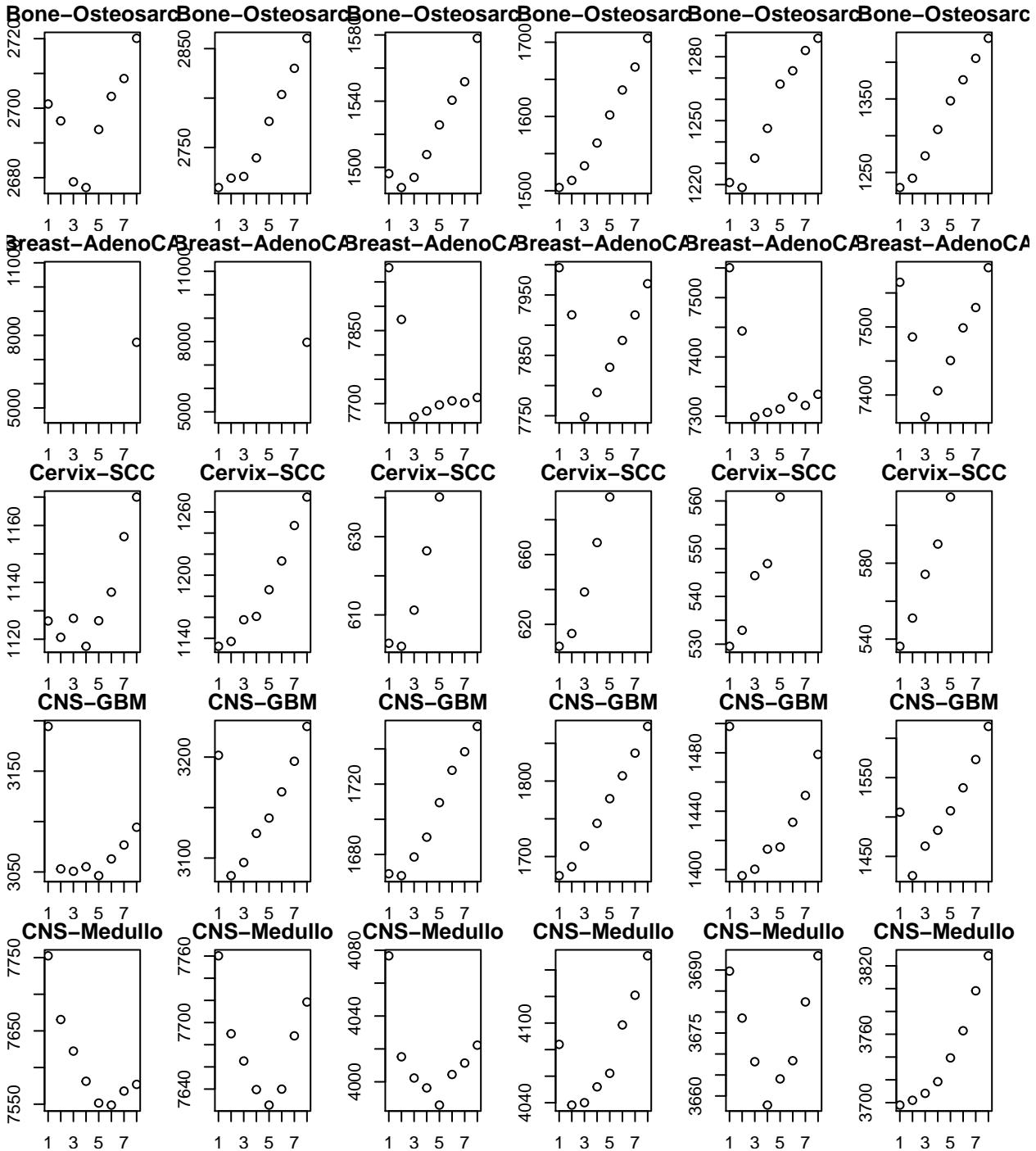
| | pvals_fullRE_M | pvals_diagRE_DM | pvals_DM | pvals_DMnonexo |
|-------------------------|----------------|-----------------|----------|----------------|
| Bone-Osteosarc | 0.00 | 0.00 | 0.00 | |
| Breast-AdenoCA | 0.00 | 0.00 | 0.00 | 0.00 |
| Cervix-SCC | 0.00 | 0.11 | 0.12 | 0.01 |
| CNS-GBM | 0.00 | 0.00 | 0.03 | 0.00 |
| CNS-Medullo | 0.00 | 0.02 | 0.02 | 0.47 |
| CNS-Oligo | 0.00 | 0.03 | 0.03 | |
| CNS-PiloAstro | 0.00 | 0.03 | 0.03 | 0.64 |
| ColoRect-AdenoCA | 0.00 | 0.00 | 0.00 | 0.00 |
| Eso-AdenoCA | 0.00 | 0.00 | 0.00 | 0.00 |
| Head-SCC | 0.00 | 0.00 | 0.00 | 0.00 |
| Kidney-ChRCC | 0.00 | 0.00 | 0.00 | 0.64 |
| Kidney-RCC.clearcell | 0.00 | 0.00 | 0.00 | 0.00 |
| Kidney-RCC.papillary | 0.00 | 0.00 | 0.00 | 0.00 |
| Liver-HCC | 0.00 | 0.00 | 0.00 | 0.00 |
| Lung-AdenoCA | 0.00 | 0.01 | 0.00 | 0.01 |
| Lung-SCC | 0.00 | 0.00 | 0.00 | 0.17 |
| Lymph-BNHL | 0.00 | 0.00 | 0.00 | 0.00 |
| Lymph-CLL | 0.00 | 0.00 | 0.00 | |
| Myeloid-MPN | 0.00 | 0.00 | 0.00 | |
| Ovary-AdenoCA | 0.00 | 0.00 | 0.00 | 0.00 |
| Panc-AdenoCA | 0.00 | 0.00 | 0.00 | 0.00 |
| Panc-Endocrine | 0.00 | 0.00 | 0.00 | 0.00 |
| Prost-AdenoCA | 0.00 | 0.00 | 0.00 | 0.00 |
| Skin-Melanoma.acral | 0.00 | 0.18 | 0.15 | |
| Skin-Melanoma.cutaneous | 0.00 | 0.00 | 0.00 | |
| Stomach-AdenoCA | 0.00 | 0.00 | 0.00 | 0.08 |
| Thy-AdenoCA | 0.00 | 0.03 | 0.02 | 0.47 |
| Uterus-AdenoCA | 0.00 | 0.00 | 0.00 | 0.00 |

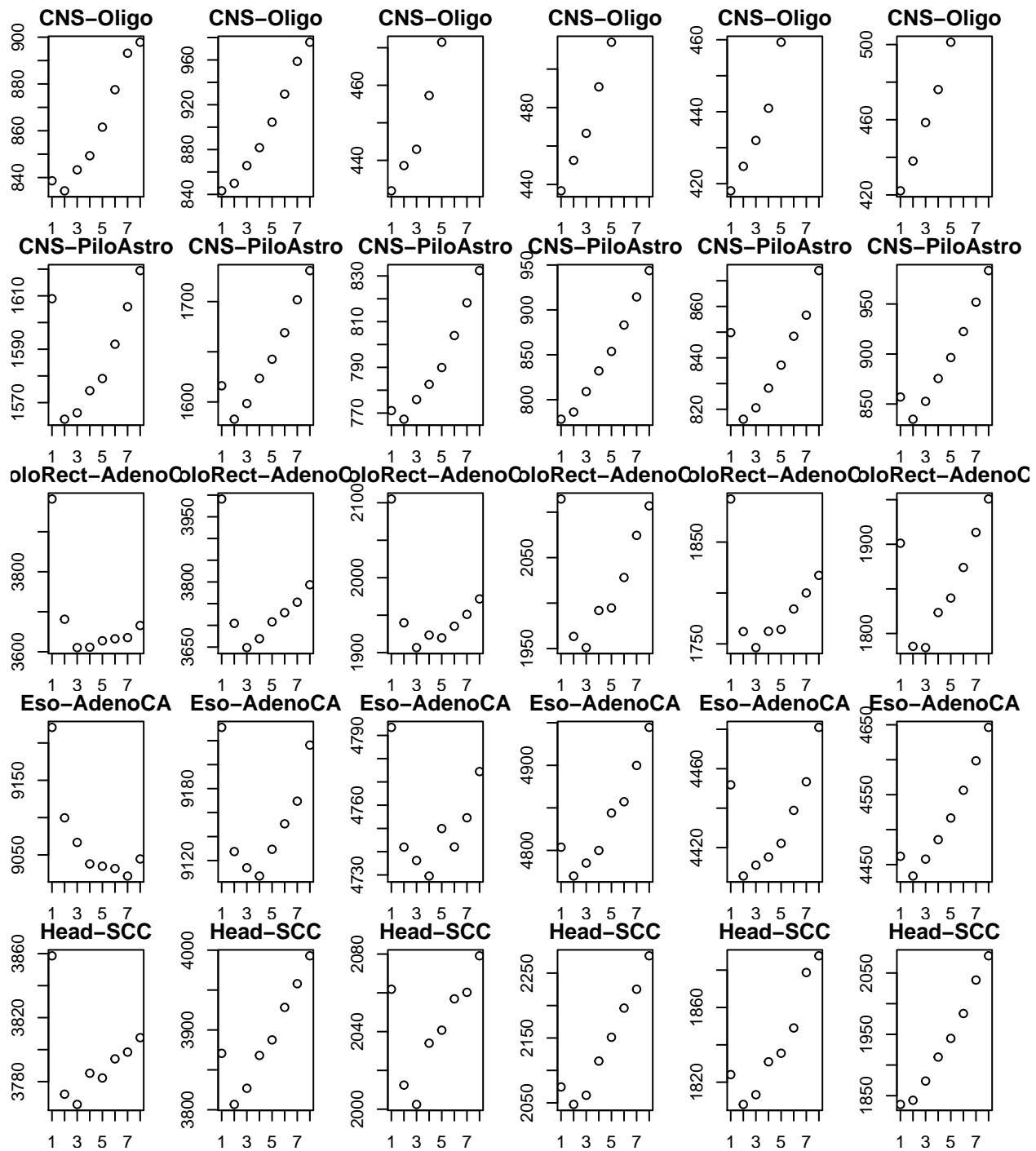
Dirichlet-Multinomial Mixtures

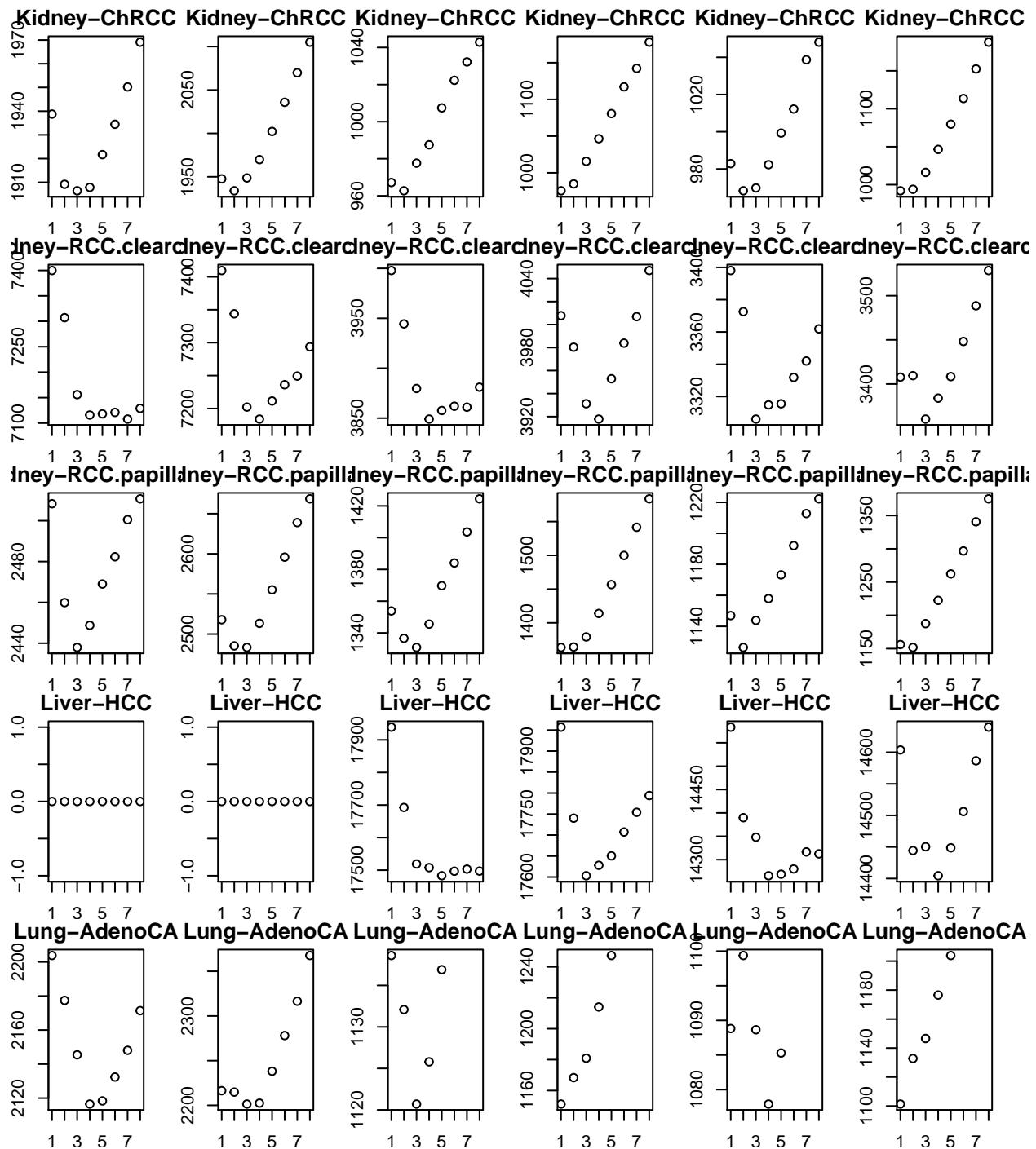
We run the software MicrobeDMMv1.0 to determine whether we are facing DMM mixtures or not.

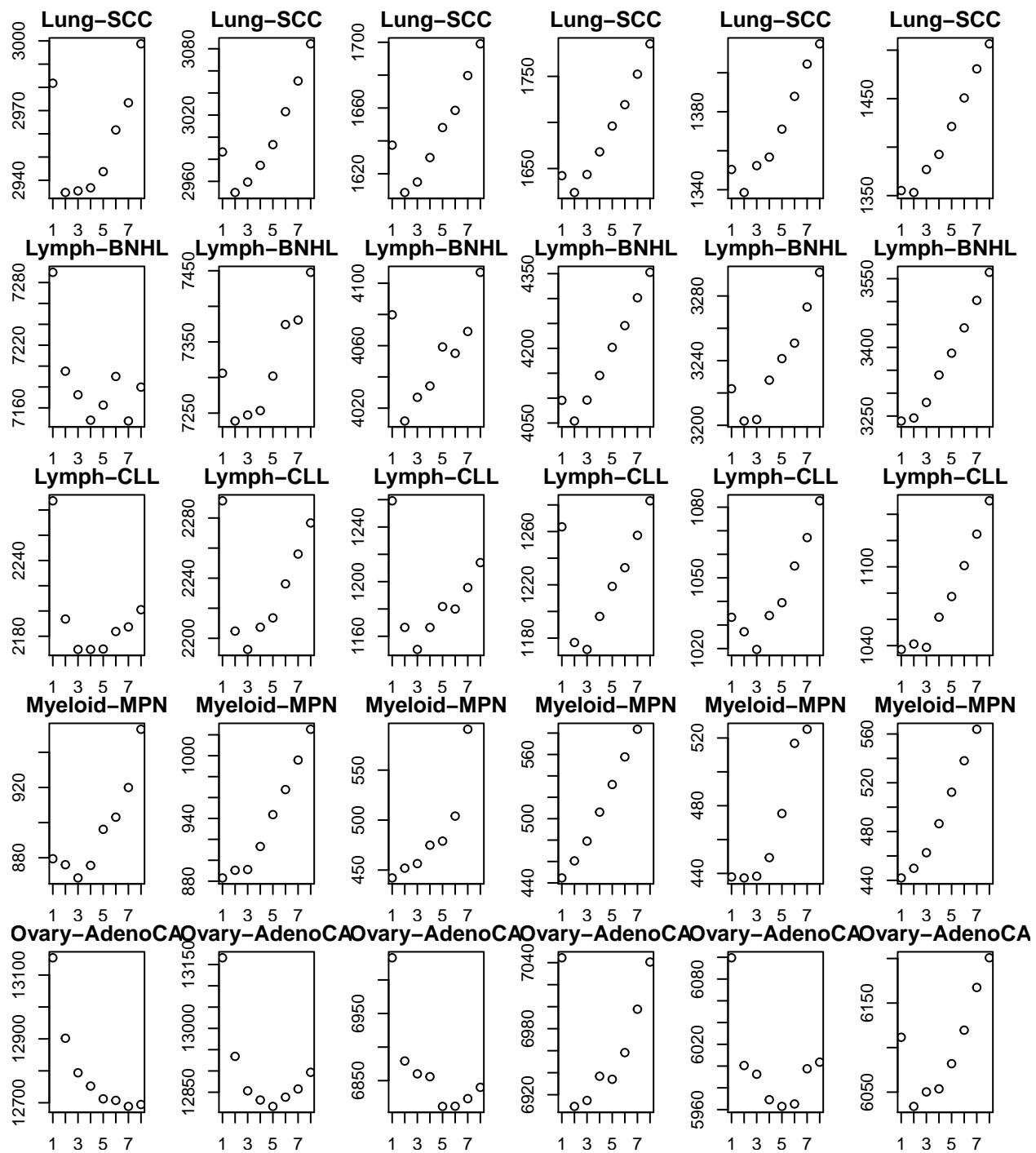
We save the files in two ways: all of the samples - early or not - together, and separately.

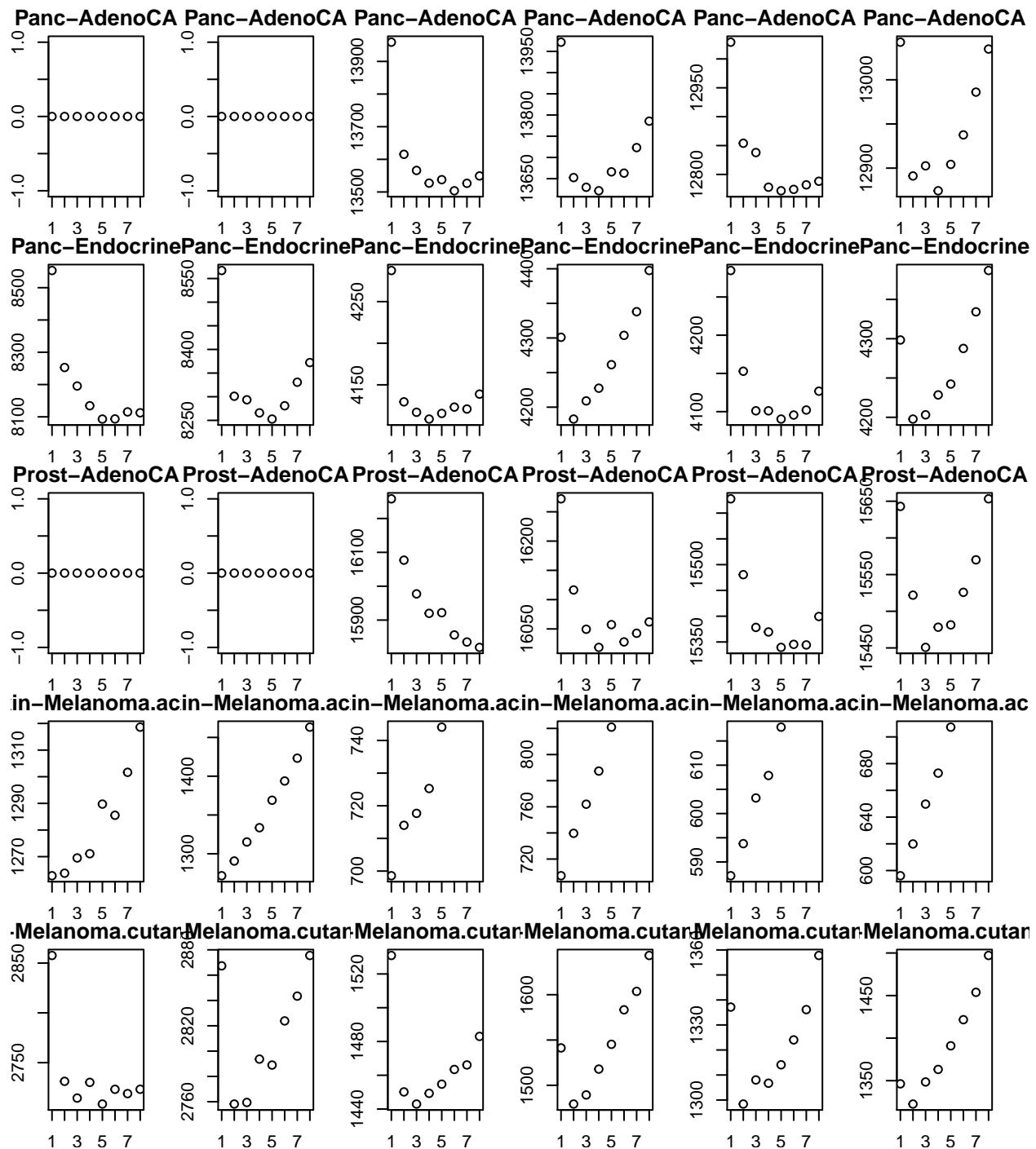
In some cases DMM says that there is an error with the input file - in this case the AIC or BIC is not plotted. If all of them are missing, all BIC and AIC are set to zero.

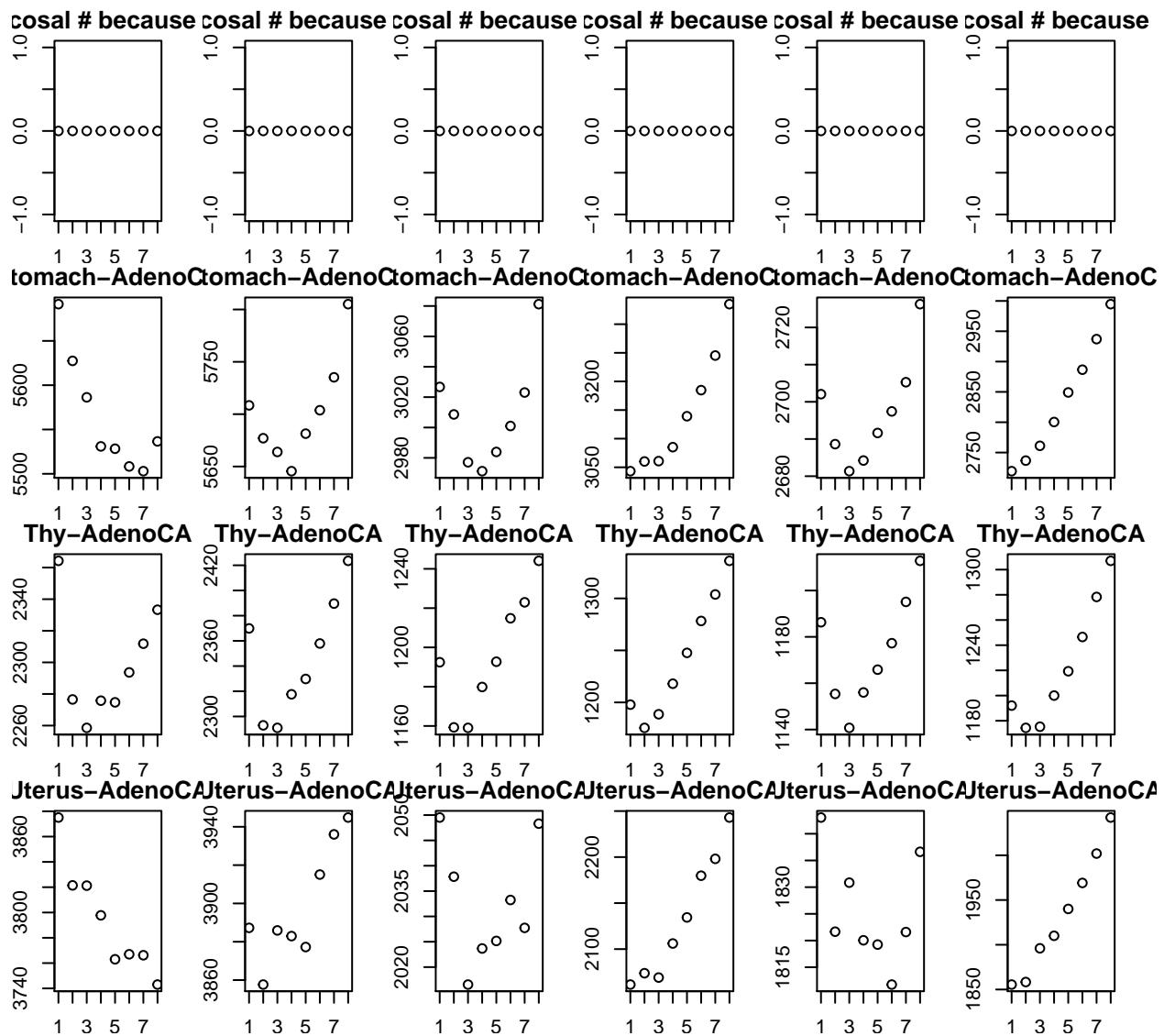




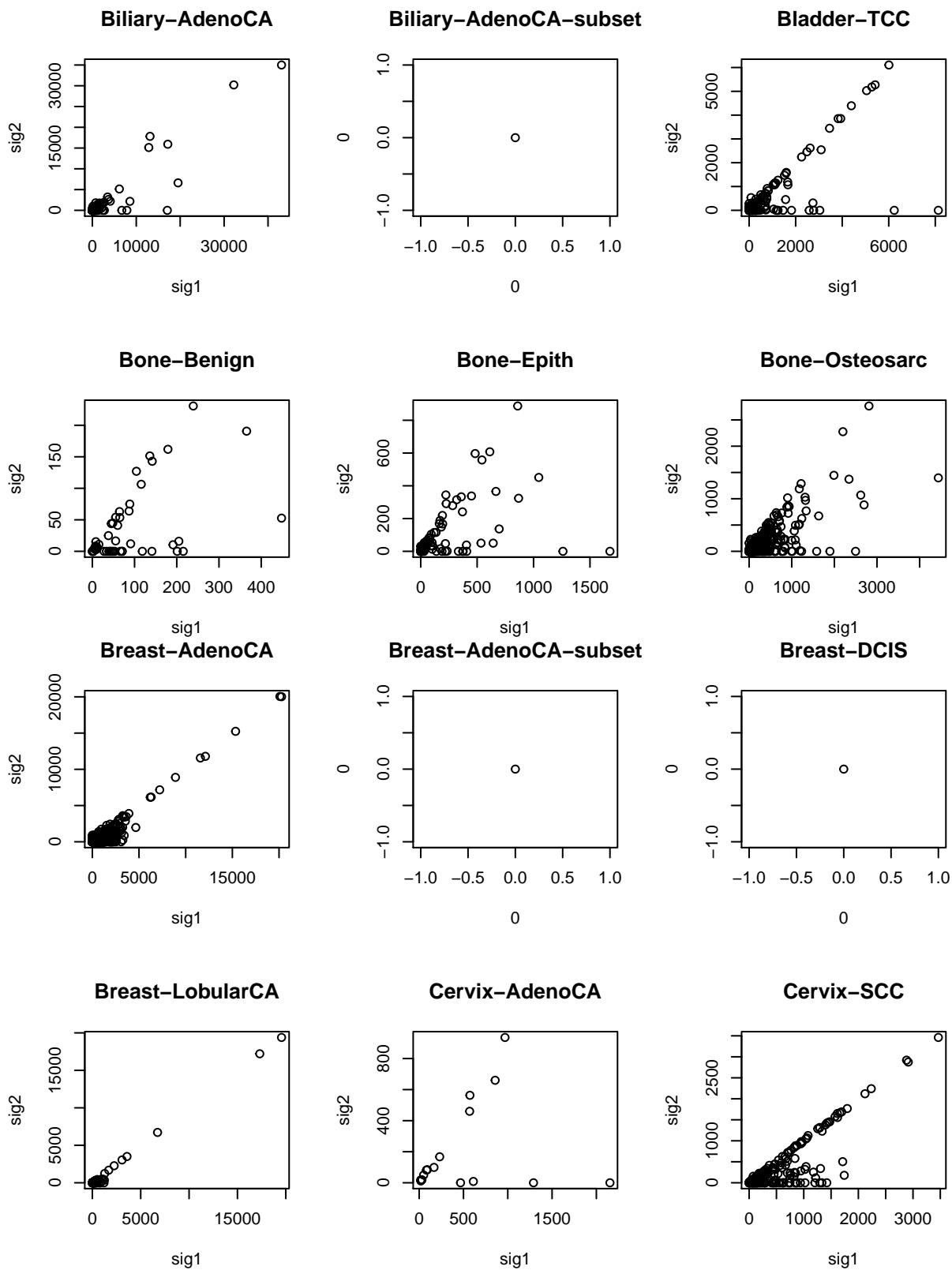


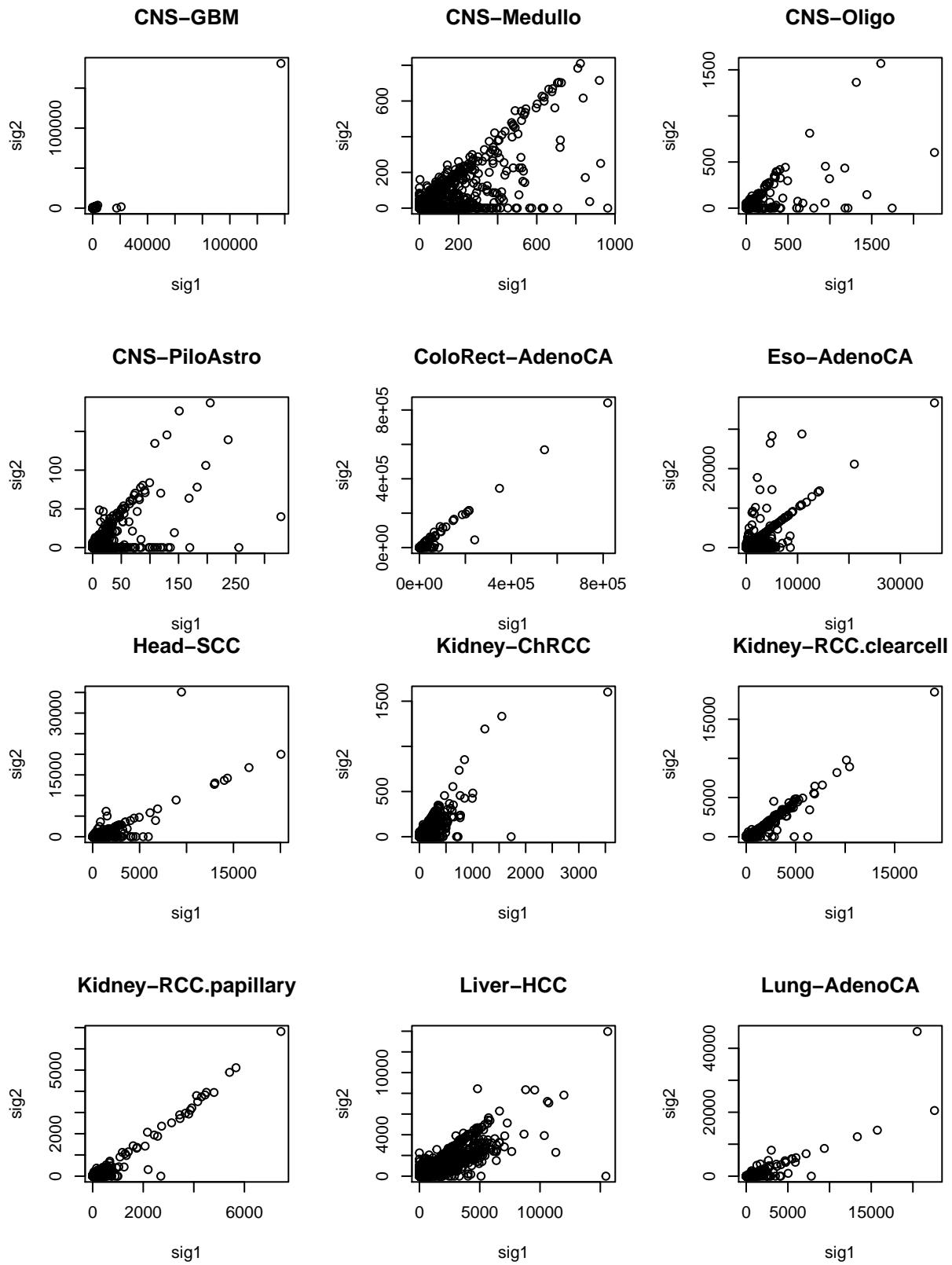


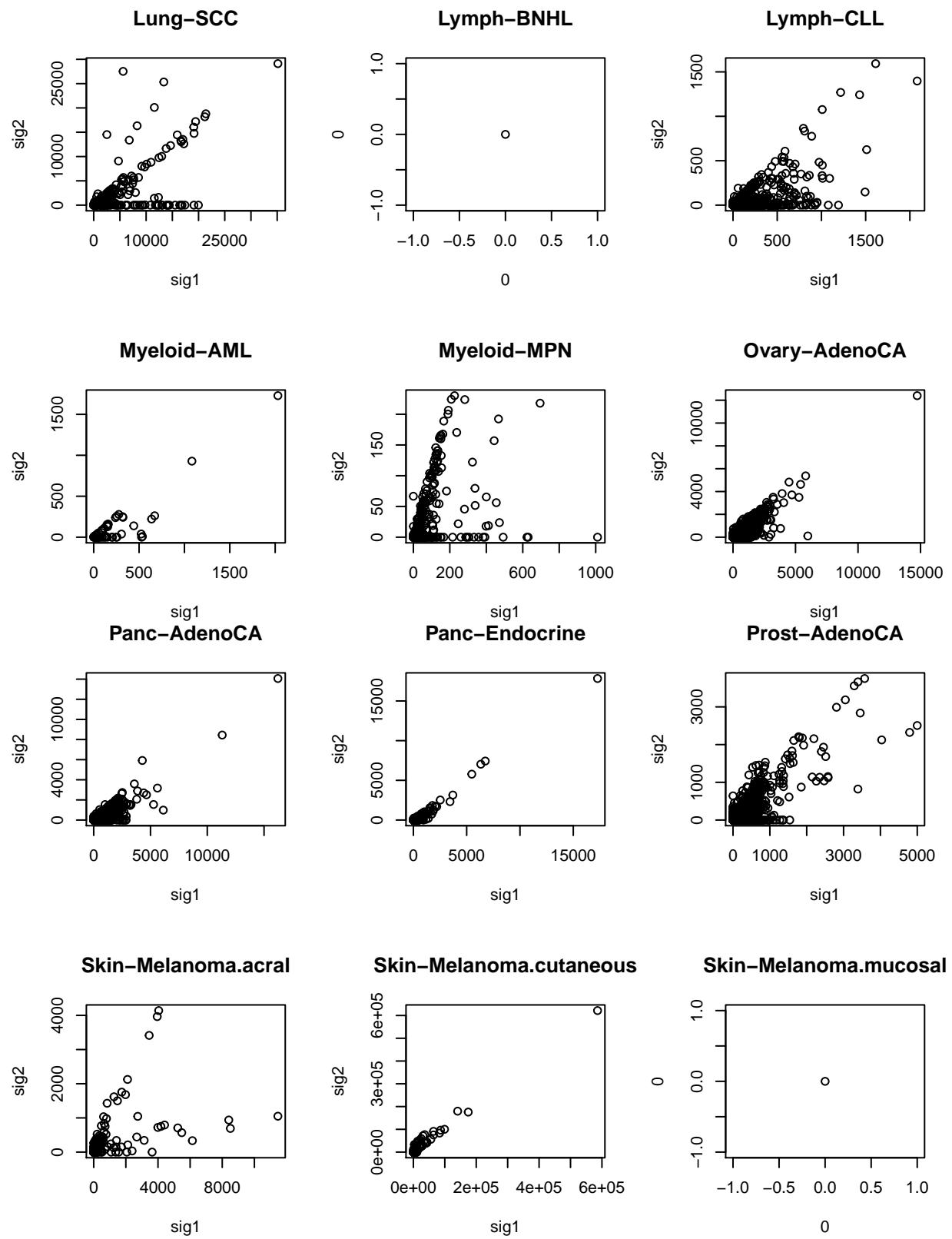


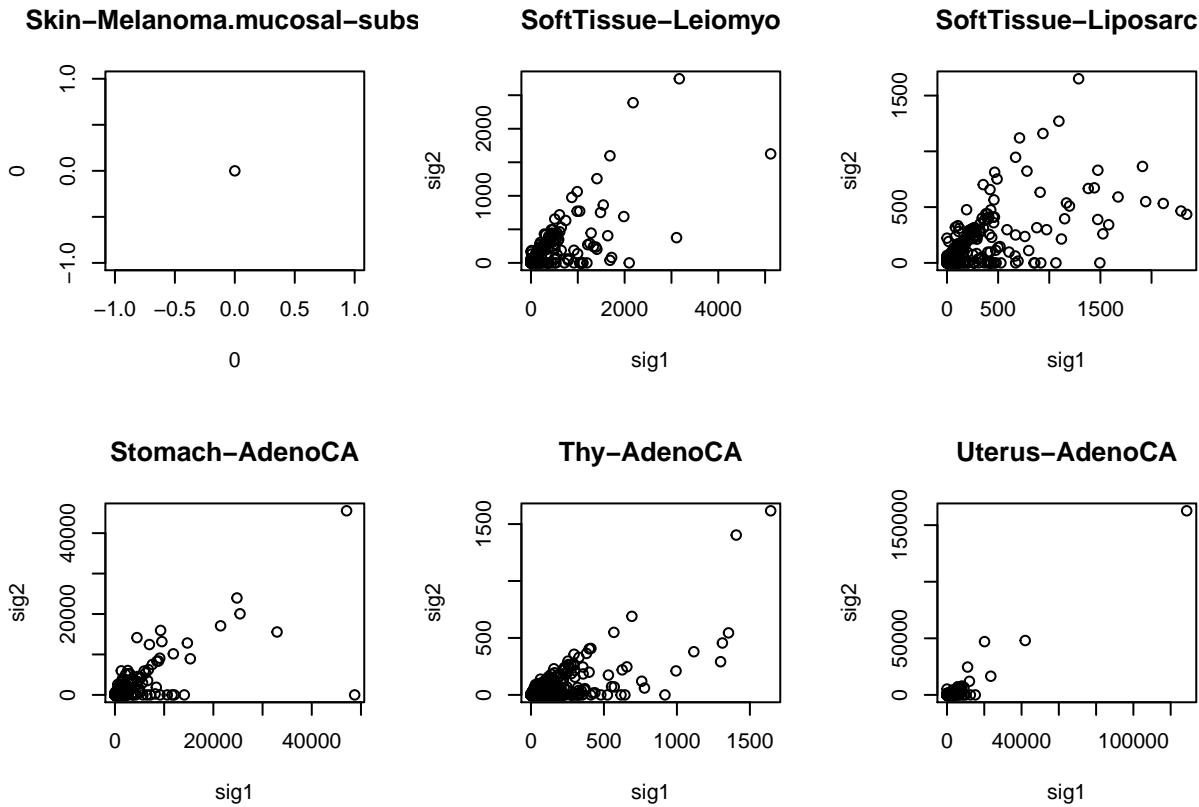


Comparison of signature exposures with QP and mutsigextractor









Correlation of p-values and number of samples

```

ggplot(data.frame(num_samples=num_samples[match(all_pvals$ct, names(num_samples))],
                  pvalue=all_pvals$pvalue,
                  ct=all_pvals$ct), aes(x=num_samples, y=pvalue, label=ct))+  

  geom_point() + scale_y_continuous(trans = "log2") +  

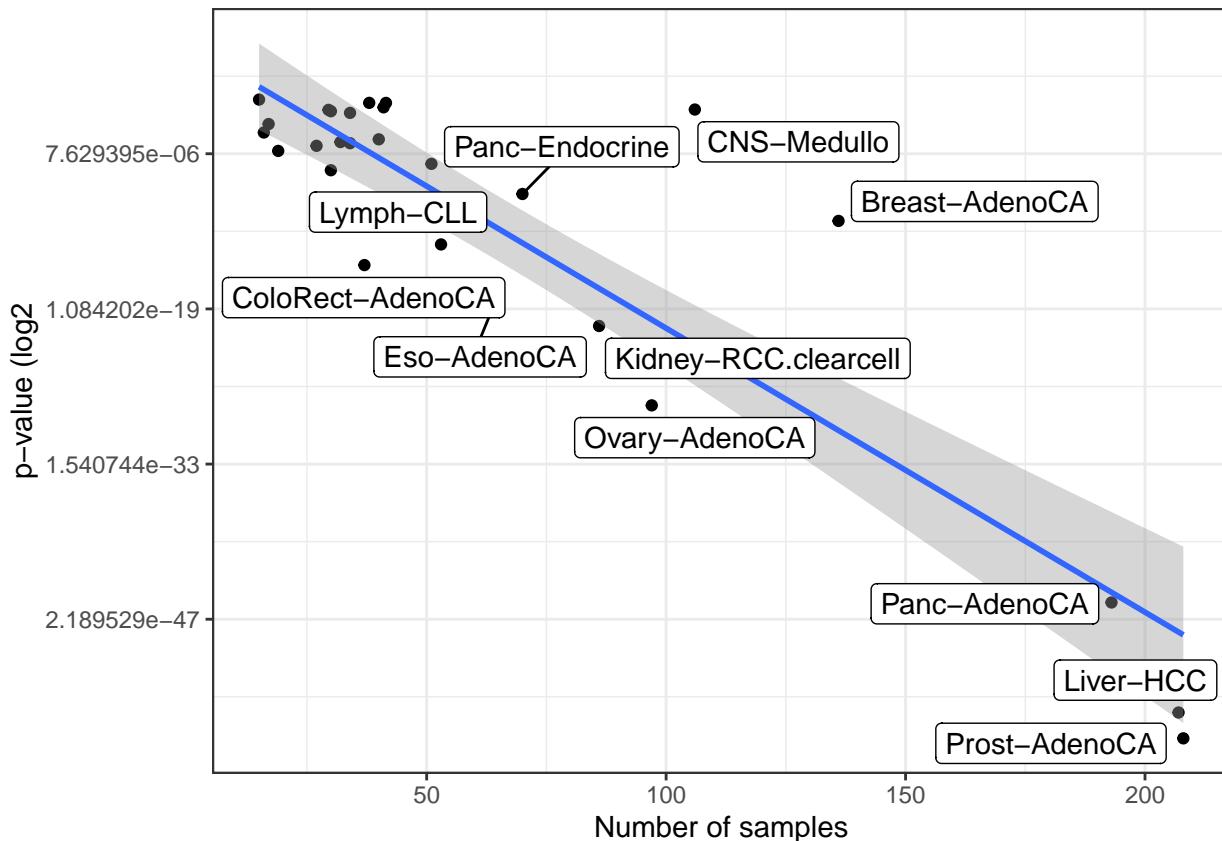
  geom_smooth(method = lm) + theme_bw() +  

  geom_label_repel() + geom_hline(yintercept = log2(0.05), lty='dashed') +  

  labs(x='Number of samples', y = 'p-value (log2)')

## Warning in log(x, base): NaNs produced
## Warning: Transformation introduced infinite values in continuous y-axis
## `geom_smooth()` using formula 'y ~ x'
## Warning: Removed 1 rows containing non-finite values (stat_smooth).
## Warning: Removed 1 rows containing missing values (geom_point).
## Warning: Removed 1 rows containing missing values (geom_label_repel).
## Warning: Removed 1 rows containing missing values (geom_hline).
## Warning: ggrepel: 16 unlabeled data points (too many overlaps). Consider
## increasing max.overlaps

```



Effect size

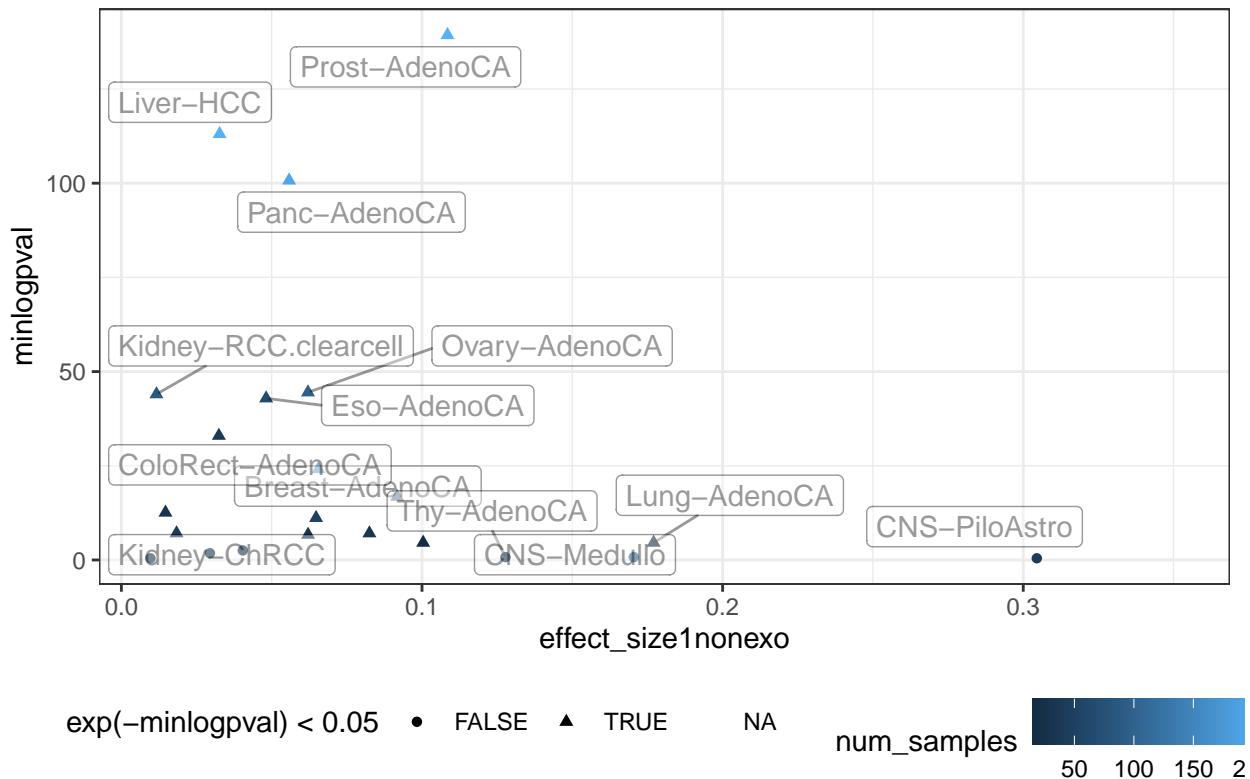
We are dealing with multivariate data, and it is not clear how we could come up with a metric to show the change between two sets of paired mutational signatures.

- From the Aitchison school, the ‘perturbation’ is what is used, and is a $d - 1$ -dimensional vector. We must turn this value into a single value.

$$e_1 = \frac{\sum_{i=1}^n (\bar{W}_i^l - \bar{W}_i^e)^2}{n}$$

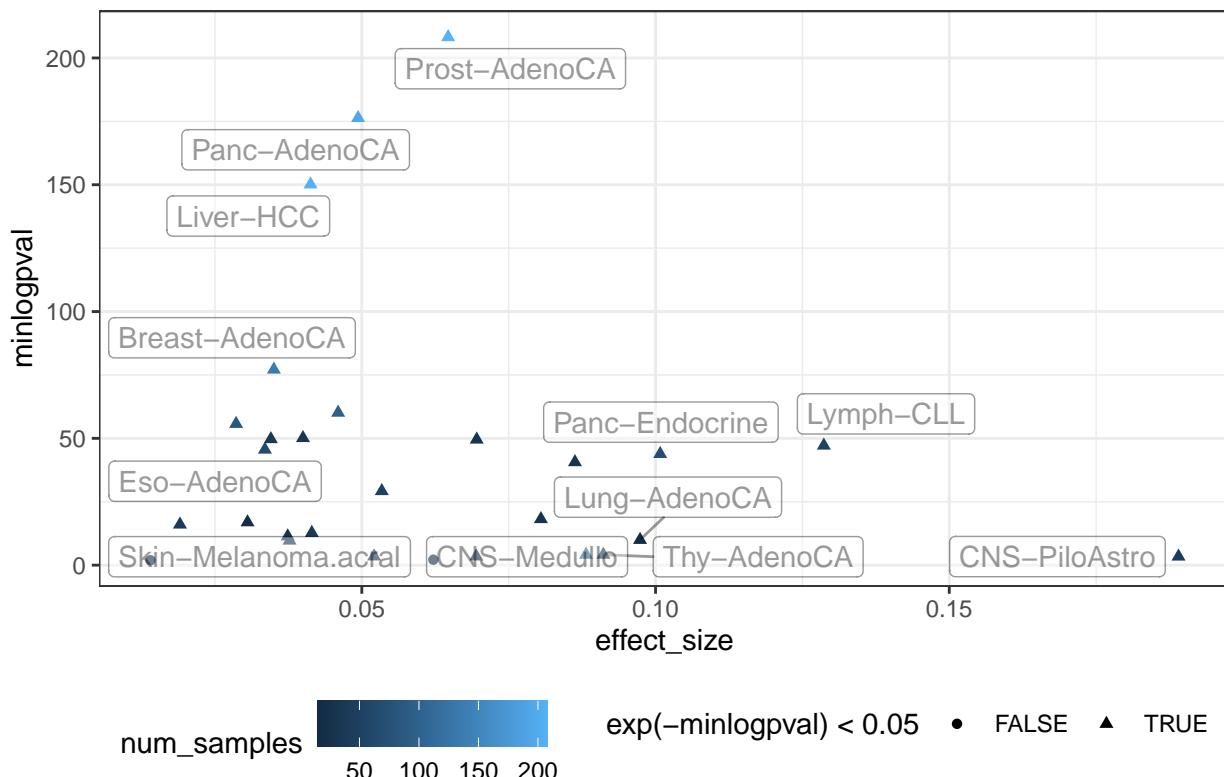
```
## Warning: Removed 6 rows containing missing values (geom_point).
## Warning: Removed 6 rows containing missing values (geom_label_repel).
## Warning: ggrepel: 9 unlabeled data points (too many overlaps). Consider
## increasing max.overlaps
```

Effect size #1, nonexo



```
## Warning: ggrepel: 16 unlabeled data points (too many overlaps). Consider
## increasing max.overlaps
```

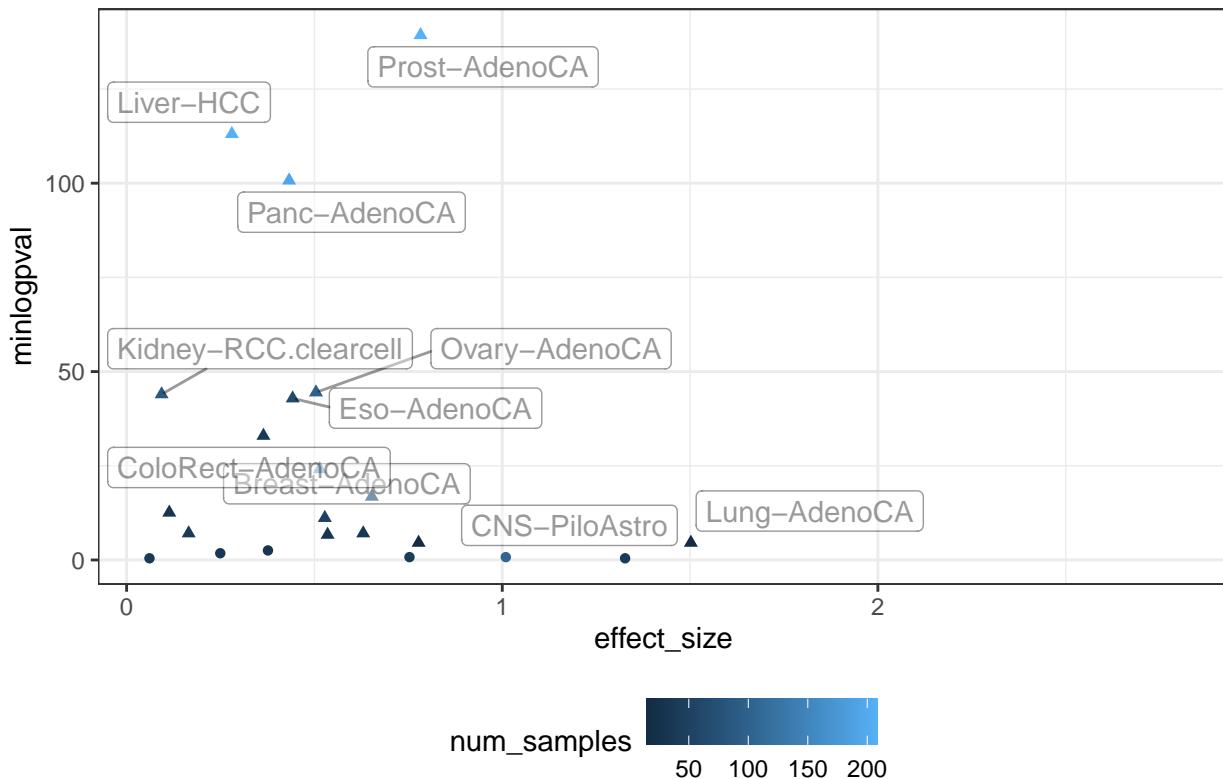
Effect size #1, all sigs



$$e_2 = \frac{\sum_{i=1}^n (\bar{W}_i^l - \bar{W}_i^e)^2}{n} \cdot \log \left(\frac{\sum_{i=1}^n \sum_{j=1}^k W_{ij}}{n} \right)$$

```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
## Warning: Removed 6 rows containing missing values (geom_point).
## Warning: Removed 6 rows containing missing values (geom_label_repel).
## Warning: ggrepel: 12 unlabeled data points (too many overlaps). Consider
## increasing max.overlaps
```

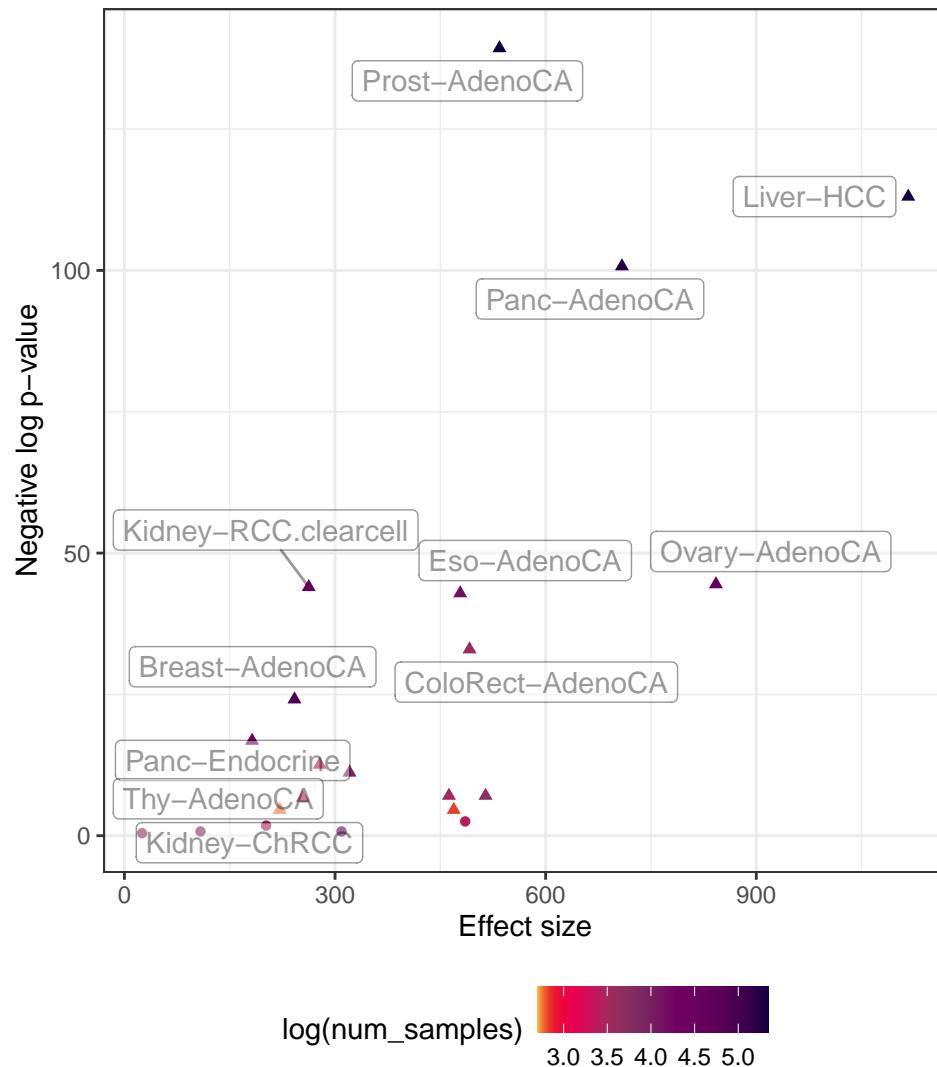
Effect size #2, nonexo



Signature-averaged perturbation

```
## Error in apply(pert, 1, function(i) sqrt(sum((i - 1/(ncol(exposures_cancertype_obj$Y)))^2))) :
##   dim(X) must have a positive length
## Error in apply(pert, 1, function(i) sqrt(sum((i - 1/(ncol(exposures_cancertype_obj$Y)))^2))) :
##   dim(X) must have a positive length
## Warning: NAs introduced by coercion
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
## Warning: Removed 7 rows containing missing values (geom_point).
## Warning: Removed 7 rows containing missing values (geom_label_repel).
## Warning: ggrepel: 10 unlabeled data points (too many overlaps). Consider
## increasing max.overlaps
```

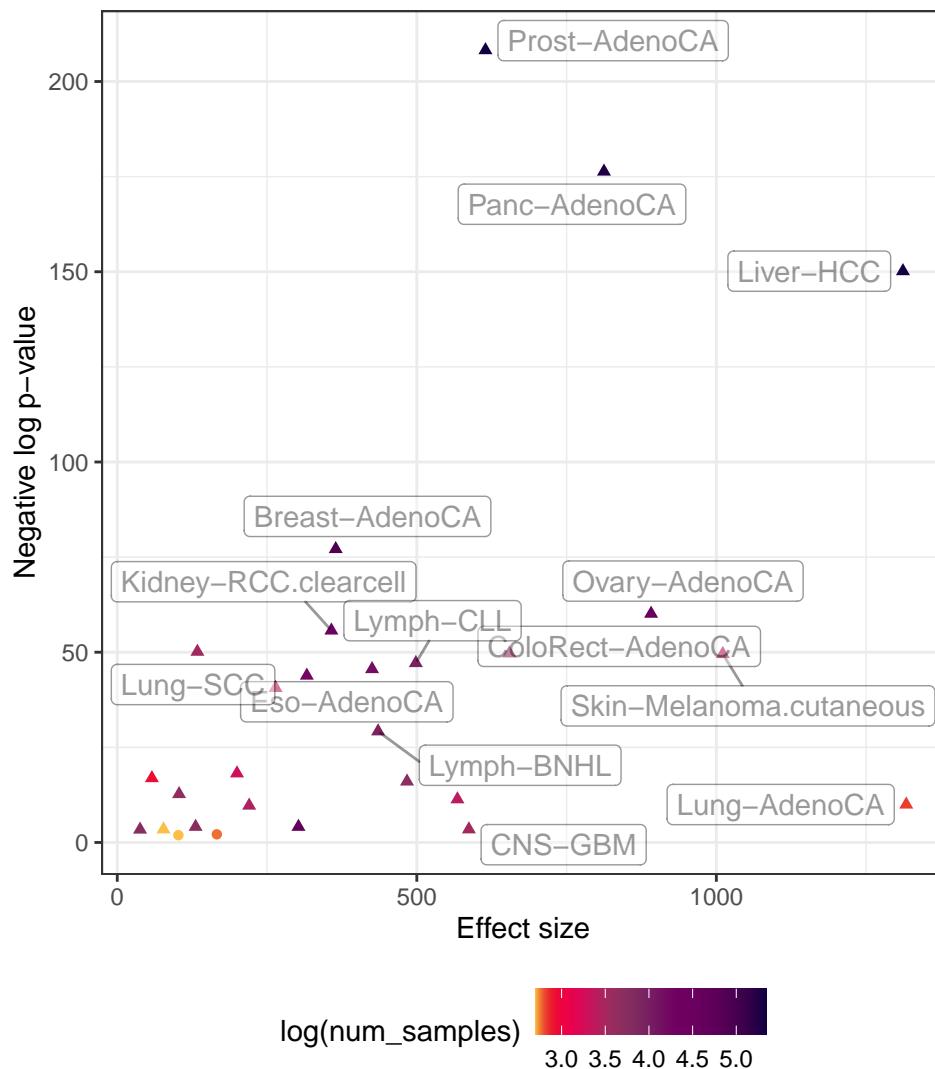
Total perturbation, non-exogenous signatures



Signature-averaged perturbation (all sigs)

```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
## Warning: ggrepel: 14 unlabeled data points (too many overlaps). Consider
## increasing max.overlaps
```

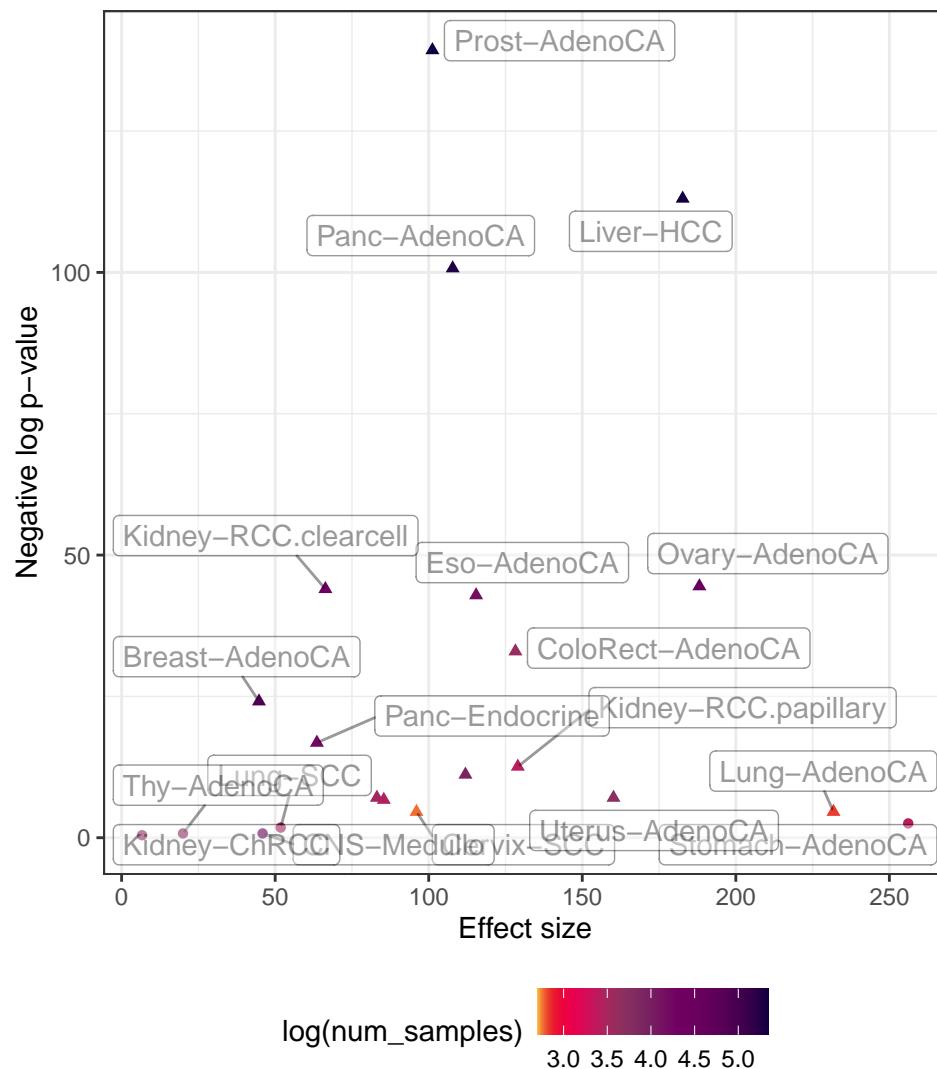
Total perturbation, all signatures



Total perturbation (sample-averaged)

```
## Error in apply(pert, 2, function(i) sqrt(sum((i - 1/(ncol(exposures_cancertype_obj$Y)))^2))) :
##   dim(X) must have a positive length
## Error in apply(pert, 2, function(i) sqrt(sum((i - 1/(ncol(exposures_cancertype_obj$Y)))^2))) :
##   dim(X) must have a positive length
## Warning: NAs introduced by coercion
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
## Warning: Removed 7 rows containing missing values (geom_point).
## Warning: Removed 7 rows containing missing values (geom_label_repel).
## Warning: ggrepel: 3 unlabeled data points (too many overlaps). Consider
## increasing max.overlaps
```

Total perturbation, non-exogenous signatures

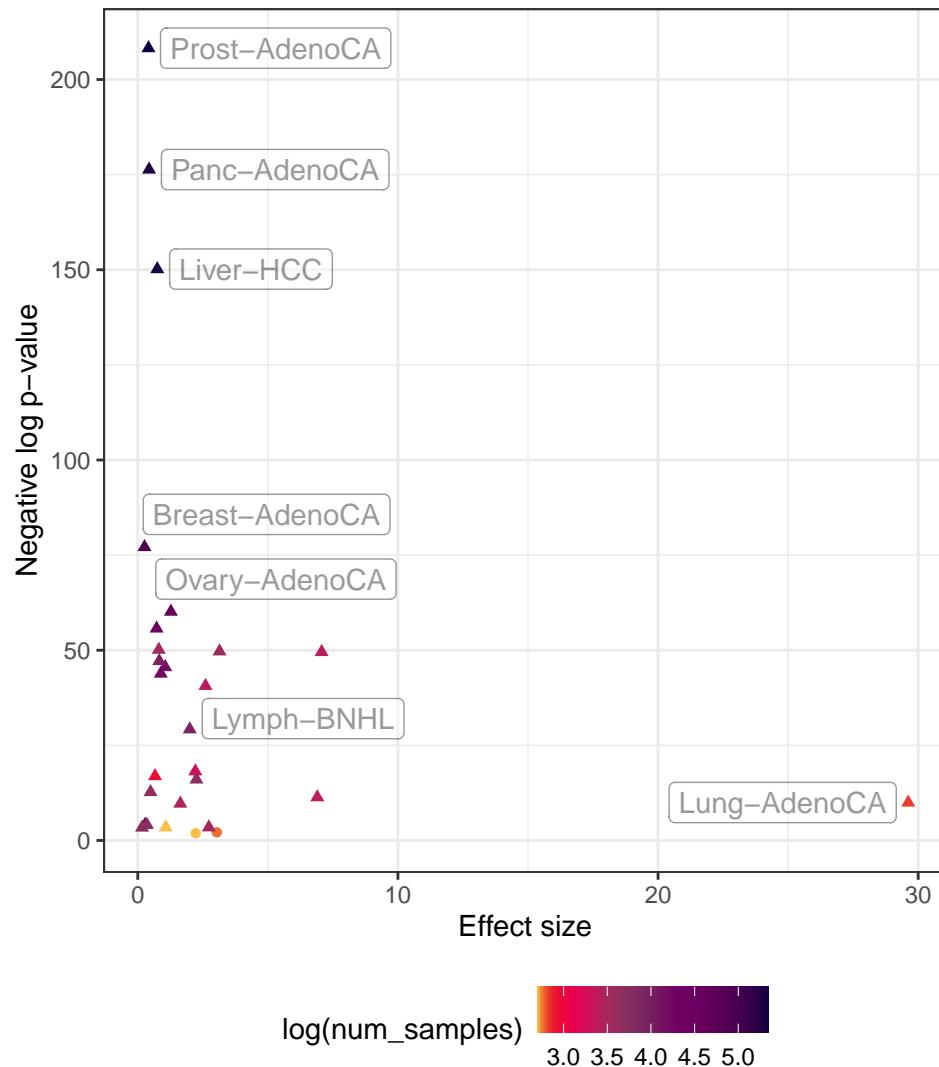


Weighted total perturbation

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

## Warning: ggrepel: 21 unlabeled data points (too many overlaps). Consider
## increasing max.overlaps
```

Weighted total perturbation, all signatures



Which inferred covariance matrices are not positive semi-definite?

```

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i))
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

```



```

## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error : $ operator is invalid for atomic vectors

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error : $ operator is invalid for atomic vectors
## Error : $ operator is invalid for atomic vectors
## Error : $ operator is invalid for atomic vectors

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :

```

```

## replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
## replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
## replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
## replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
## replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
## replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
## replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
## replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
## replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
## replacement has length zero

```

```

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
##   replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
##   replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
##   replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
##   replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
##   replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
##   replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
##   replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
##   replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
##   replacement has length zero

```

```

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
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## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
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## Error : $ operator is invalid for atomic vectors

```

```

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
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## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

```

```

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## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
##   replacement has length zero

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```

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##   replacement has length zero

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##   replacement has length zero

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##   replacement has length zero

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## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

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##   replacement has length zero
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##   replacement has length zero

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## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
##   replacement has length zero
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## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
##   replacement has length zero
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## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

```

```
## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
##   replacement has length zero

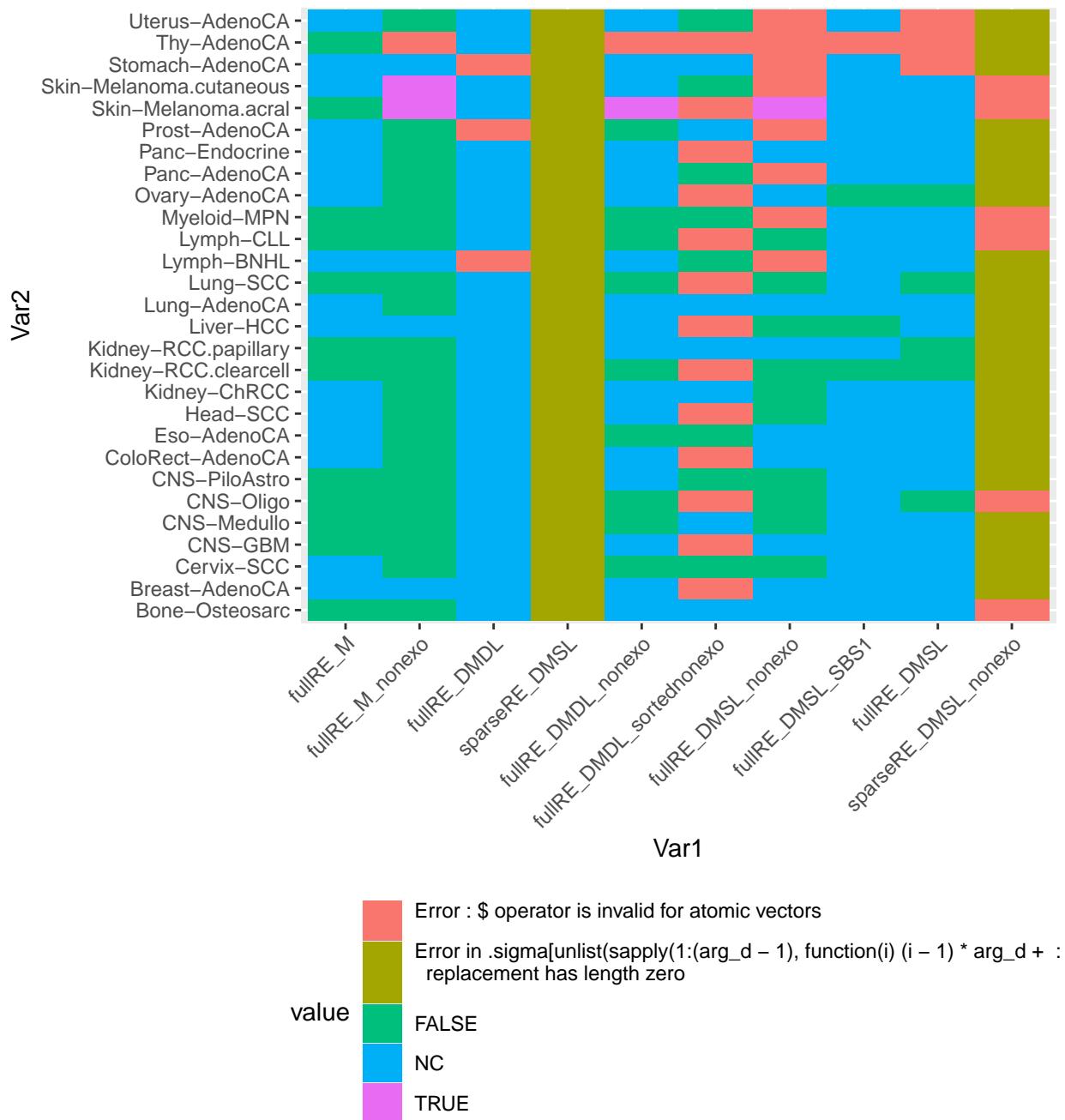
## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
##   replacement has length zero

## Warning in fill_covariance_matrix(arg_d = length(python_like_select_name(get(i)
## [[ct]]$par.fixed, : This function had been incorrect until now (30 july 2021)

## Error in m[unlist(sapply(2:nrow(m), function(rw) seq(from = rw, length.out = (rw - :
##   replacement has length zero

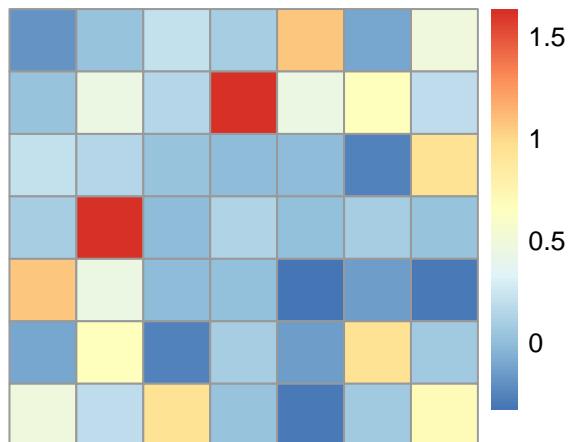
## [1] 11 28
## [1] 308   3
## [1] "Var1"  "Var2"  "value"
```



Comparison of the inferred covariance matrices and the matrices from the fitted intercepts

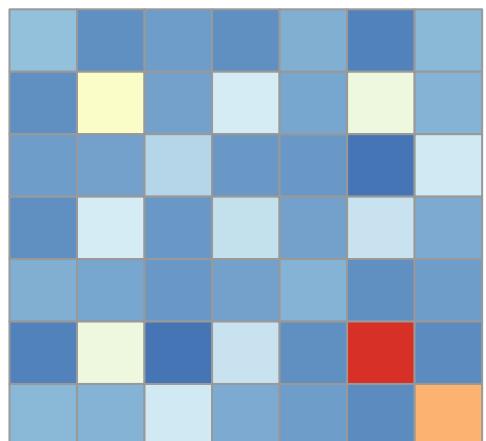
```
## [1] "Bone-Osteosarc"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```

Bone-Osteosarc
inferred

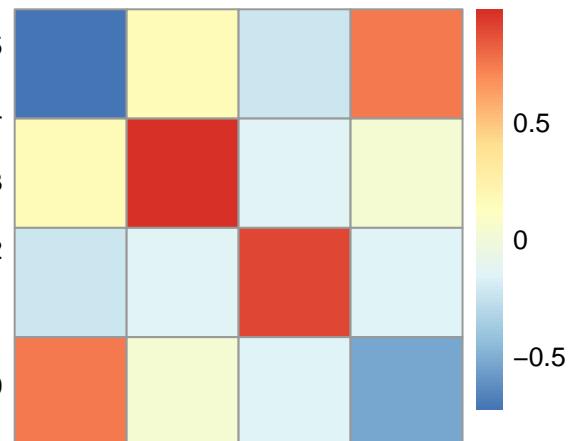


```
## [1] "CNS-GBM"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```

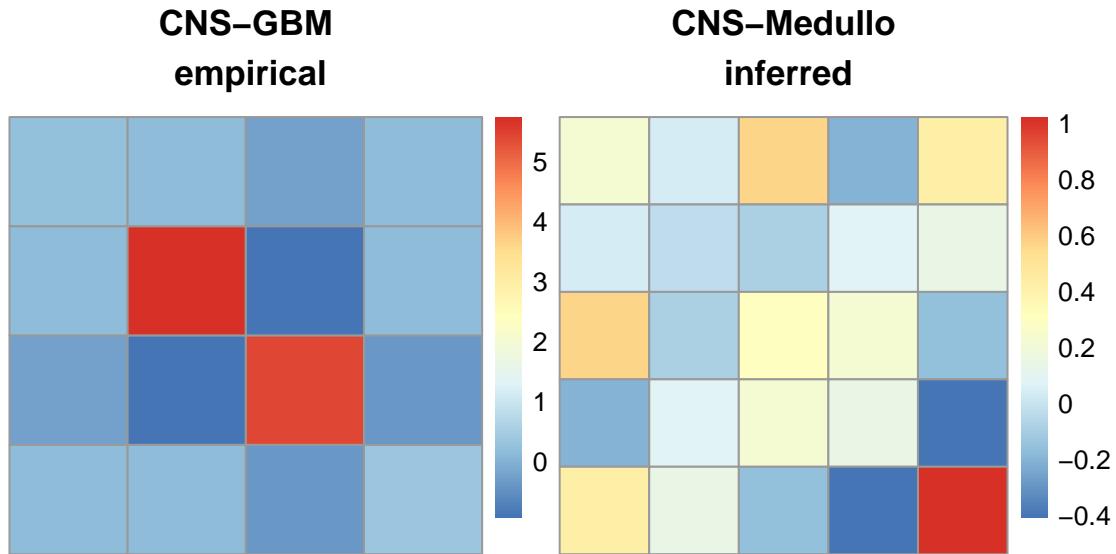
Bone-Osteosarc
empirical



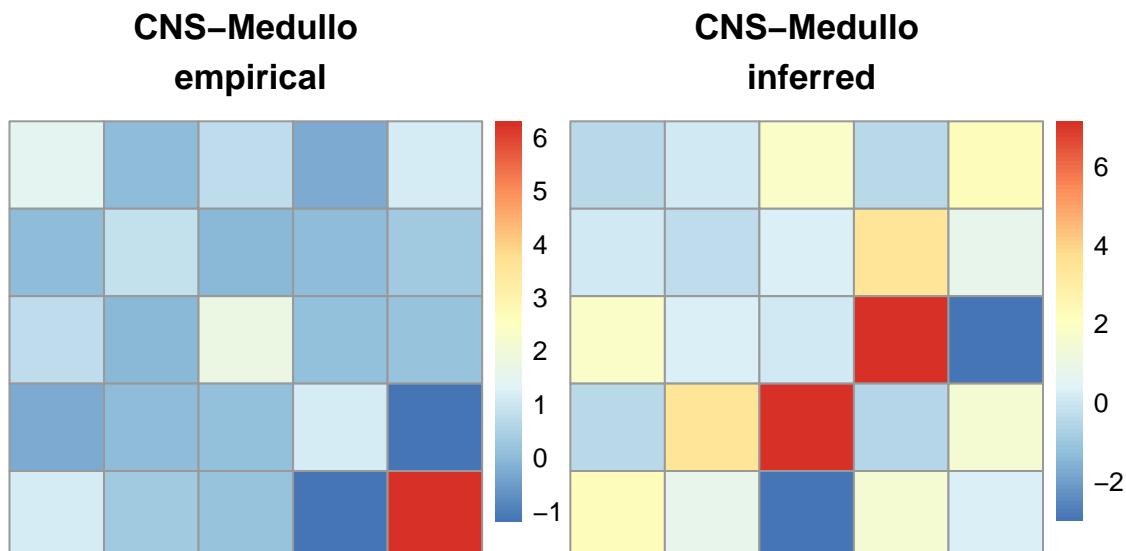
CNS-GBM
inferred



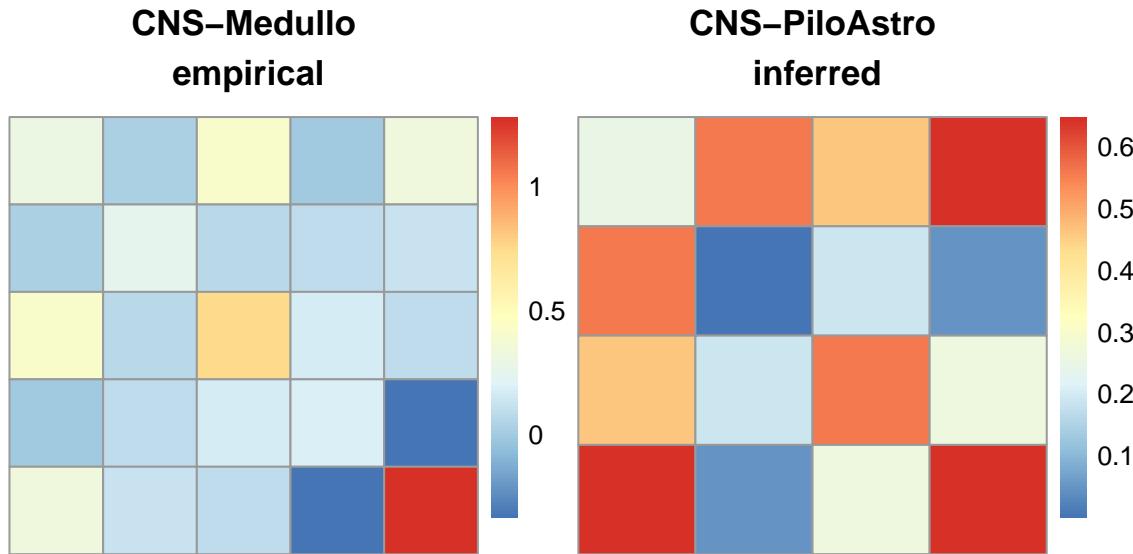
```
## [1] "CNS-Medullo"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```



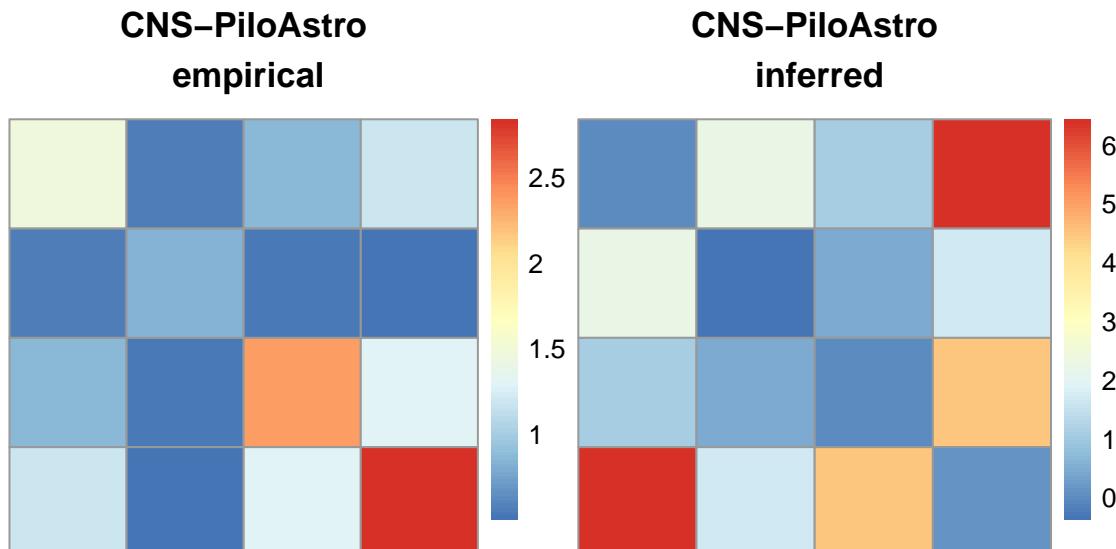
```
## [1] "CNS-Medullo"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```



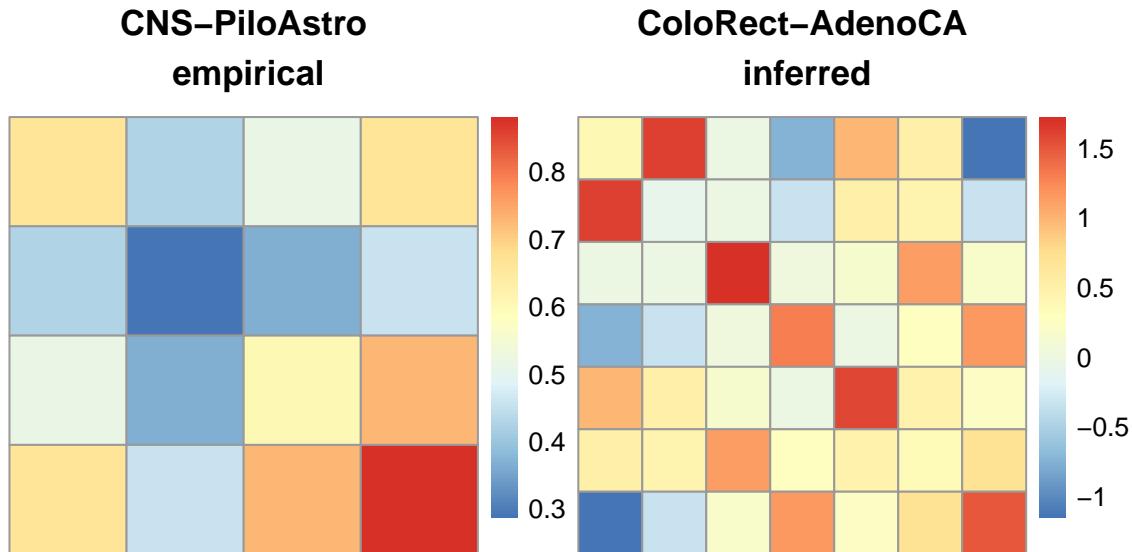
```
## [1] "CNS-PiloAstro"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```



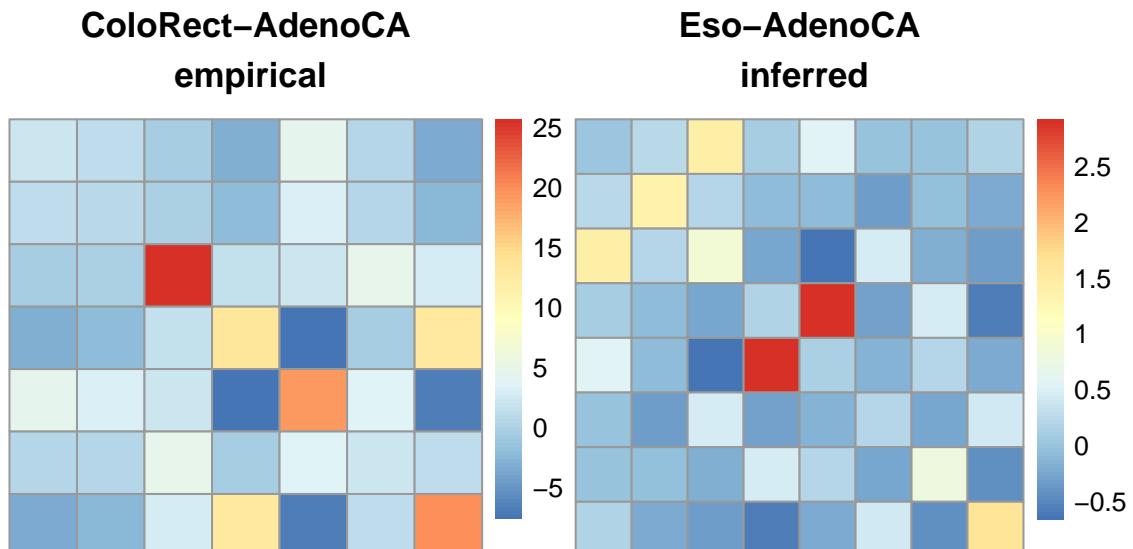
```
## [1] "CNS-PiloAstro"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```



```
## [1] "ColoRect-AdenoCA"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```

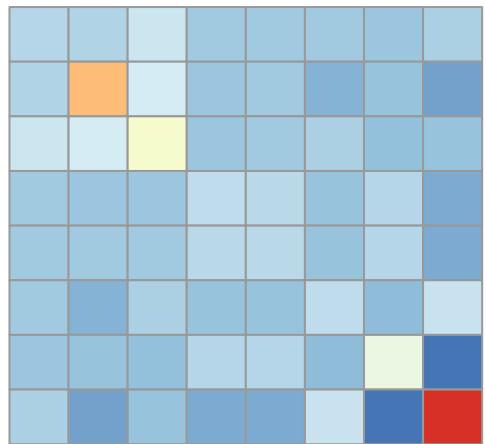


```
## [1] "Eso-AdenoCA"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```

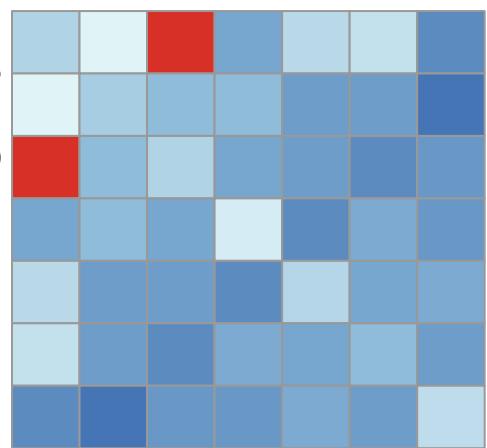


```
## [1] "Head-SCC"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```

Eso-AdenoCA
empirical

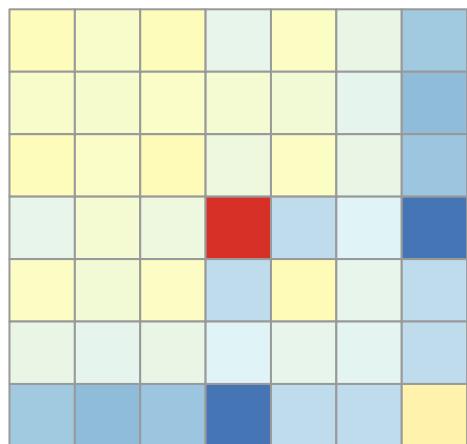


Head-SCC
inferred

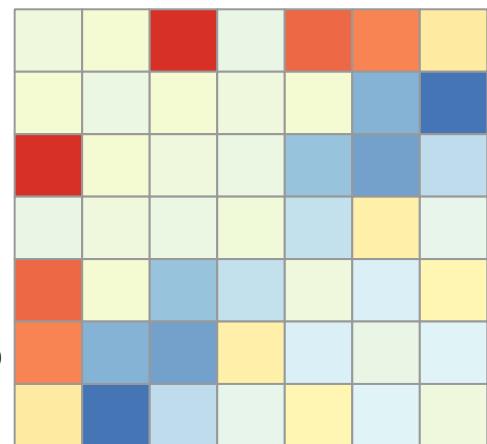


```
## [1] "Head-SCC"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```

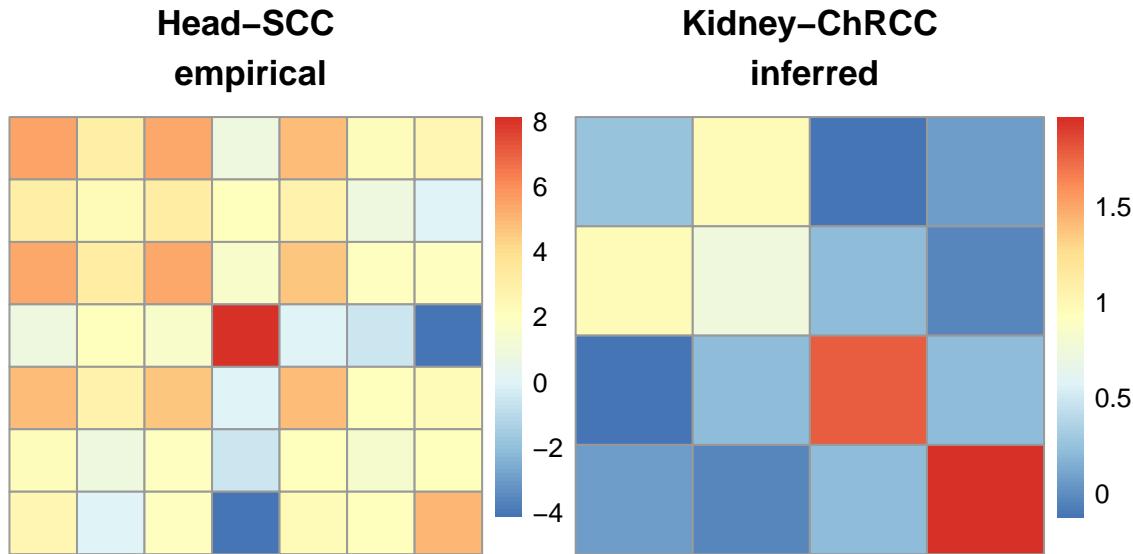
Head-SCC
empirical



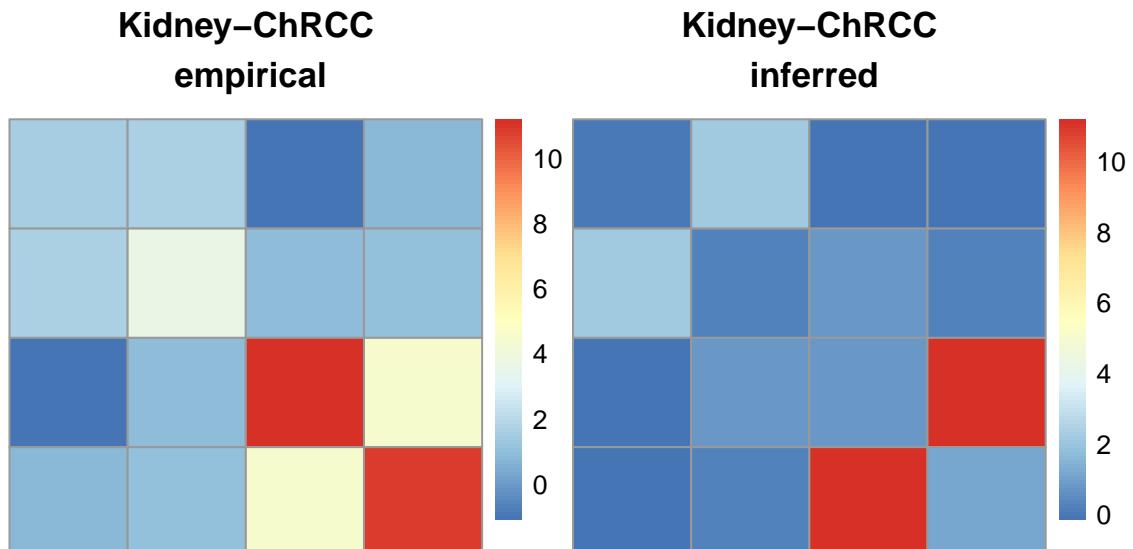
Head-SCC
inferred



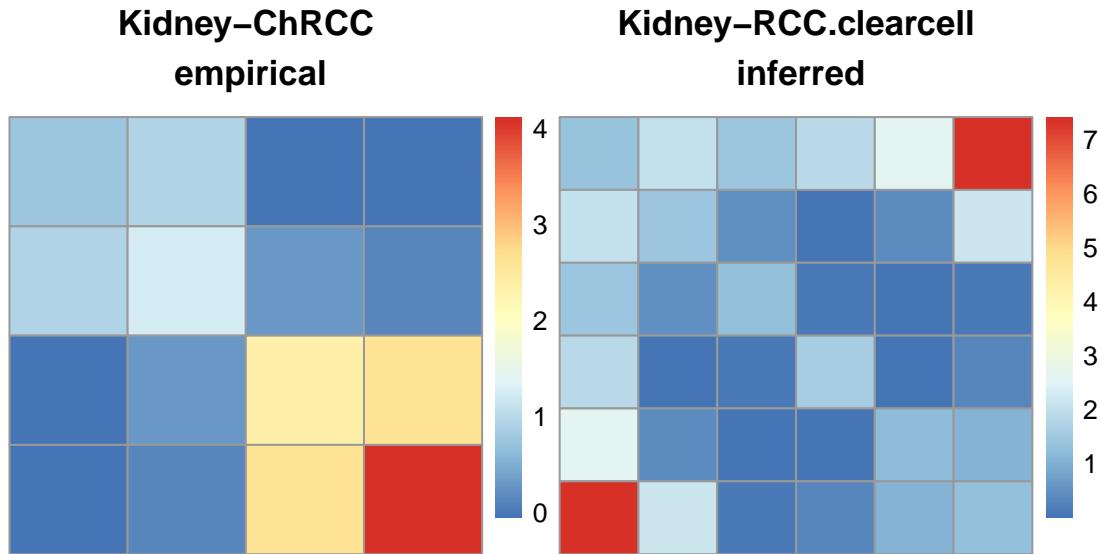
```
## [1] "Kidney-ChRCC"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```



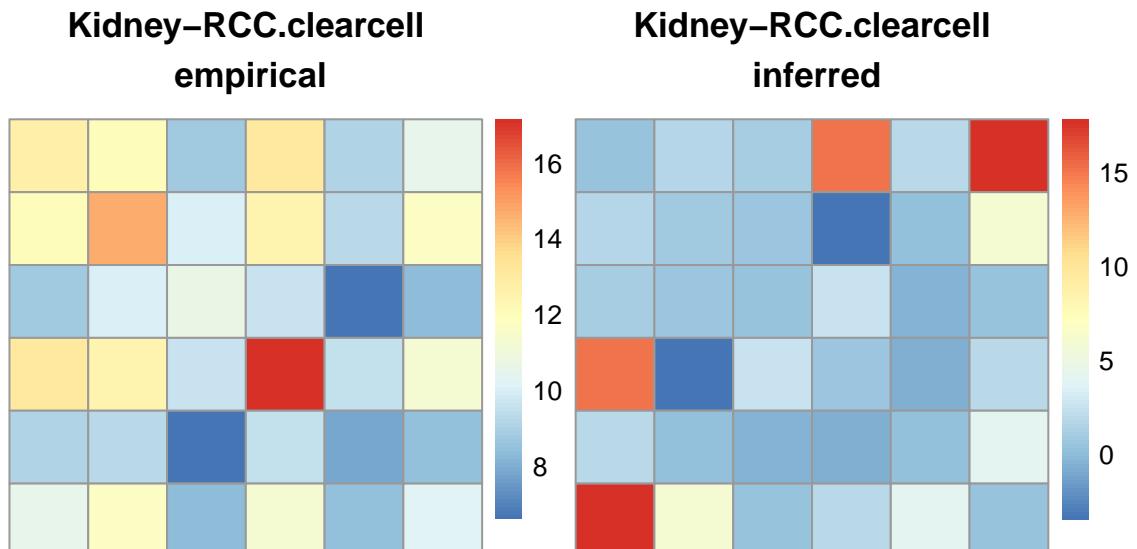
```
## [1] "Kidney-ChRCC"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```



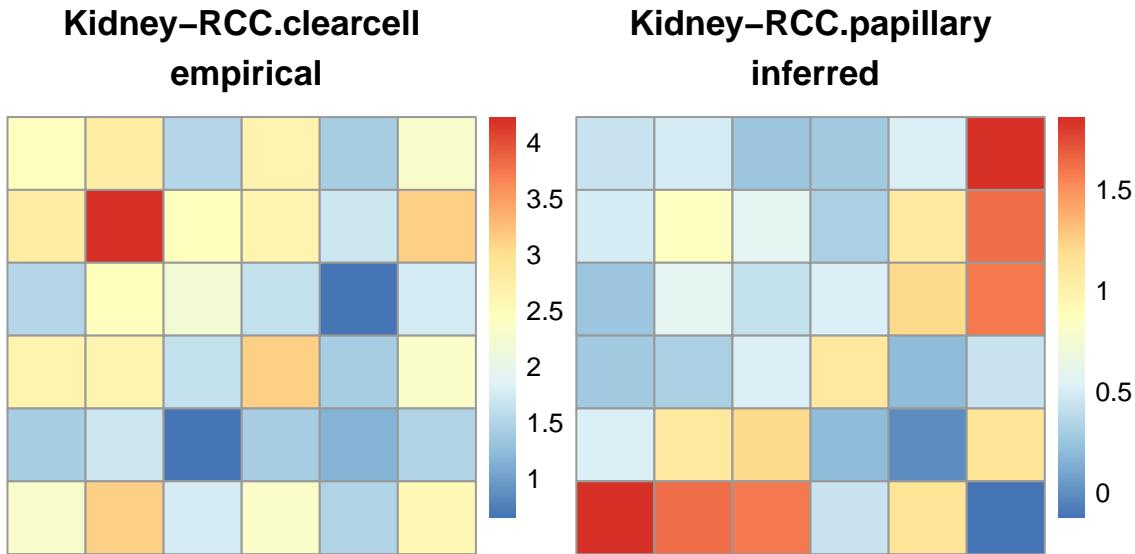
```
## [1] "Kidney-RCC.clearcell"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```



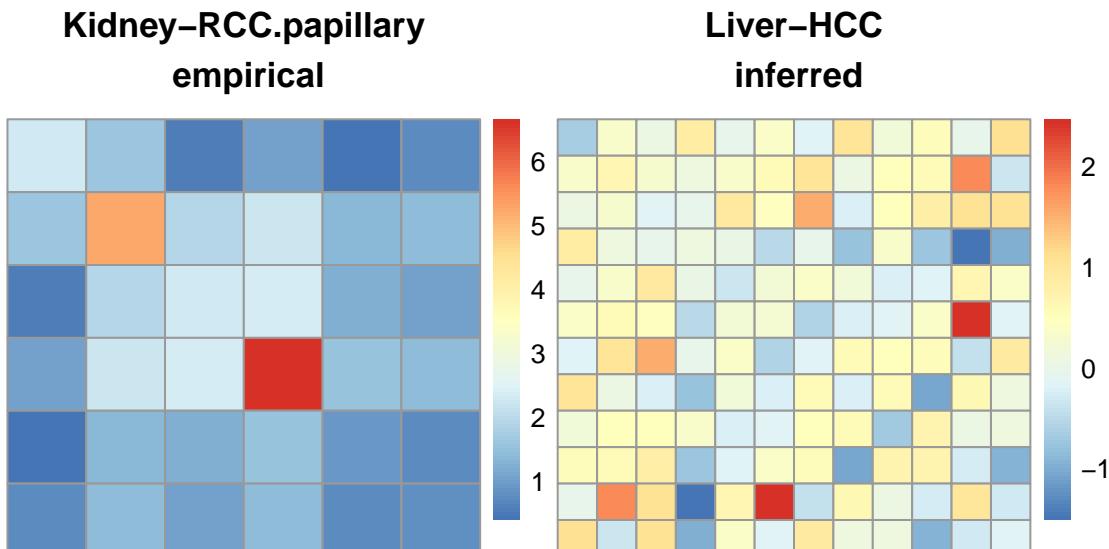
```
## [1] "Kidney-RCC.clearcell"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```



```
## [1] "Kidney-RCC.papillary"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```

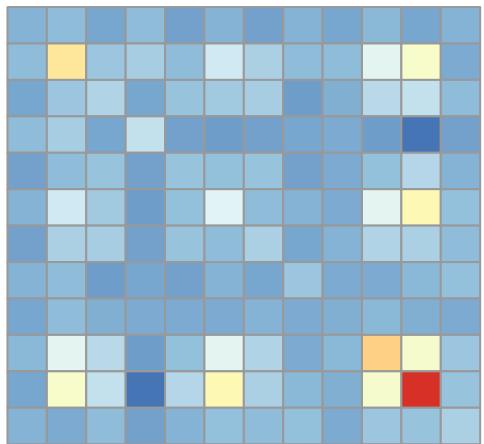


```
## [1] "Liver-HCC"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```

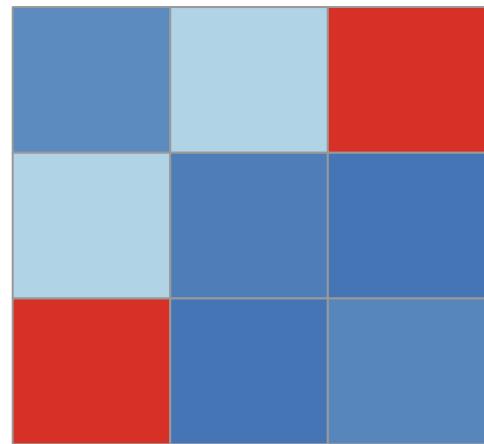


```
## [1] "Lung-SCC"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```

Liver-HCC
empirical

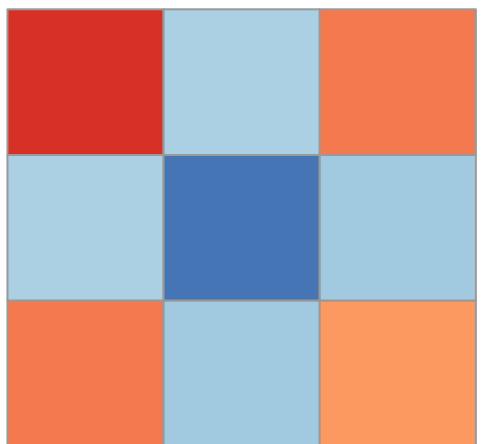


Lung-SCC
inferred

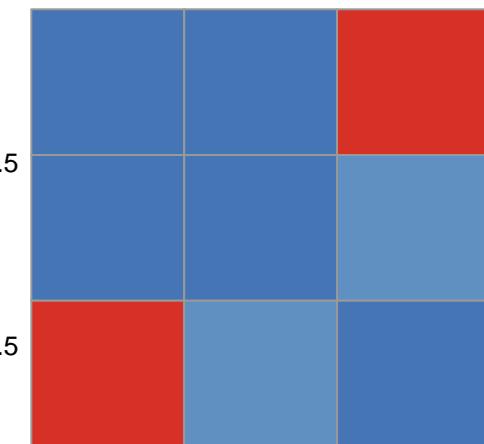


```
## [1] "Lung-SCC"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```

Lung-SCC
empirical

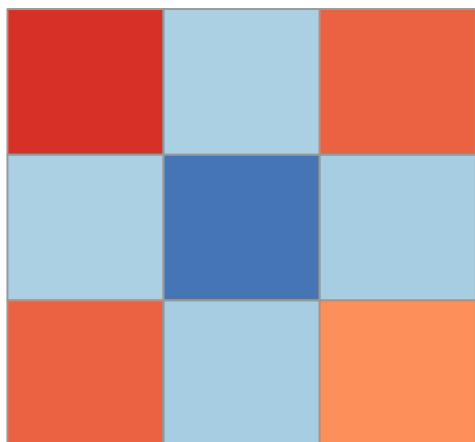


Lung-SCC
inferred

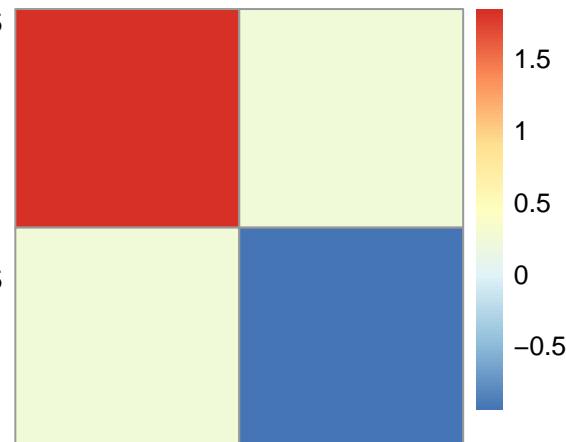


```
## Error : $ operator is invalid for atomic vectors
## [1] "Lymph-CLL"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```

**Lung-SCC
empirical**

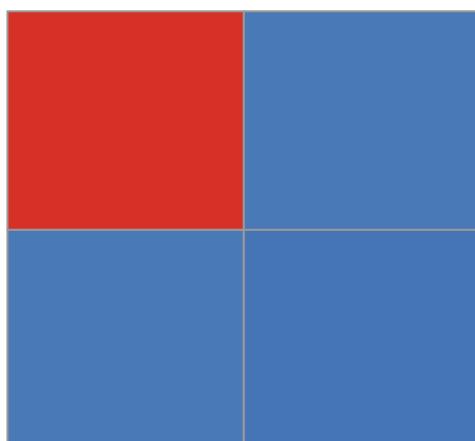


**Lymph-CLL
inferred**



```
## [1] "Lymph-CLL"  
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =  
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been  
## incorrect until now (30 july 2021)
```

**Lymph-CLL
empirical**

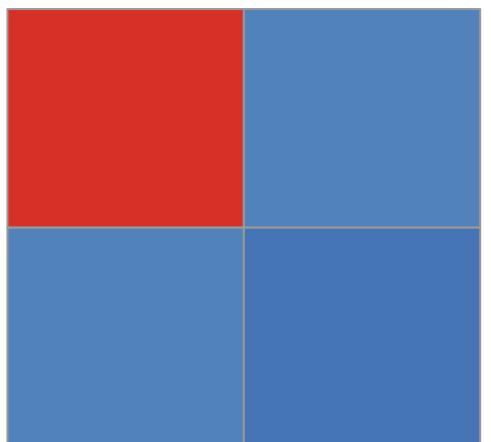


**Lymph-CLL
inferred**

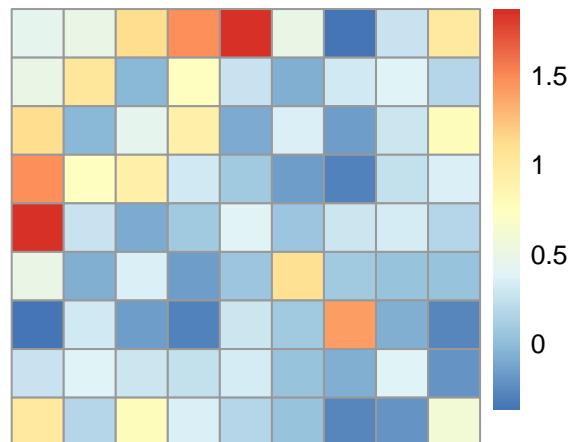


```
## [1] "Ovary-AdenoCA"  
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =  
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been  
## incorrect until now (30 july 2021)
```

Lymph–CLL
empirical

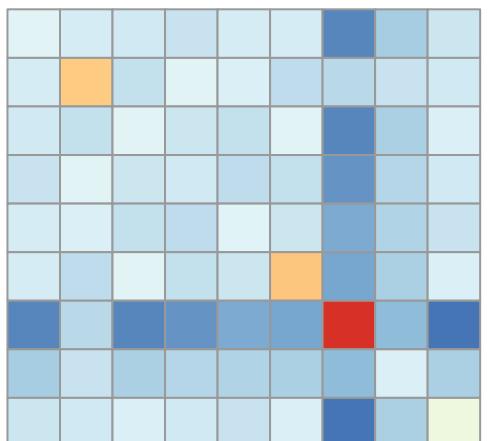


Ovary–AdenoCA
inferred

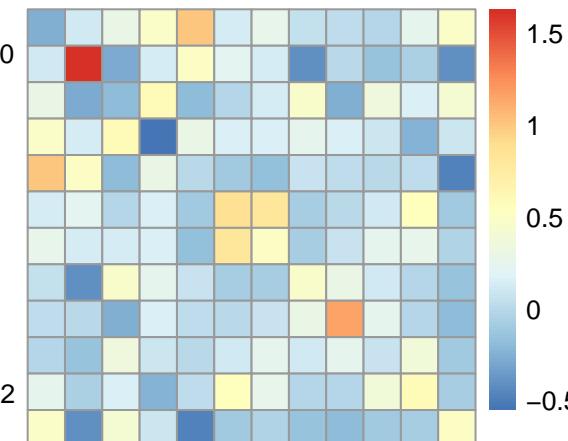


```
## [1] "Panc-AdenoCA"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```

Ovary–AdenoCA
empirical

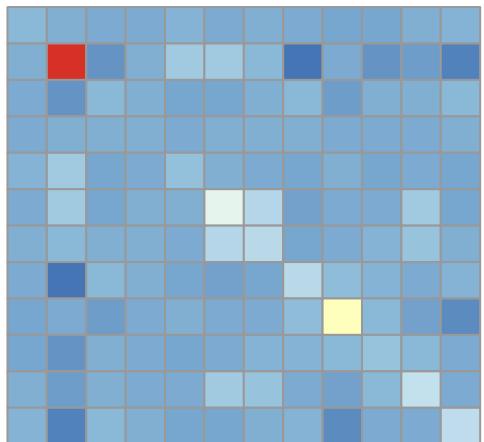


Panc–AdenoCA
inferred

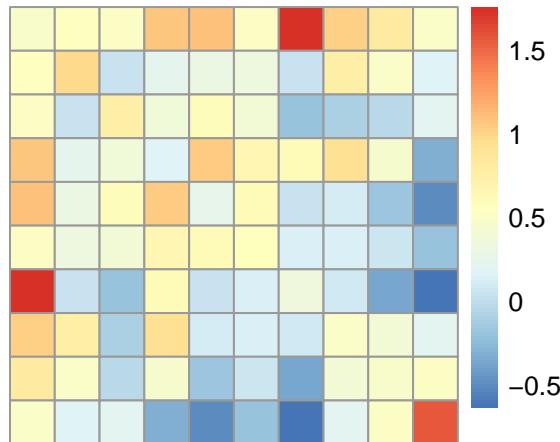


```
## Error : $ operator is invalid for atomic vectors
## [1] "Panc-Endocrine"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```

Panc–AdenoCA
empirical

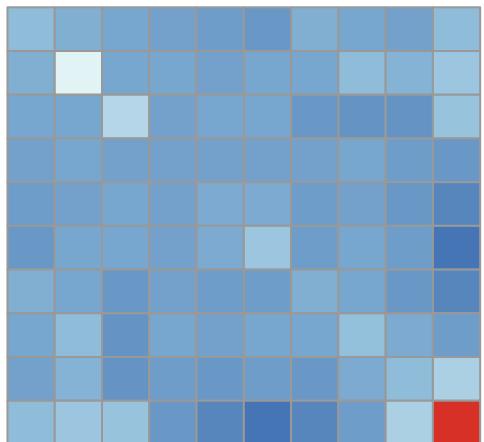


Panc–Endocrine
inferred

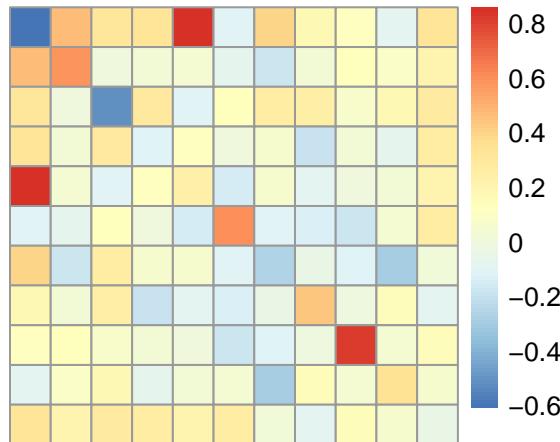


```
## [1] "Prost–AdenoCA"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```

Panc–Endocrine
empirical

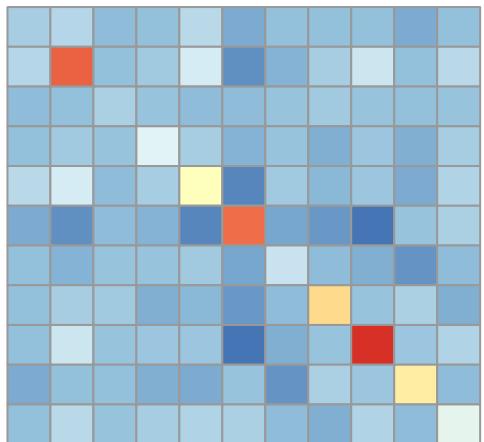


Prost–AdenoCA
inferred

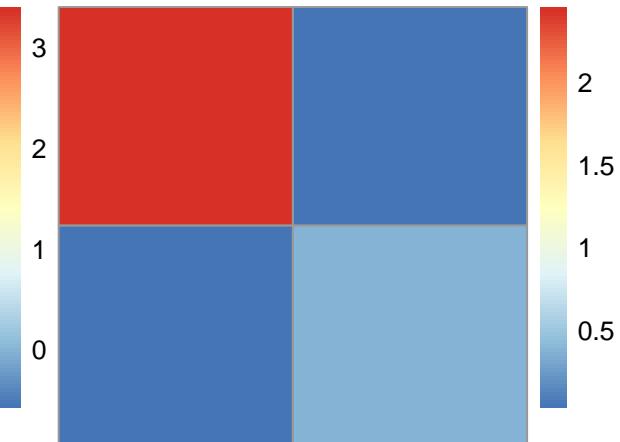


```
## Error : $ operator is invalid for atomic vectors
## [1] "Skin–Melanoma.cutaneous"
## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```

Prost–AdenoCA
empirical



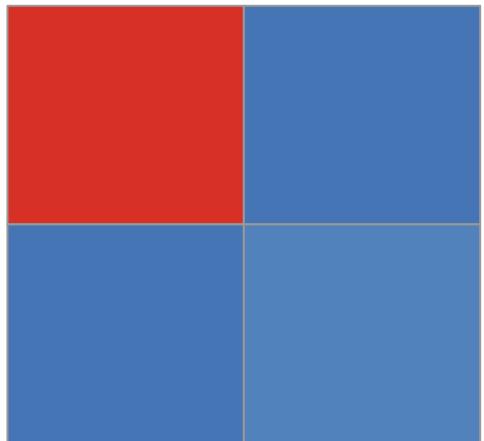
Skin–Melanoma.cutaneous
inferred



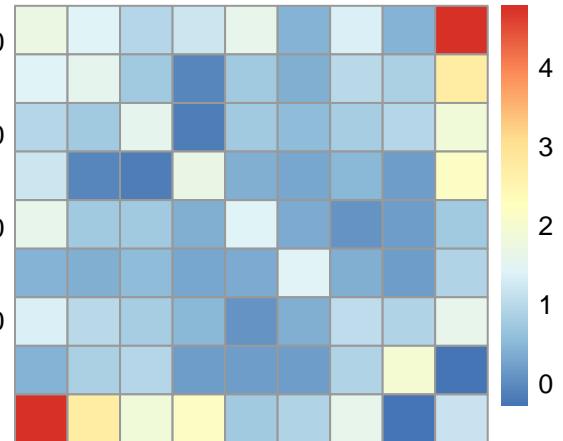
```
## Error : $ operator is invalid for atomic vectors
## Error : $ operator is invalid for atomic vectors
## Error : $ operator is invalid for atomic vectors
## Error : $ operator is invalid for atomic vectors
## [1] "Uterus–AdenoCA"

## Warning in fill_covariance_matrix(arg_d = .d_logR, arg_entries_var =
## python_like_select_name(get(i)[[ct]]$par.fixed, : This function had been
## incorrect until now (30 july 2021)
```

Skin–Melanoma.cutaneous
empirical



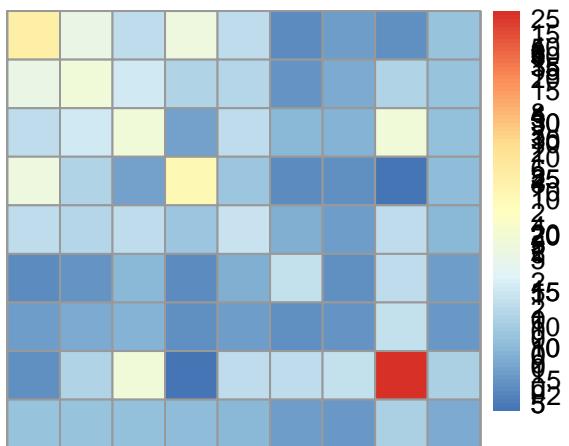
Uterus–AdenoCA
inferred



```
## Error : $ operator is invalid for atomic vectors
```

Skirtomyiasus

empirical



```
## $`Bone-Osteosarc`  
## $`Bone-Osteosarc`$fullRE_M_nonexo  
##  
## $`Bone-Osteosarc`$fullRE_DMSL_nonexo  
## [1] "No convergence"  
##  
##  
## $`Breast-AdenoCA`  
##     fullRE_M_nonexo fullRE_DMSL_nonexo  
##     "No convergence"    "No convergence"  
##  
## $`CNS-GBM`  
## $`CNS-GBM`$fullRE_M_nonexo  
##  
## $`CNS-GBM`$fullRE_DMSL_nonexo  
## [1] "No convergence"  
##  
##  
## $`CNS-Medullo`  
##     fullRE_M_nonexo fullRE_DMSL_nonexo  
## tree_row NA             NA  
## tree_col NA             NA  
## kmeans   NA             NA  
## gtable   List,12        List,12  
##  
## $`CNS-PiloAstro`  
##     fullRE_M_nonexo fullRE_DMSL_nonexo  
## tree_row NA             NA  
## tree_col NA             NA  
## kmeans   NA             NA  
## gtable   List,12        List,12  
##  
## $`ColoRect-AdenoCA`  
## $`ColoRect-AdenoCA`$fullRE_M_nonexo
```

```

## 
## $`ColoRect-AdenoCA`$fullRE_DMSL_nonexo
## [1] "No convergence"
##
## 
## $`Eso-AdenoCA`
## $`Eso-AdenoCA`$fullRE_M_nonexo
##
## $`Eso-AdenoCA`$fullRE_DMSL_nonexo
## [1] "No convergence"
##
## 
## $`Head-SCC`
##           fullRE_M_nonexo fullRE_DMSL_nonexo
## tree_row NA             NA
## tree_col NA             NA
## kmeans   NA             NA
## gtable   List,12        List,12
##
## $`Kidney-ChRCC`
##           fullRE_M_nonexo fullRE_DMSL_nonexo
## tree_row NA             NA
## tree_col NA             NA
## kmeans   NA             NA
## gtable   List,12        List,12
##
## $`Kidney-RCC.clearcell`
##           fullRE_M_nonexo fullRE_DMSL_nonexo
## tree_row NA             NA
## tree_col NA             NA
## kmeans   NA             NA
## gtable   List,12        List,12
##
## $`Kidney-RCC.papillary`
## $`Kidney-RCC.papillary`$fullRE_M_nonexo
##
## $`Kidney-RCC.papillary`$fullRE_DMSL_nonexo
## [1] "No convergence"
##
## 
## $`Liver-HCC`
## $`Liver-HCC`$fullRE_M_nonexo
## [1] "No convergence"
##
## $`Liver-HCC`$fullRE_DMSL_nonexo
##
## 
## $`Lung-SCC`
##           fullRE_M_nonexo fullRE_DMSL_nonexo
## tree_row NA             NA
## tree_col NA             NA

```

```

## kmeans NA NA
## gtable List,12 List,12
##
## $`Lymph-BNHL`
## fullRE_M_nonexo
## "No convergence"
## fullRE_DMSL_nonexo
## "Error : $ operator is invalid for atomic vectors\n"
##
## $`Lymph-CLL`
## fullRE_M_nonexo fullRE_DMSL_nonexo
## tree_row NA NA
## tree_col NA NA
## kmeans NA NA
## gtable List,12 List,12
##
## $`Ovary-AdenoCA`
## $`Ovary-AdenoCA`$fullRE_M_nonexo
##
## $`Ovary-AdenoCA`$fullRE_DMSL_nonexo
## [1] "No convergence"
##
##
## $`Panc-AdenoCA`
## $`Panc-AdenoCA`$fullRE_M_nonexo
##
## $`Panc-AdenoCA`$fullRE_DMSL_nonexo
## [1] "Error : $ operator is invalid for atomic vectors\n"
## attr(,"class")
## [1] "try-error"
## attr(,"condition")
## <simpleError: $ operator is invalid for atomic vectors>
##
##
## $`Panc-Endocrine`
## $`Panc-Endocrine`$fullRE_M_nonexo
##
## $`Panc-Endocrine`$fullRE_DMSL_nonexo
## [1] "No convergence"
##
##
## $`Prost-AdenoCA`
## $`Prost-AdenoCA`$fullRE_M_nonexo
##
## $`Prost-AdenoCA`$fullRE_DMSL_nonexo
## [1] "Error : $ operator is invalid for atomic vectors\n"
## attr(,"class")
## [1] "try-error"
## attr(,"condition")
## <simpleError: $ operator is invalid for atomic vectors>
##

```

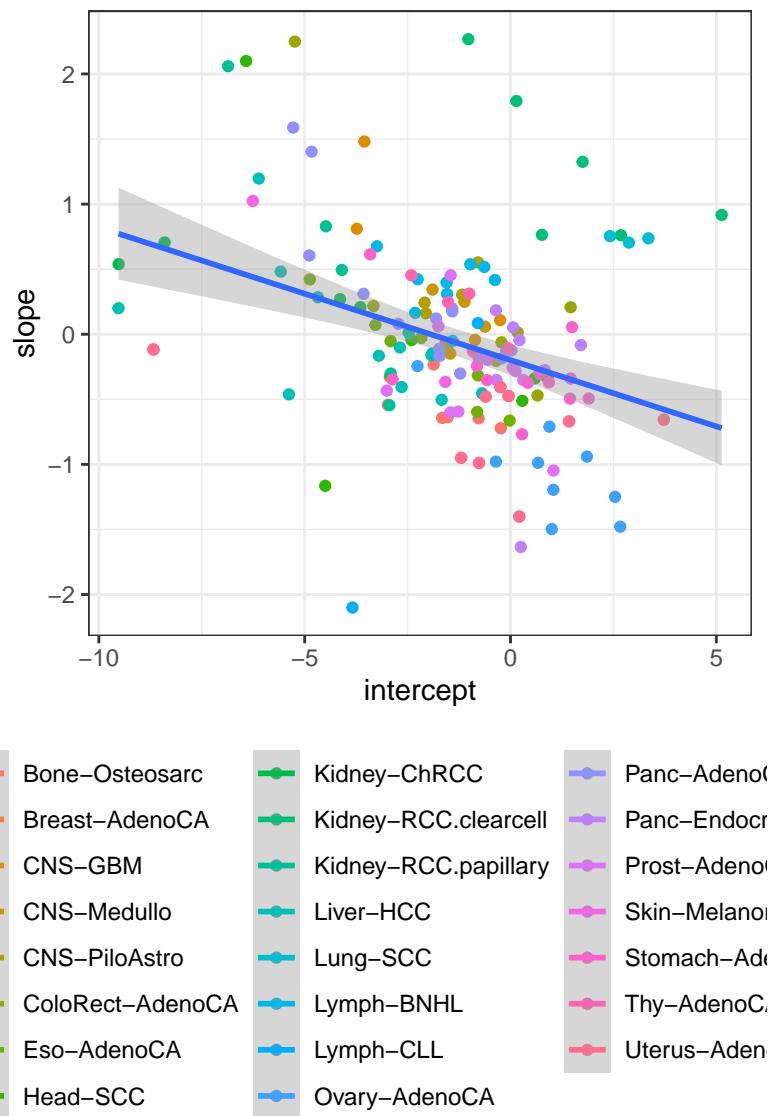
```

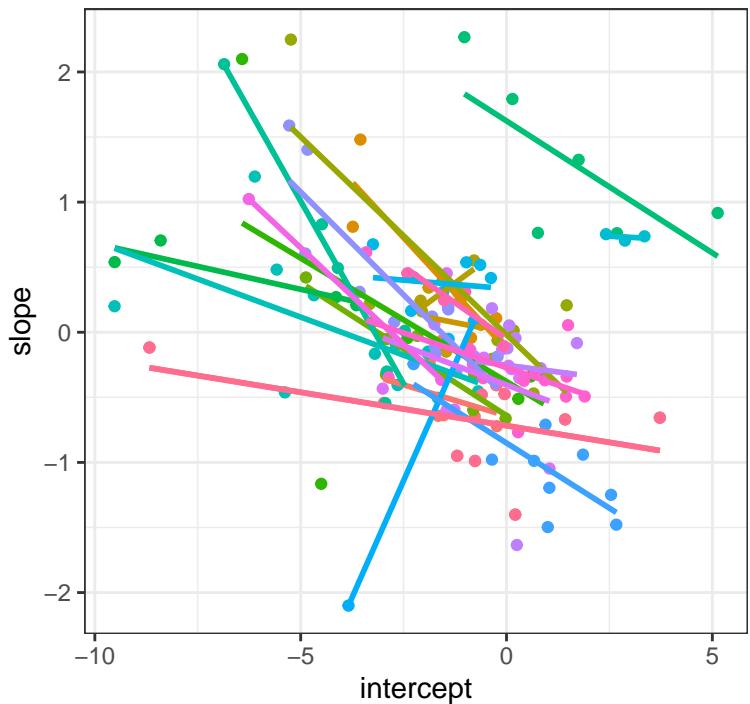
## 
## $`Skin-Melanoma.cutaneous`$fullRE_M_nonexo
## 
## $`Skin-Melanoma.cutaneous`$fullRE_DMSL_nonexo
## [1] "Error : $ operator is invalid for atomic vectors\n"
## attr(,"class")
## [1] "try-error"
## attr(,"condition")
## <simpleError: $ operator is invalid for atomic vectors>
## 
## 
## $`Stomach-AdenoCA`$fullRE_M_nonexo
##                               "No convergence"
## $`Stomach-AdenoCA`$fullRE_DMSL_nonexo
## "Error : $ operator is invalid for atomic vectors\n"
## 
## $`Thy-AdenoCA`$fullRE_M_nonexo
##                               "No convergence"
## $`Thy-AdenoCA`$fullRE_DMSL_nonexo
## "Error : $ operator is invalid for atomic vectors\n"
## 
## $`Uterus-AdenoCA`$fullRE_M_nonexo
## $`Uterus-AdenoCA`$fullRE_DMSL_nonexo
## [1] "Error : $ operator is invalid for atomic vectors\n"
## attr(,"class")
## [1] "try-error"
## attr(,"condition")
## <simpleError: $ operator is invalid for atomic vectors>

```

Correlation of intercept and slope values

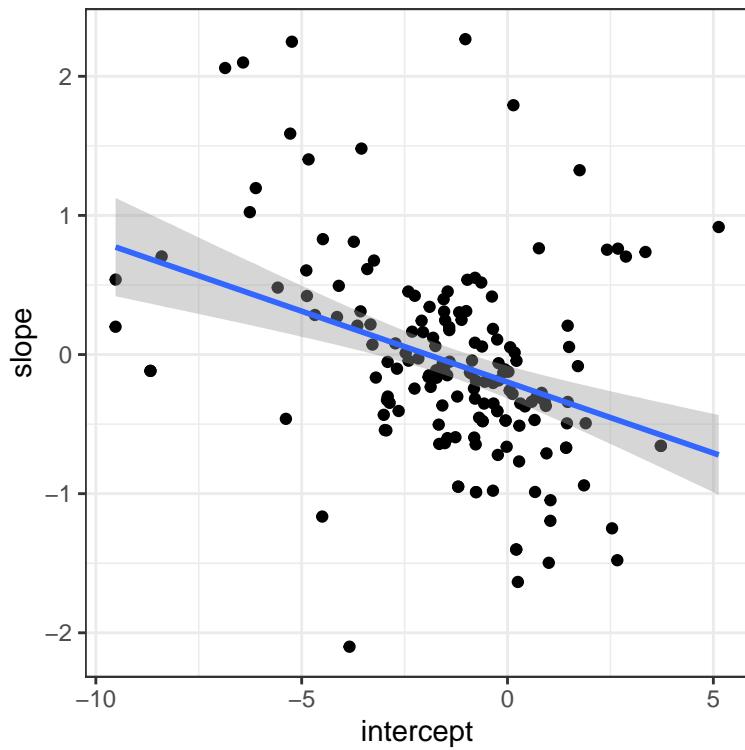
```
## `geom_smooth()` using formula 'y ~ x'
```



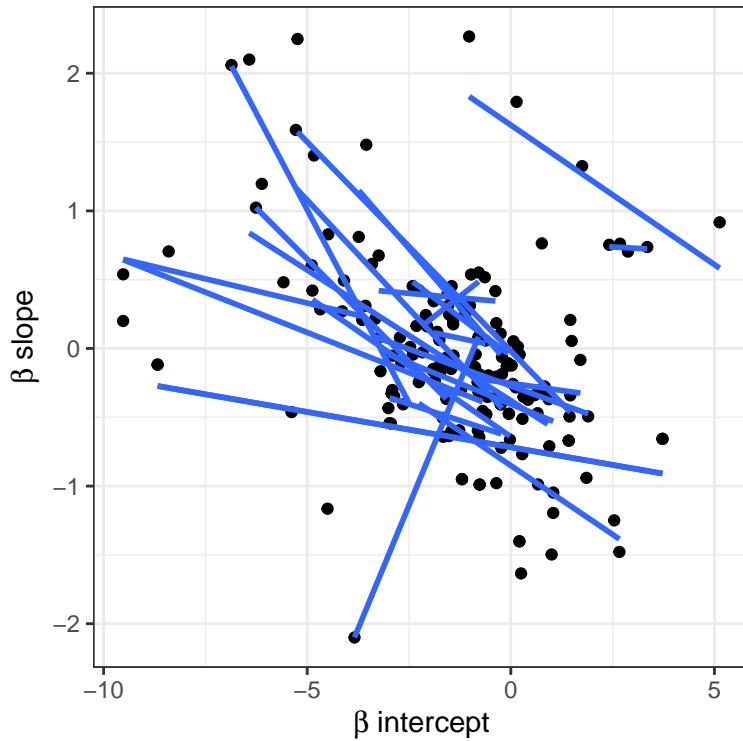


- Bone–Osteosarc ▲ Kidney–ChRCC ○ Panc–AdenoC
- Breast–AdenoCA ▲ Kidney–RCC.clearcell △ Panc–Endocr
- CNS–GBM ▲ Kidney–RCC.papillary □ Prost–AdenoC
- CNS–Medullo ▲ Liver–HCC ▨ Skin–MelanoC
- CNS–PiloAstro ▲ Lung–SCC ▨ Stomach–AdenoC
- ColoRect–AdenoCA ▲ Lymph–BNHL ▨ Thy–AdenoC.
- Eso–AdenoCA ▲ Lymph–CLL ▨ Uterus–Aden
- Head–SCC ▲ Ovary–AdenoCA

```
## `geom_smooth()` using formula 'y ~ x'
```

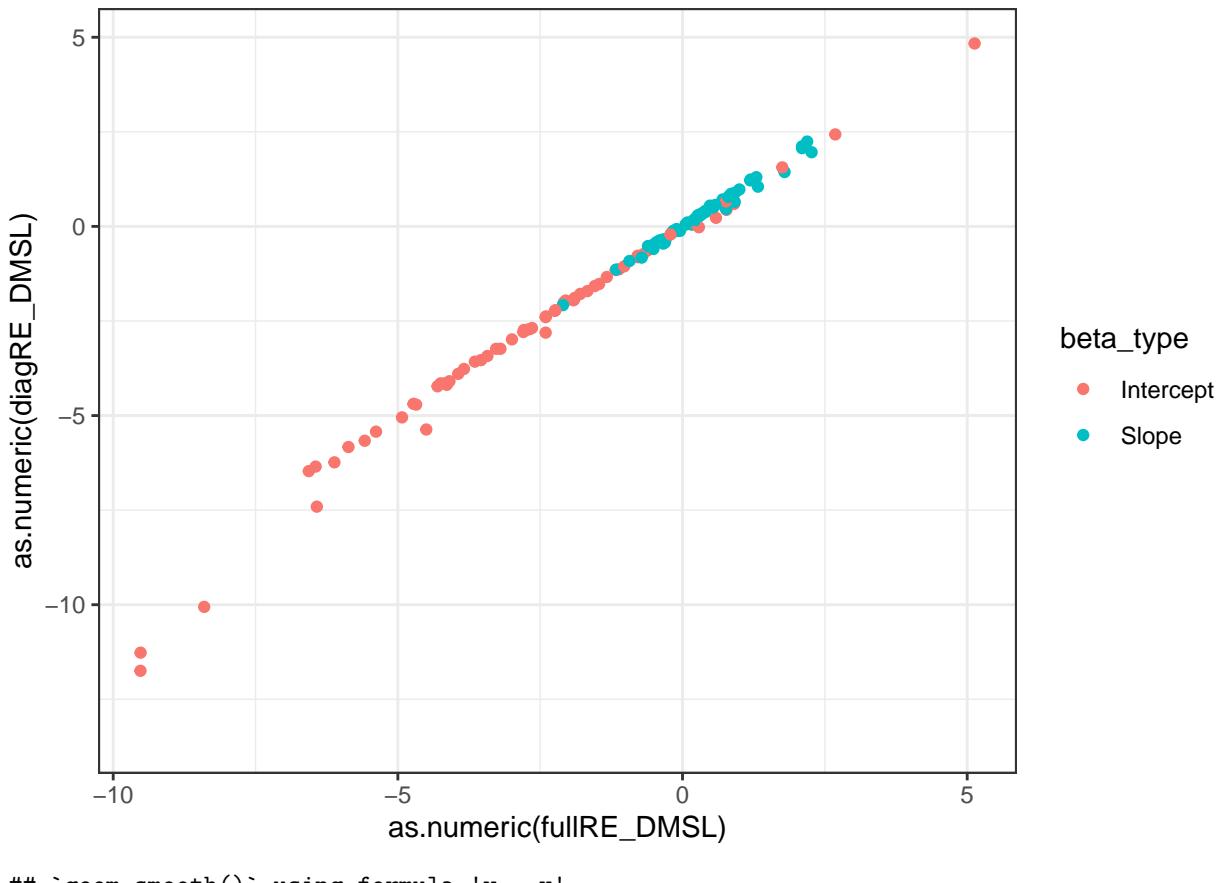


```
## `geom_smooth()` using formula 'y ~ x'
```

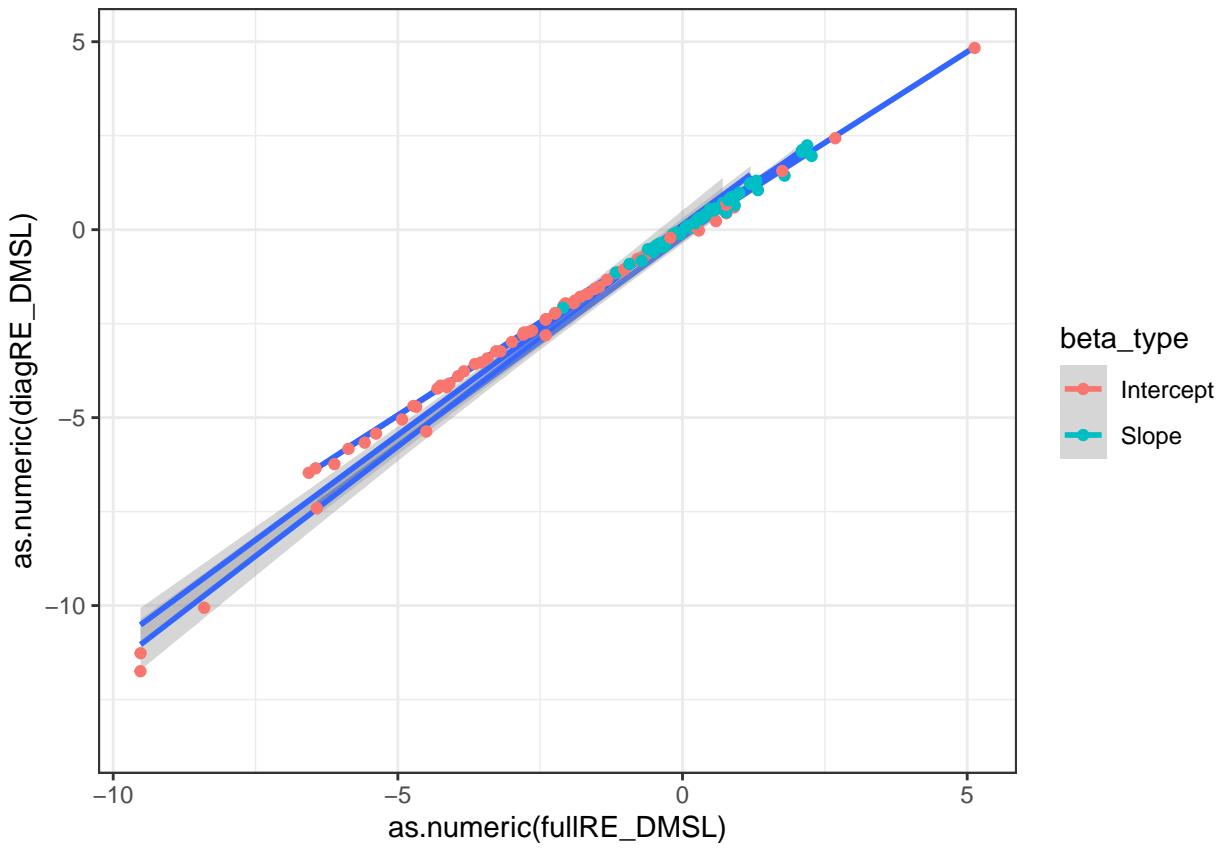


For the cancer types for which we have both fullRE and diagRE, see how the beta coefficients change in these two models, in a scatterplot where we show beta intercepts and slopes.

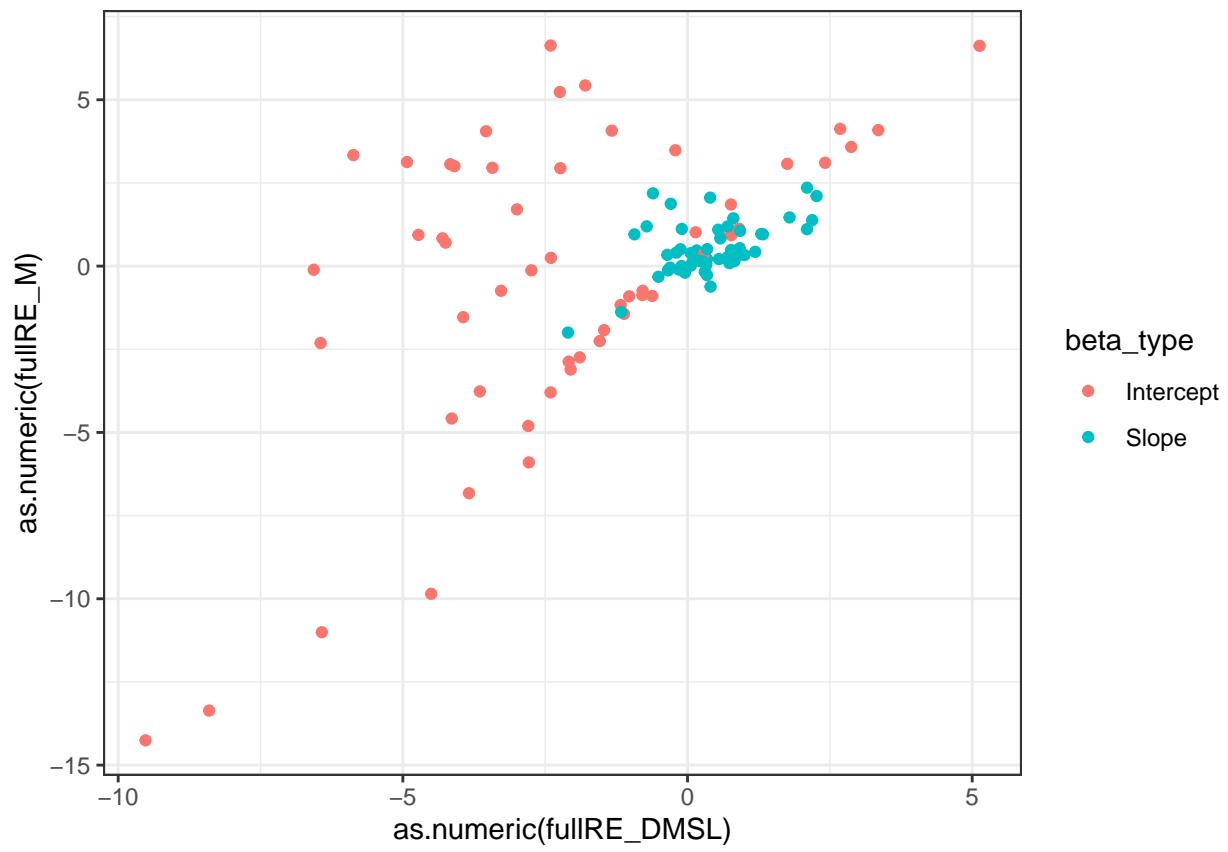
Note that not all fullRE M or diagM have converged - I have removed those which haven't. In some cases I ran DMSL with a subset of signatures, so that diagRE DMSL (with more signatures) cannot be compared to fullRE DMSL.



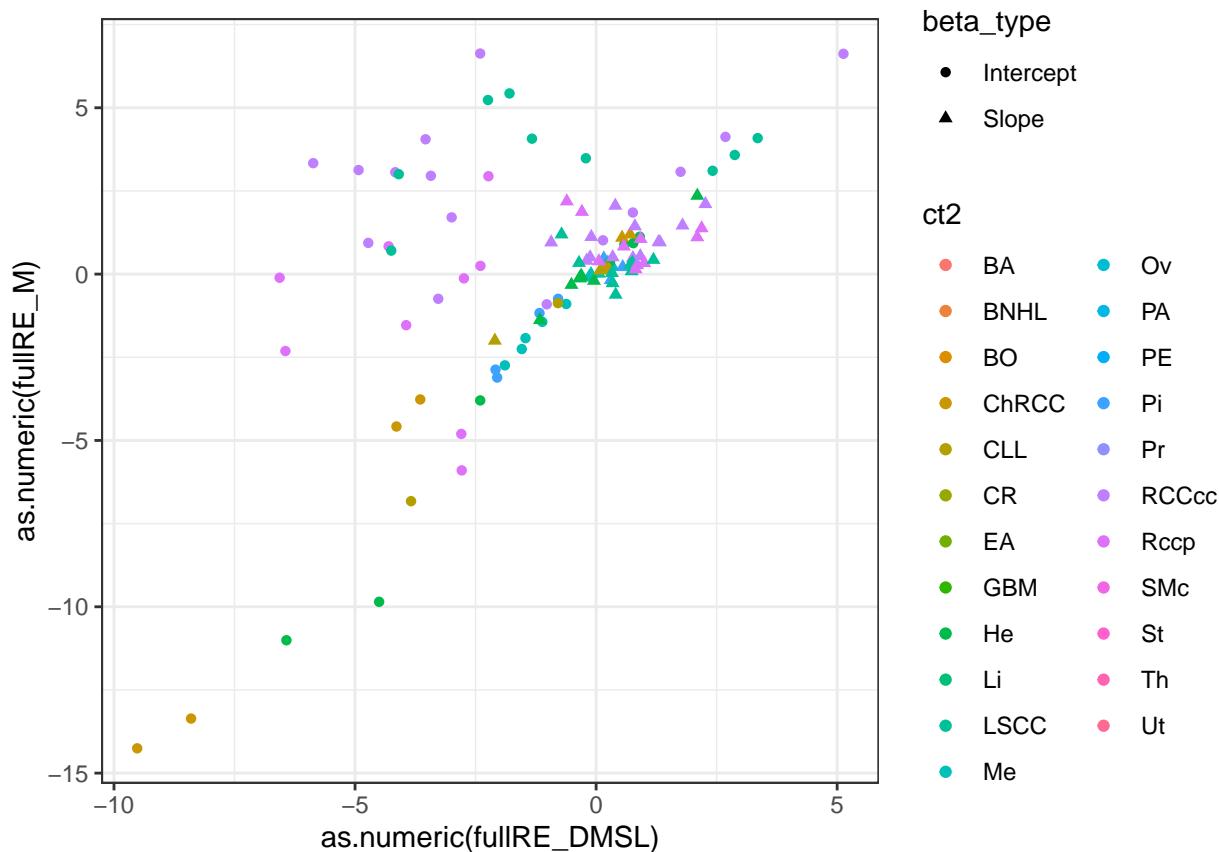
```
## `geom_smooth()` using formula 'y ~ x'  
## Warning: Removed 678 rows containing non-finite values (stat_smooth).  
## Warning: Removed 678 rows containing missing values (geom_point).
```



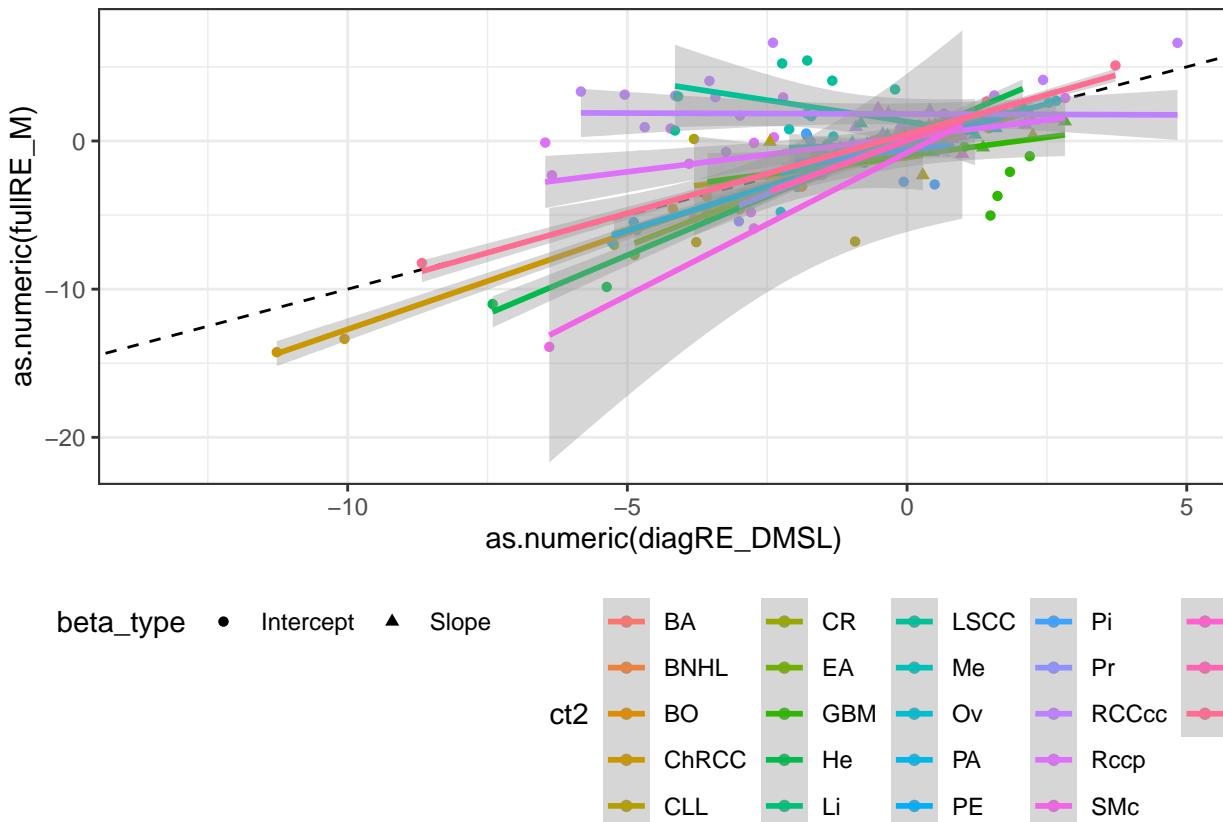
```
## Warning: Removed 696 rows containing missing values (geom_point).
```



```
## Warning: Removed 696 rows containing missing values (geom_point).
```



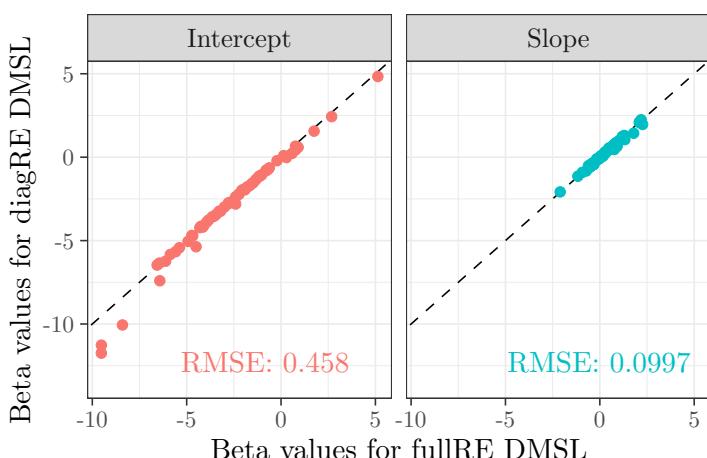
```
## `geom_smooth()` using formula 'y ~ x'
## Warning: Removed 450 rows containing non-finite values (stat_smooth).
## Warning: Removed 450 rows containing missing values (geom_point).
```



```
##   rmse_diag_full_DMSL rmse_fullDMSL_fullM beta_type
## 1          0.09972866          0.7838289     Slope
## 2          0.45761210          4.1215070 Intercept

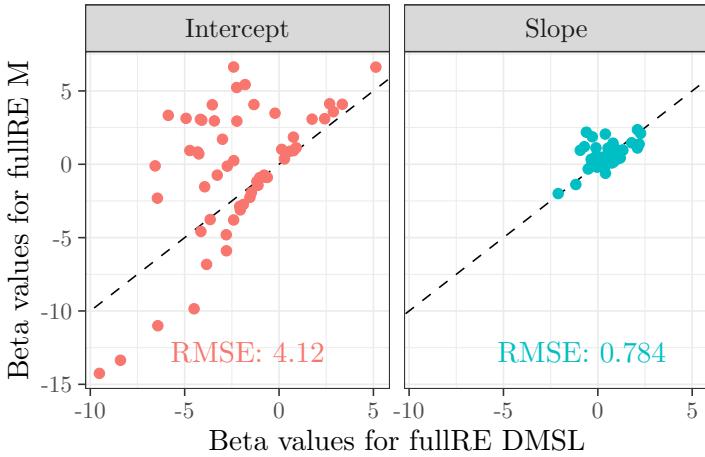
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.

## Warning: Removed 678 rows containing missing values (geom_point).
```



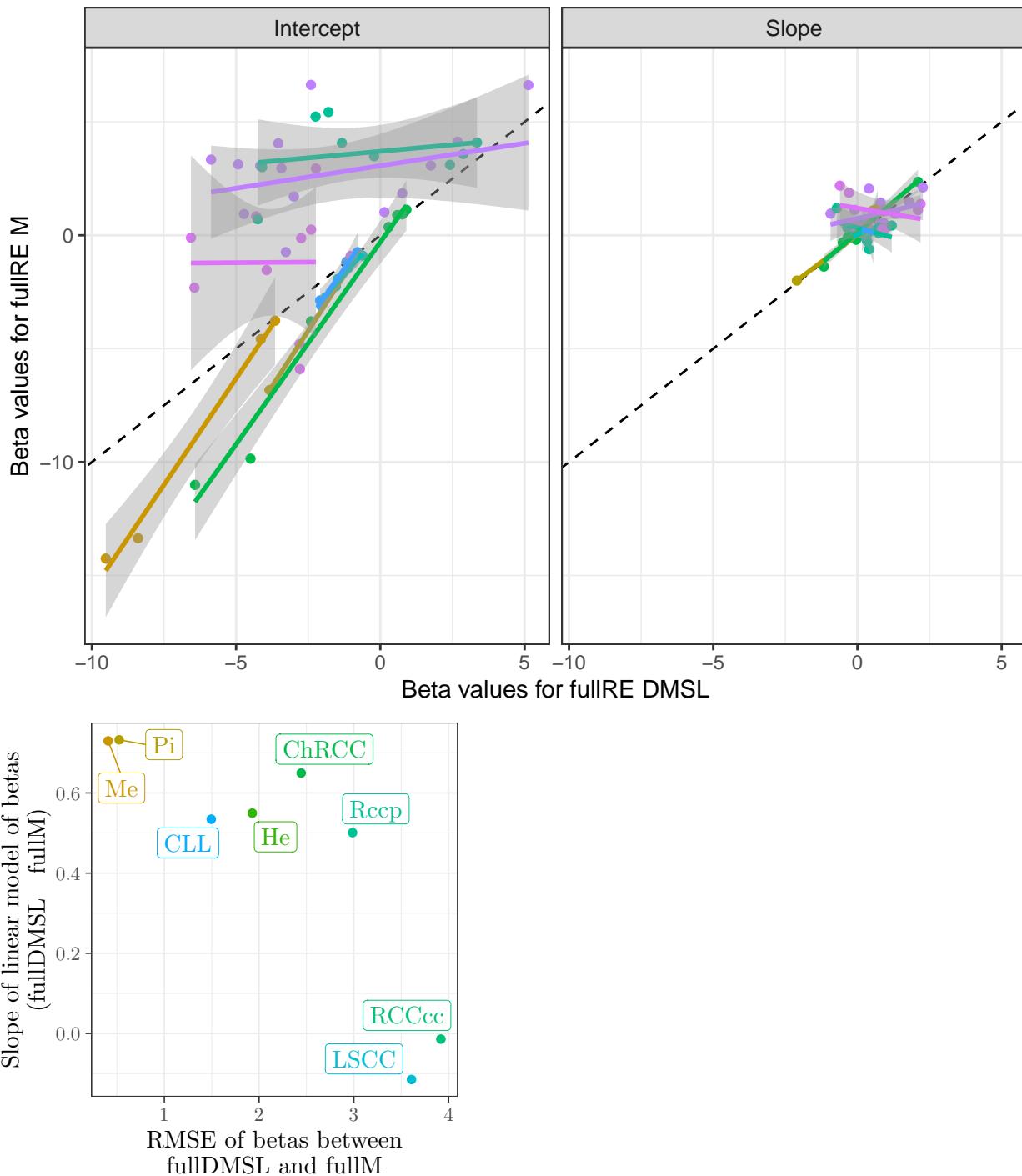
```
## Warning: `guides(<scale> = FALSE)` is deprecated. Please use `guides(<scale> =
## "none")` instead.
```

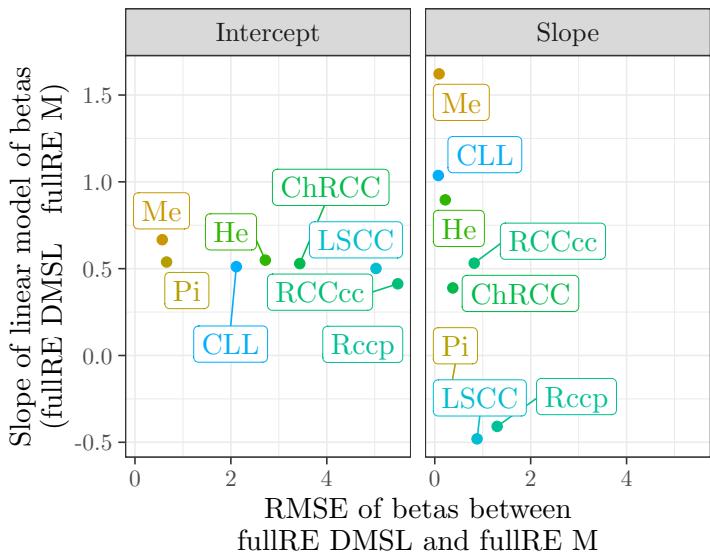
Warning: Removed 696 rows containing missing values (geom_point).



| | | | | |
|-------|-------------------------|----------------------|-----------|-----------|
| ## 14 | Lymph-BNHL | NaN | | NA |
| ## 15 | Lymph-CLL | 0.01890391 | | 0.9998600 |
| ## 16 | Ovary-AdenoCA | NaN | | NA |
| ## 17 | Panc-AdenoCA | NaN | | NA |
| ## 18 | Panc-Endocrine | NaN | | NA |
| ## 19 | Prost-AdenoCA | NaN | | NA |
| ## 20 | Skin-Melanoma.cutaneous | NaN | | NA |
| ## 21 | Stomach-AdenoCA | NaN | | NA |
| ## 22 | Thy-AdenoCA | NaN | | NA |
| ## 23 | Uterus-AdenoCA | NaN | | NA |
| ## 24 | Bone-Osteosarc | NaN | | NA |
| ## 25 | Breast-AdenoCA | NaN | | NA |
| ## 26 | CNS-GBM | NaN | | NA |
| ## 27 | CNS-Medullo | 0.03219255 | | 1.0027564 |
| ## 28 | CNS-PiloAstro | 0.06126289 | | 1.0620811 |
| ## 29 | ColoRect-AdenoCA | NaN | | NA |
| ## 30 | Eso-AdenoCA | NaN | | NA |
| ## 31 | Head-SCC | 0.57577998 | | 0.9145442 |
| ## 32 | Kidney-ChRCC | 1.20493056 | | 0.7500070 |
| ## 33 | Kidney-RCC.clearcell | 0.12124177 | | 1.0300353 |
| ## 34 | Kidney-RCC.papillary | 0.05713314 | | 1.0202147 |
| ## 35 | Liver-HCC | 0.64474403 | | 0.8268624 |
| ## 36 | Lung-SCC | 0.04132926 | | 1.0154875 |
| ## 37 | Lymph-BNHL | NaN | | NA |
| ## 38 | Lymph-CLL | 0.05207686 | | 1.0313870 |
| ## 39 | Ovary-AdenoCA | NaN | | NA |
| ## 40 | Panc-AdenoCA | NaN | | NA |
| ## 41 | Panc-Endocrine | NaN | | NA |
| ## 42 | Prost-AdenoCA | NaN | | NA |
| ## 43 | Skin-Melanoma.cutaneous | NaN | | NA |
| ## 44 | Stomach-AdenoCA | NaN | | NA |
| ## 45 | Thy-AdenoCA | NaN | | NA |
| ## 46 | Uterus-AdenoCA | NaN | | NA |
| ## | rmse_fullDMSL_fullM | slope_fullDMSL_fullM | beta_type | ct2 |
| ## 1 | NaN | NA | Slope | BO |
| ## 2 | NaN | NA | Slope | BA |
| ## 3 | NaN | NA | Slope | GBM |
| ## 4 | 0.09059152 | 1.621940968 | Slope | Me |
| ## 5 | 0.33664739 | -0.191799809 | Slope | Pi |
| ## 6 | NaN | NA | Slope | CR |
| ## 7 | NaN | NA | Slope | EA |
| ## 8 | 0.21918157 | 0.896372091 | Slope | He |
| ## 9 | 0.37670836 | 0.389119063 | Slope | ChRCC |
| ## 10 | 0.82278832 | 0.531725788 | Slope | RCCcc |
| ## 11 | 1.30070772 | -0.408535086 | Slope | Rccp |
| ## 12 | NaN | NA | Slope | Li |
| ## 13 | 0.88196759 | -0.480178978 | Slope | LSCC |
| ## 14 | NaN | NA | Slope | BNHL |
| ## 15 | 0.07406513 | 1.036692829 | Slope | CLL |
| ## 16 | NaN | NA | Slope | Ov |
| ## 17 | NaN | NA | Slope | PA |

| | | | | |
|-------|------------|--------------|-----------|-------|
| ## 18 | NaN | NA | Slope | PE |
| ## 19 | NaN | NA | Slope | Pr |
| ## 20 | NaN | NA | Slope | SMc |
| ## 21 | NaN | NA | Slope | St |
| ## 22 | NaN | NA | Slope | Th |
| ## 23 | NaN | NA | Slope | Ut |
| ## 24 | NaN | NA Intercept | BO | |
| ## 25 | NaN | NA Intercept | BA | |
| ## 26 | NaN | NA Intercept | GBM | |
| ## 27 | 0.56916461 | 0.666803710 | Intercept | Me |
| ## 28 | 0.65905520 | 0.538204984 | Intercept | Pi |
| ## 29 | NaN | NA Intercept | CR | |
| ## 30 | NaN | NA Intercept | EA | |
| ## 31 | 2.71848733 | 0.549152181 | Intercept | He |
| ## 32 | 3.43614717 | 0.529239927 | Intercept | ChRCC |
| ## 33 | 5.47957627 | 0.412829456 | Intercept | RCCcc |
| ## 34 | 4.01789367 | 0.003543566 | Intercept | Rccp |
| ## 35 | NaN | NA Intercept | Li | |
| ## 36 | 5.02604140 | 0.501340467 | Intercept | LSCC |
| ## 37 | NaN | NA Intercept | BNHL | |
| ## 38 | 2.11315976 | 0.511657714 | Intercept | CLL |
| ## 39 | NaN | NA Intercept | Ov | |
| ## 40 | NaN | NA Intercept | PA | |
| ## 41 | NaN | NA Intercept | PE | |
| ## 42 | NaN | NA Intercept | Pr | |
| ## 43 | NaN | NA Intercept | SMc | |
| ## 44 | NaN | NA Intercept | St | |
| ## 45 | NaN | NA Intercept | Th | |
| ## 46 | NaN | NA Intercept | Ut | |





Compare the random effects intercepts. We cannot compare across cancer types because the number of observation is different. For each cancer type, compare the intercept fullRE DMSL of each patient to the intercept of fullRE M and diagRE DMSL. I.e. for each cancer type we have a boxplot.

```

## Error : $ operator is invalid for atomic vectors
## Error : $ operator is invalid for atomic vectors

## Warning in FUN(X[[i]], ...): NAs introduced by coercion

## Error : $ operator is invalid for atomic vectors
## Error : $ operator is invalid for atomic vectors

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## Warning in FUN(X[[i]], ...): NAs introduced by coercion

## Error : $ operator is invalid for atomic vectors
## Error : $ operator is invalid for atomic vectors

```

```

## Warning in FUN(X[[i]], ...): NAs introduced by coercion
## Error : $ operator is invalid for atomic vectors
## Error : $ operator is invalid for atomic vectors
## Error : $ operator is invalid for atomic vectors
## Warning in FUN(X[[i]], ...): NAs introduced by coercion
## Error : $ operator is invalid for atomic vectors
## Warning in FUN(X[[i]], ...): NAs introduced by coercion
## Error : $ operator is invalid for atomic vectors
## Error : $ operator is invalid for atomic vectors
## Warning in FUN(X[[i]], ...): NAs introduced by coercion

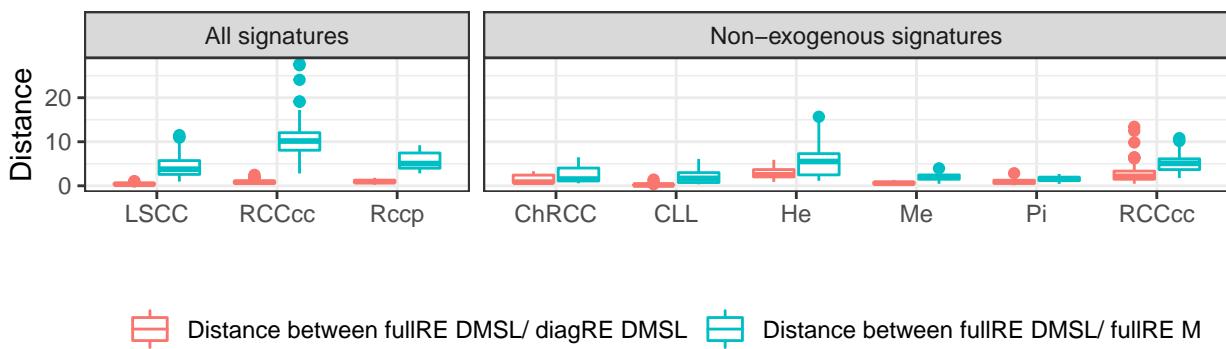
```

Would like to have the picture below in computer modern, but I cannot make boxplot work with tikz

```

## `summarise()` has grouped output by 'ct'. You can override using the `~.groups` argument.
## `summarise()` has grouped output by 'ct'. You can override using the `~.groups` argument.

```



Distance between fullRE DMSL/ diagRE DMSL Distance between fullRE DMSL/ fullRE M