# Appendix 7

## Code for the derivation of the genetic AML prediction model

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# Discriminating evolution of acute myeloid leukaemia from age-related clonal haematopoiesis

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# 1 Preliminaries

## 1.1 Libraries

```
library(CoxHD)
library(survAUC)
library(survivalROC)
library(glmnet)
library(RColorBrewer)
library(stringr)
library(dplyr)
library(readr)

set1 <- RColorBrewer::brewer.pal(8, "Set1")
```

Helper functions

```
superSet <- function(x, s, fill=NA){
    i <- intersect(colnames(x), s)
    n <- setdiff(s, colnames(x))
    y <- x[,i]
    if(length(n) > 0)
        y <- cbind(y,  matrix(fill, ncol=length(n), dimnames=list(NULL, n)) )[,s]
    return(y)
}
```

# 2 AML incidence data

Use known AML incidence to correct bias using weighted controls. The expected incidence of AML was calculated from the UK office of national statistics, available at http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/incidence (http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/incidence). Spline function to interpolate Male denoted by 1 and female by 0

```
age_incidence <- read.table("data/aml_age_incidence.txt", header=TRUE, sep="\t")
head(age_incidence)
```

| | Age.Range <fctr> | Male.Cases <int> | Female.Cases <int> | Male.Rates <dbl> | Female.Rates <dbl> |
|---|---|---|---|---|---|
| 1 | 0 to 04 | 18 | 12 | 0.9 | 0.6 |
| 2 | 05 to 09 | 10 | 10 | 0.5 | 0.5 |
| 3 | 10 to 14 | 8 | 10 | 0.4 | 0.6 |
| 4 | 15 to 19 | 15 | 14 | 0.7 | 0.8 |
| 5 | 20 to 24 | 21 | 18 | 1.0 | 0.8 |
| 6 | 25 to 29 | 22 | 20 | 1.0 | 0.9 |

6 rows

```
tail(age_incidence)
```

| | Age.Range <fctr> | Male.Cases <int> | Female.Cases <int> | Male.Rates <dbl> | Female.Rates <dbl> |
|---|---|---|---|---|---|
| 14 | 65 to 69 | 205 | 140 | 12.2 | 7.9 |

| | | | | | |
|---|---|---|---|---|---|
| 15 | 70 to 74 | 256 | 162 | 21.2 | 12.0 |
| 16 | 75 to 79 | 270 | 179 | 28.3 | 15.7 |
| 17 | 80 to 84 | 235 | 165 | 36.1 | 18.4 |
| 18 | 85 to 89 | 139 | 122 | 40.4 | 20.7 |
| 19 | 90+ | 53 | 85 | 35.6 | 22.2 |

6 rows

```
str(age_incidence)
```

```
## 'data.frame':    19 obs. of  5 variables:
##  $ Age.Range   : Factor w/ 19 levels "0 to 04","05 to 09",..: 1 2 3 4 5 6 7 8 9
10 ...
##  $ Male.Cases  : int  18 10 8 15 21 22 21 34 39 51 ...
##  $ Female.Cases: int  12 10 10 14 18 20 20 23 39 53 ...
##  $ Male.Rates  : num  0.9 0.5 0.4 0.7 1 1 1 1.7 1.8 2.2 ...
##  $ Female.Rates: num  0.6 0.5 0.6 0.8 0.8 0.9 0.9 1.2 1.7 2.2 ...
```

```
aml_inc <- function(gender, x){
    if(gender==1)
        splinefun(x=c(seq(0,90,5)), y=c(cumsum(age_incidence$Male.Rates/100000)*5)
, method="mono")(x)
    else
        splinefun(x=c(seq(0,90,5)), y=c(cumsum(age_incidence$Female.Rates/100000)*
5), method="mono")(x)
}
```

All cause mortality from the office of national statistics (https://www.ons.gov.uk/ (https://www.ons.gov.uk/)).

```
all_cause_mortality <- read.table("data/all_cause_mortality.txt", sep="\t", skip=1
, header=TRUE)
head(all_cause_mortality)
```

| | x <int> | mx <dbl> | qx <dbl> | lx <dbl> | dx <dbl> | ex <dbl> | X <lgl> | mx.1 <dbl> | qx.1 <dbl> |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 0 | 0.004234 | 0.004225 | 100000.0 | 422.5 | 79.17 | *NA* | 0.003521 | 0.003515 |
| 2 | 1 | 0.000306 | 0.000306 | 99577.5 | 30.5 | 78.51 | *NA* | 0.000246 | 0.000246 |
| 3 | 2 | 0.000163 | 0.000163 | 99547.1 | 16.2 | 77.53 | *NA* | 0.000137 | 0.000137 |
| 4 | 3 | 0.000127 | 0.000127 | 99530.8 | 12.6 | 76.54 | *NA* | 0.000105 | 0.000105 |
| 5 | 4 | 0.000090 | 0.000090 | 99518.2 | 8.9 | 75.55 | *NA* | 0.000081 | 0.000081 |
| 6 | 5 | 0.000092 | 0.000092 | 99509.3 | 9.2 | 74.56 | *NA* | 0.000067 | 0.000067 |

6 rows | 1-10 of 13 columns

```
all_surv <- function(gender, age1, age2){
    if(gender==1)
        s <- all_cause_mortality$lx
    else
        s <- all_cause_mortality$lx.1
    f <- function(x) exp(splinefun(all_cause_mortality$x, log(s), method="mono")(x
))
    f(age2) / f(age1)
}
```

Function combining both

```
aml_inc_cr <- Vectorize(function(gender, age1, age2) sum(diff(aml_inc(gender, seq(
age1,age2,1) ))*all_surv(gender, age1, seq(age1,age2-1,1)) ), c("gender","age1","a
ge2"))
```

# 3 Discovery cohort

## 3.1 Data

4 (of 95) cases that were sampled within 6 months of AML diagnosis are excluded to avoid skewing model towards significance

```
f = "data/DC_vaf_matrix_414ctrl_91aml.csv"
```

```
torontoData <- read.csv(f)
torontoData$gender <- ifelse(torontoData$Sex == "male", 1, 0)
torontoData$gender <- as.numeric(torontoData$gender)
colnames(torontoData)
```

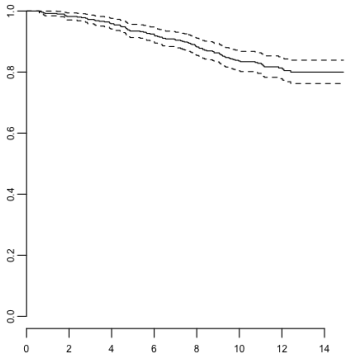
```
##  [1] "Sample"     "ASXL1"      "BCOR"       "CALR"       "CBL"        "DNMT3A"
"IDH1"       "IDH2"
##  [9] "JAK2"       "KDM6A"      "KIT"        "KMT2C"      "KRAS"       "NF1"
"NRAS"       "PHF6"
## [17] "PTPN11"     "RUNX1"      "SF3B1"      "SRSF2"      "TET2"       "TP53"
"U2AF1"      "Diagnosis"
## [25] "fu_years"   "age"        "Sex"        "no_drivers" "gender"
```

Manually standardize

```
torontoData <- torontoData[!duplicated(torontoData),]

gene_vars <- c("CALR", "NRAS", "DNMT3A", "SF3B1", "IDH1", "KIT", "TET2", "RAD21",
"JAK2", "CBL", "KRAS", "PTPN11", "IDH2", "TP53", "NF1", "SRSF2", "CEBPA", "ASXL1",
"RUNX1", "U2AF1", "BCOR", "KDM6A", "PHF6", "KMT2C", "KMT2D")

torontoX <- torontoData[, colnames(torontoData) %in% c(gene_vars, "age", "gender")
]

torontoX <- as.data.frame(torontoX)
```

Only include genes in model if mutated in >2 samples

```
thr <- 2
torontoX <- torontoX[,colSums(torontoX != 0)>=thr]

torontoGroups <- factor(names(torontoX) %in% c("age","gender")+1, level=1:2, label
s=c("Genes","Demographics"))

torontoX$age <- torontoX$age/10
names(torontoX)[which(names(torontoX)=="age")] <- "age_10"
g <- torontoGroups == "Genes"
torontoX[,g] <- torontoX[,g]*10
names(torontoX)[g] <- paste(names(torontoX)[g], "0.1",sep="_")

torontoSurv <- Surv(time = torontoData$fu_years, event = torontoData$Diagnosis=="A
ML")
plot(survfit(torontoSurv~ 1))
```




# 4 Validation cohort

## 4.1 Data

```
f = "data/VC_vaf_matrix_no_duplicates_262ctrl_29aml_nodates.csv"
sangerData <- read.csv(f)
colnames(sangerData)
```

```
##  [1] "X"          "Sample"     "ASXL1"      "BCOR"       "CBL"        "CEBPA"
"DNMT3A"     "IDH1"
##  [9] "IDH2"       "JAK2"       "KMT2C"      "KMT2D"      "KRAS"       "NF1"
```

```
"NRAS"       "PTPN11"
## [17] "RAD21"      "SF3B1"      "SRSF2"      "TET2"       "TP53"       "U2AF1"
"Individual" "hcdate"
## [25] "Diagnosis"  "age"        "gender"     "systol"     "diastol"    "bmi"
"cholestl"   "triglyc"
## [33] "hdl"        "ldl"        "lym"        "mcv"        "rdw"        "wbc"
"rbc"        "hct"
## [41] "plt"        "hgb"        "dodx"
```

```
head(sangerData[, c("Sample", "gender")]) #male=1, female=0
```

| | Sample<br><fctr> | gender<br><int> |
|---|---|---|
| 1 | PD29762b | 0 |
| 2 | PD29764b | 0 |
| 3 | PD29792b | 0 |
| 4 | PD29804c | 0 |
| 5 | PD29810c | 1 |
| 6 | PD29836c | 0 |

6 rows

NB all dates are jittered

```
sangerData$hcdate <- as.Date(sangerData$hcdate)
sangerData$dodx <- as.Date(sangerData$dodx)

sangerPatients <- sub("[a-z]+$","", sangerData$Sample)
o <- order(sangerPatients, as.numeric(sangerData$hcdate))

sangerData <- sangerData[o,]
sangerPatients <- sangerPatients[o]

clinical_vars <- c("systol", "diastol", "bmi", "cholestl", "triglyc", "hdl", "ldl"
, "lym", "mcv", "rdw", "wbc", "plt", "hgb")
sangerX <- sangerData[, colnames(sangerData) %in% c(gene_vars, "age","gender",clin
ical_vars)]
sangerX <- as.data.frame(sangerX)

sangerX <- sangerX[,colSums(sangerX != 0,na.rm=TRUE)>=thr]
sangerGroups <- factor(grepl("^[a-z]", colnames(sangerX))*2, levels=0:2, labels=c(
"Genes", "Demographics", "Blood"))
sangerGroups[names(sangerX) %in% c("age","gender")] <- "Demographics"
table(sangerGroups)
```

```
## sangerGroups
##        Genes Demographics        Blood
##           15            2           13
```

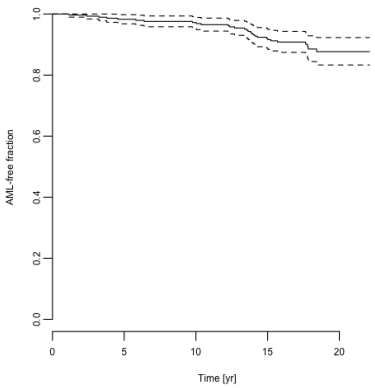
```
g <- sangerGroups=="Genes"
sangerX[g] <- sangerX[g] * 10
names(sangerX)[g] <- paste(names(sangerX[g]),"0.1", sep="_")
y <- StandardizeMagnitude(sangerX[!g])
sangerX <- cbind(sangerX[g],y)

poorMansImpute <- function(x) {x[is.na(x)] <- mean(x, na.rm=TRUE); return(x)}
sangerX <- as.data.frame(sapply(sangerX, poorMansImpute))

foo <- split(sangerData[,c("Diagnosis","hcdate","dodx")], sangerPatients)
```

```
bar <- do.call("rbind",lapply(foo, function(x){
                    y <- x
                    n <- nrow(y)
                    y[-n,"Diagnosis"] <- "Control"
                    start <- as.numeric(y$hcdate - y$hcdate[1])/365.25
                    end <- c(as.numeric(y$hcdate - y$hcdate[1])[-1]/365.25, as.num
eric(y$dodx[n] - y$hcdate[1])/365.25)
                    return(data.frame(Diagnosis=y[,"Diagnosis"], start=start, end=
end))
                }))

bar[1:6, ]
```

| | Diagnosis<br><fctr> | start<br><dbl> | end<br><dbl> |
|---|---|---|---|
| PD29762 | AML | 0 | 9.754962 |
| PD29764 | AML | 0 | 10.360027 |
| PD29792 | AML | 0 | 14.108145 |
| PD29804 | Control | 0 | 5.138946 |
| PD29810 | Control | 0 | 18.573580 |
| PD29836.1 | Control | 0 | 2.414784 |

6 rows

```
sangerPatientsSplit <- unlist(sapply(names(foo), function(n) rep(n, nrow(foo[[n]])
)))

sangerSurv <- Surv(time = bar$start, time2 = bar$end, event = bar$Diagnosis!="Cont
rol", origin = 0)
plot(survfit(sangerSurv ~ 1), ylab="AML-free fraction", xlab="Time [yr]")
```




# 5 Expected AML incidence

## 5.1 Validation cohort

```
w <- c(which(sangerSurv[,1]==0)[-1]-1, nrow(sangerSurv))
head(sangerSurv[w,])
```

```
## [1] (0.000000, 9.754962]  (0.000000,10.360027]  (0.000000,14.108145]  (0.000000
, 5.138946+] (0.000000,18.573580+]
## [6] (2.414784,10.023272]
```

```
sangerSurv2 <- Surv(sangerSurv[w,2], sangerSurv[w,3])

expected_rate_sanger_cr <- mean(aml_inc_cr(sangerX[w,"gender"],sangerX[w,"age_10"]
*10, sangerX[w,"age_10"]*10+ pmax(1,sangerSurv2[,1]))[!sangerSurv2[,2]])

n_total_sanger <- sum(sangerSurv2[,2])/expected_rate_sanger_cr
n_total_sanger
```

```
## [1] 10406.64
```

## 5.2 Discovery cohort

```
expected_rate_toronto_cr <- mean(aml_inc_cr(torontoX[,"gender"],torontoX[,"age_10"
]*10, torontoX[,"age_10"]*10+ pmax(1,torontoSurv[,1]))[!torontoSurv[,2]])

n_total_toronto <- sum(torontoSurv[,2])/expected_rate_toronto_cr
n_total_toronto
```

```
## [1] 72377.73
```

# 6 Combined data

Survival

```
allSurv <- rbind(sangerSurv, Surv(rep(0, nrow(torontoSurv)), torontoSurv[,1], toro
ntoSurv[,2]))
allSurv <- Surv(allSurv[,1], allSurv[,2], allSurv[,3])
```

Data matrix

```
cohort <- c(rep("Sanger", nrow(sangerX)), rep("Toronto", nrow(torontoX)))
i <- c(sort(setdiff(gene_vars,"CALR")),"age","gender")
allX <- rbind(superSet(sangerData,i,fill=0), superSet(torontoData,i,fill=0))
colnames(allX)
```

```
##  [1] "ASXL1"  "BCOR"   "CBL"    "CEBPA"  "DNMT3A" "IDH1"   "IDH2"   "JAK2"   "K
DM6A"  "KIT"    "KMT2C"  "KMT2D"
## [13] "KRAS"   "NF1"    "NRAS"   "PHF6"   "PTPN11" "RAD21"  "RUNX1"  "SF3B1"  "S
RSF2"  "TET2"   "TP53"   "U2AF1"
## [25] "age"    "gender"
```

```
allX <- allX[,colSums(allX>0)>=thr]
allX <- cbind(allX, cohort=cohort=="Sanger") + 0
allGroups <- factor(grepl("^[A-Z]",colnames(allX))+0, levels=1:0, labels=c("Genes"
,"Demographics"))

g <- allGroups=="Genes"
allX <- cbind(10*allX[,g], StandardizeMagnitude(allX[,!g]))
colnames(allX)[g] <- paste(colnames(allX)[g],"0.1",sep="_")
control <- c(sangerData$Diagnosis=="Control", torontoData$Diagnosis=="Control")
```

Weights

```
weights <- rep(1, nrow(allX))
weights[cohort=="Sanger" & control] <- n_total_sanger/sum(cohort=="Sanger" & contr
ol & allSurv[,1]==0)
weights[cohort=="Toronto" & control] <- n_total_toronto/sum(cohort=="Toronto" & co
ntrol)

n_total <- n_total_sanger + n_total_toronto
n_total
```

```
## [1] 82784.38
```

Kaplan-Meier analysis

```
X = allX
surv = allSurv
pal1 <- c("#C32B4A", "#3F76B4", "#57B2AB", "#5E4FA2", "#EB6046")

colnames(X)
```

```
##  [1] "ASXL1_0.1"  "BCOR_0.1"   "CBL_0.1"    "DNMT3A_0.1" "IDH1_0.1"   "IDH2_0.1
"   "JAK2_0.1"   "KDM6A_0.1"
##  [9] "KMT2C_0.1"  "KMT2D_0.1"  "KRAS_0.1"   "NF1_0.1"    "NRAS_0.1"   "PHF6_0.1
"   "PTPN11_0.1" "RAD21_0.1"
## [17] "RUNX1_0.1"  "SF3B1_0.1"  "SRSF2_0.1"  "TET2_0.1"   "TP53_0.1"   "U2AF1_0.
1"  "age_10"     "gender"
## [25] "cohort"
```

```
names(X) <- str_replace(names(X), "[_]{1}[0-9]{1,}[\\.]{0,1}[0-9]{0,2}", "")
X$no_drivers <- rowSums((X[, colnames(X) %in% gene_vars]>0))
summary(X$no_drivers)
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##  0.0000  0.0000  0.0000  0.5263  1.0000  5.0000
```

```
X$max_vaf <- apply(X[, intersect(gene_vars, colnames(X))], 1, max, na.rm = TRUE)

genes <- c("DNMT3A", "TET2", "TP53", "U2AF1")

n_drivers <- cut(X$no_drivers, c( -1, 0, 1,  max(X$no_drivers)))
levels(n_drivers) <- c(0,1,"2+")

mvaf <- cut(X$max_vaf*10, c( -1, 0, 4, 8, max(X$max_vaf*10)))  #multiply by 10 to
reverse VAF standardisation
levels(mvaf) <- c("0", "0 - 4", "4 - 8", "8+")

par(mfrow=c(2,4), mar = c(1.8, 1.9, 1.7, 0.1) + 0.1, mgp=c(2.2,0.4,0), bty="L", xp
d=TRUE, las=1, tcl=-0.15, cex.axis=1, cex.lab = 1)
for (i in 1:length(genes)) {
  #i <- 1
  gene <- genes[i]
  plot(survfit(surv ~ X[[gene]] == 0), col= pal1, bty='L', yaxs='i', ylim=c(0,1.01
), mark.time = T, conf.int = F)
  mtext(gene, font=3, side = 3, line = 0.1, cex = 0.7)
  legend("bottomleft", col=pal1[1:2], lty=1, c("MT","WT"), lwd = 1.1, bty="n", nco
l = 1, cex = 0.9)
}
plot(survfit(surv ~ n_drivers), col=rev(pal1[1:3]), conf.int = F, mark.time = T, b
ty='L', yaxs='i', ylim=c(0,1.01))
mtext("Number of drivers", font=1, side = 3, line = 0.4, cex = 0.7)
legend("bottomleft", legend = levels(n_drivers), col= rev(pal1[1:3]), lty=1, lwd =
1.1, bty='n', title="", cex = 0.9)
plot(survfit(surv ~ mvaf), col= rev(pal1[1:4]), conf.int = F, mark.time = T, bty='
L', yaxs='i', ylim=c(0,1.01))
mtext("Maximum VAF (%)", font=1, side = 3, line = 0.4, cex = 0.7)
legend("bottomleft", levels(mvaf), col=rev(pal1[1:4]), lty=1, lwd = 1.1, bty='n',
title="", cex = 0.9)

genes <- intersect(colnames(X), gene_vars)
length(genes)
```

```
## [1] 22
```

```
png("./figures/CombinedCohorts.KM.curves.png", width = 35, height = 20, units = "c
m", res = 300)
par(mfrow=c(4,7), mar = c(3.7, 3.5, 1.6, 1) + 0.1, mgp=c(1.9,0.4,0), bty="L", xpd=
TRUE, las=1, tcl=-0.2, cex.axis=1, cex.lab = 1.2)
for (i in 1:length(genes)) {
  #i <- 1
  gene <- genes[i]
  plot(survfit(surv ~ X[[gene]] == 0), col= pal1, xlab='Time (years)', ylab = 'AML
-free fraction', bty='L', yaxs='i', ylim=c(0,1.01), mark.time = T, conf.int = F)
  mtext(gene, font=4, side = 3, cex = 0.9, line = 0.35)
}
plot.new(); par(xpd=NA)
legend(x = -0.5, y = 0.5, col=pal1[1:2], lty=1, c("Mutated","Wildtype"), cex=1.4,
lwd = 2, bty="n", ncol = 1)
dev.off()
```

```
## pdf
##   2
```

# 7 Coxph model fits

```
sigma0 <- 0.1
nu <- 1
which.mu <- "Genes"
```

# 7.1 Discovery cohort

## 7.1.1 Non-adjusted

```
fitToronto <- CoxRFX(torontoX, torontoSurv, groups=torontoGroups, which.mu=which.m
u, nu=nu, sigma0=sigma0)
waldToronto <- WaldTest(fitToronto)
```

```
##                   group    coef   coef-mu     sd      z df  p.value sig
## ASXL1_0.1         Genes  0.6715  3.40e-02 0.1169  5.745  1 9.19e-09 ***
## CALR_0.1          Genes  0.6168 -2.07e-02 0.0717  8.603  1 7.76e-18 ***
## CBL_0.1           Genes  0.5158 -1.22e-01 0.1311  3.935  1 8.30e-05 ***
## DNMT3A_0.1        Genes  0.5860 -5.15e-02 0.1017  5.761  1 8.36e-09 ***
## IDH1_0.1          Genes  0.6818  4.43e-02 0.1269  5.373  1 7.74e-08 ***
## IDH2_0.1          Genes  0.5153 -1.22e-01 0.1159  4.446  1 8.74e-06 ***
## JAK2_0.1          Genes  0.6967  5.92e-02 0.1249  5.580  1 2.40e-08 ***
## KDM6A_0.1         Genes  0.6375  2.36e-05 0.0581 10.982  1 4.67e-28 ***
## KMT2C_0.1         Genes  0.6602  2.27e-02 0.0618 10.689  1 1.14e-26 ***
## KRAS_0.1          Genes  0.6350 -2.46e-03 0.0581 10.932  1 8.12e-28 ***
## NF1_0.1           Genes  0.6359 -1.61e-03 0.0581 10.947  1 6.86e-28 ***
## PHF6_0.1          Genes  0.6429  5.40e-03 0.0586 10.978  1 4.87e-28 ***
## PTPN11_0.1        Genes  0.6546  1.71e-02 0.0583 11.224  1 3.11e-29 ***
## RUNX1_0.1         Genes  0.3926 -2.45e-01 0.0927  4.236  1 2.27e-05 ***
## SF3B1_0.1         Genes  0.7605  1.23e-01 0.1045  7.274  1 3.49e-13 ***
## SRSF2_0.1         Genes  0.4847 -1.53e-01 0.0944  5.134  1 2.83e-07 ***
## TET2_0.1          Genes  0.6127 -2.48e-02 0.1300  4.712  1 2.46e-06 ***
## TP53_0.1          Genes  0.8595  2.22e-01 0.0875  9.823  1 8.99e-23 ***
## U2AF1_0.1         Genes  0.8524  2.15e-01 0.0785 10.860  1 1.79e-27 ***
## age_10      Demographics -0.0387 -3.87e-02 0.0943 -0.410  1 6.82e-01
## gender      Demographics -0.0434 -4.34e-02 0.1069 -0.406  1 6.85e-01
```

```
survConcordance(fitToronto$surv ~ fitToronto$linear.predictors)
```

```
## Call:
## survConcordance(formula = fitToronto$surv ~ fitToronto$linear.predictors)
##
##   n= 505
## Concordance= 0.7426378 se= 0.03079247
## concordant discordant  tied.risk  tied.time   std(c-d)
##  28925.000  10024.000      0.000      1.000   2398.672
```

## 7.1.2 Adjusted

```
fitWeightedToronto <- CoxRFX(torontoX, torontoSurv, torontoGroups, which.mu=which.
mu, sigma0=sigma0, nu=nu, weights=weights[cohort=="Toronto"])
waldWeightedToronto <- WaldTest(fitWeightedToronto)
```

```
##                   group    coef coef-mu     sd      z df  p.value sig
## ASXL1_0.1         Genes  1.9481  0.0184 0.1452 13.415  1 4.92e-41 ***
## CALR_0.1          Genes  0.8664 -1.0633 0.7205  1.202  1 2.29e-01
## CBL_0.1           Genes  0.3846 -1.5451 0.3618  1.063  1 2.88e-01
## DNMT3A_0.1        Genes  0.7091 -1.2206 0.1236  5.736  1 9.70e-09 ***
## IDH1_0.1          Genes  2.3976  0.4679 0.3353  7.151  1 8.63e-13 ***
## IDH2_0.1          Genes  0.8112 -1.1185 0.2286  3.548  1 3.88e-04 ***
## JAK2_0.1          Genes  1.9253 -0.0044 0.1819 10.586  1 3.45e-26 ***
## KDM6A_0.1         Genes  1.9404  0.0107 0.1355 14.323  1 1.56e-46 ***
## KMT2C_0.1         Genes  2.4139  0.4841 0.6457  3.739  1 1.85e-04 ***
## KRAS_0.1          Genes  1.8253 -0.1044 0.1565 11.665  1 1.93e-31 ***
## NF1_0.1           Genes  1.8627 -0.0670 0.1522 12.238  1 1.94e-34 ***
## PHF6_0.1          Genes  2.1738  0.2441 0.1301 16.706  1 1.19e-62 ***
## PTPN11_0.1        Genes  2.5509  0.6212 0.2150 11.867  1 1.76e-32 ***
## RUNX1_0.1         Genes  0.7839 -1.1458 0.1361  5.761  1 8.38e-09 ***
## SF3B1_0.1         Genes  3.1354  1.2057 0.3087 10.156  1 3.11e-24 ***
## SRSF2_0.1         Genes  1.3985 -0.5312 0.1706  8.196  1 2.49e-16 ***
## TET2_0.1          Genes  0.6793 -1.2504 0.2014  3.373  1 7.43e-04 ***
## TP53_0.1          Genes  4.8882  2.9585 0.4224 11.572  1 5.69e-31 ***
## U2AF1_0.1         Genes  3.9699  2.0402 0.3601 11.024  1 2.94e-28 ***
## age_10     Demographics -0.0869 -0.0869 0.0996 -0.872  1 3.83e-01
## gender     Demographics -0.0443 -0.0443 0.1112 -0.399  1 6.90e-01
```

```
survConcordance(fitWeightedToronto$surv ~ fitWeightedToronto$linear.predictors, we
ights=weights[cohort=="Toronto"])
```

```
## Call:
## survConcordance(formula = fitWeightedToronto$surv ~ fitWeightedToronto$linear.p
redictors,
##     weights = weights[cohort == "Toronto"])
##
##   n= 505
## Concordance= 0.7739557 se= 0.03055735
## concordant discordant  tied.risk  tied.time   std(c-d)
##  4719299.0  1378335.7        0.0        1.0   372655.1
```

Uno's estimator of cumulative/dynamic AUC

```
a <- AUC.uno(torontoSurv, torontoSurv, fitWeightedToronto$linear.predictors, times
= seq(0,12, 0.1))
round(a$iauc, digits = 3)
```

```
## [1] 0.761
```

```
png("./figures/DC.adj.coxph.auc.uno.png", width = 9, height = 10, units = "cm", re
s = 800)
par(mar = c(3.2, 3.2, 4, 2) + 0.1, mgp=c(2,0.5,0), bty="L",  tcl =-0.2, las = 1, c
ex=1)
plot(a$times, a$auc, xlab="Time (years)", ylab="AUC", pch=16, col="grey80", ylim =
c(0,1.0))
lines(a$times, predict(loess(a$auc ~ a$times, span=0.25)))
abline(h=a$iauc, lty = 3, lwd = 1)
legend("bottomright", bty = "n", cex = 1.2, legend = paste("AUC = ",round(a$iauc,2
)))
dev.off()
```

```
## pdf
##   2
```

Time-dependent ROC AUC

```
r <- survivalROC(Stime = torontoSurv[,1], status=torontoSurv[,2], marker=fitWeight
edToronto$linear.predictors-colMeans(fitWeightedToronto$Z) %*% fitWeightedToronto$
```

```
coefficients, predict.time = 10, method="NNE", span=0.001)
round(r$AUC, digits = 3)
```

```
## [1] 0.783
```

```
png("./figures/DC.adj.coxph.roct.png", width = 9, height = 10, units = "cm", res =
500)
par(mar = c(3.2, 3.2, 4, 2) + 0.1, mgp=c(2,0.5,0), bty="L",  tcl =-0.2, las = 1, c
ex = 1)
plot(r$FP, r$TP, type='s',
     xlab="False Positive Rate", ylab="True Positive Rate",
     col = "black")
abline(a = 0, b = 1, col = "grey70", lty = 1, lwd = 1)
legend("bottomright", bty = "n", legend = paste("AUC = ",round(r$AUC,2)))
dev.off()
```

```
## pdf
##   2
```

# 7.2 Validation cohort

## 7.2.1 Non-adjusted

```
fitSanger <- CoxRFX(sangerX, sangerSurv, groups=sangerGroups, which.mu=which.mu, n
u=nu, sigma0=sigma0)
waldSanger <- WaldTest(fitSanger)
```

```
##                    group     coef   coef-mu      sd       z df  p.value sig
## ASXL1_0.1          Genes  0.76929  0.138331 0.11468  6.7084  1 1.97e-11 ***
## CBL_0.1            Genes  0.62044 -0.010519 0.09149  6.7814  1 1.19e-11 ***
## DNMT3A_0.1         Genes  0.51590 -0.115058 0.11678  4.4176  1 9.98e-06 ***
## JAK2_0.1           Genes  0.58502 -0.045941 0.10315  5.6716  1 1.42e-08 ***
## KMT2C_0.1          Genes  0.64589  0.014930 0.08616  7.4961  1 6.57e-14 ***
## KMT2D_0.1          Genes  0.50507 -0.125896 0.15209  3.3209  1 8.97e-04 ***
## KRAS_0.1           Genes  0.63604  0.005083 0.08495  7.4876  1 7.02e-14 ***
## NF1_0.1            Genes  0.62556 -0.005397 0.08610  7.2657  1 3.71e-13 ***
## NRAS_0.1           Genes  0.63025 -0.000712 0.08492  7.4214  1 1.16e-13 ***
## RAD21_0.1          Genes  0.62875 -0.002212 0.08524  7.3763  1 1.63e-13 ***
## SF3B1_0.1          Genes  0.62728 -0.003678 0.08572  7.3181  1 2.52e-13 ***
## SRSF2_0.1          Genes  0.58180 -0.049163 0.12680  4.5883  1 4.47e-06 ***
## TET2_0.1           Genes  0.69969  0.068723 0.11185  6.2555  1 3.96e-10 ***
## TP53_0.1           Genes  0.69326  0.062294 0.08559  8.0998  1 5.51e-16 ***
## U2AF1_0.1          Genes  0.70018  0.069214 0.08556  8.1832  1 2.76e-16 ***
## age_10       Demographics  0.10777  0.107774 0.12063  0.8934  1 3.72e-01
## gender       Demographics  0.00589  0.005894 0.10667  0.0553  1 9.56e-01
## systol_100          Blood  0.03002  0.030016 0.04429  0.6777  1 4.98e-01
## diastol_100         Blood  0.04718  0.047181 0.02863  1.6478  1 9.94e-02   .
## bmi_10              Blood  0.14183  0.141832 0.07973  1.7790  1 7.52e-02   .
## cholestl_10         Blood  0.00525  0.005246 0.01501  0.3496  1 7.27e-01
## triglyc             Blood  0.00450  0.004496 0.10599  0.0424  1 9.66e-01
## hdl                 Blood -0.09452 -0.094522 0.08059 -1.1729  1 2.41e-01
## ldl                 Blood  0.11424  0.114236 0.11019  1.0367  1 3.00e-01
## lym                 Blood  0.10961  0.109610 0.10081  1.0872  1 2.77e-01
## mcv_100             Blood -0.01645 -0.016447 0.00817 -2.0136  1 4.41e-02   *
## rdw_10              Blood  0.06116  0.061157 0.01972  3.1015  1 1.93e-03  **
## wbc_10              Blood  0.01499  0.014994 0.04138  0.3623  1 7.17e-01
## plt_100             Blood  0.06837  0.068369 0.09739  0.7020  1 4.83e-01
## hgb_10              Blood  0.04890  0.048900 0.02466  1.9826  1 4.74e-02   *
```

```
survConcordance(sangerSurv ~ fitSanger$linear.predictors)
```

```
## Call:
## survConcordance(formula = sangerSurv ~ fitSanger$linear.predictors)
##
##   n= 445
## Concordance= 0.793915 se= 0.05514512
## concordant discordant  tied.risk  tied.time   std(c-d)
##  5532.0000  1436.0000     0.0000     0.0000   768.5024
```

## 7.2.2 Adjusted

```
fitWeightedSanger <- CoxRFX(sangerX, sangerSurv, sangerGroups, which.mu=which.mu,
sigma0=sigma0, nu=nu, weights=weights[cohort=="Sanger"])
```

```
waldWeightedSanger <- waldTest(fitWeightedSanger)
```

```
##                    group     coef  coef-mu      sd       z df  p.value sig
## ASXL1_0.1          Genes  2.93589  0.95179 0.45155  6.5018  1 7.93e-11 ***
## CBL_0.1            Genes  0.89451 -1.08959 1.25454  0.7130  1 4.76e-01
## DNMT3A_0.1         Genes  0.80635 -1.17775 0.22686  3.5544  1 3.79e-04 ***
## JAK2_0.1           Genes -0.33650 -2.32060 0.95076 -0.3539  1 7.23e-01
## KMT2C_0.1          Genes  2.07422  0.09012 1.10633  1.8749  1 6.08e-02   .
## KMT2D_0.1          Genes  0.05067 -1.93343 0.81191  0.0624  1 9.50e-01
## KRAS_0.1           Genes  2.45194  0.46784 0.41069  5.9702  1 2.37e-09 ***
## NF1_0.1            Genes  1.54402 -0.44008 0.90581  1.7046  1 8.83e-02   .
## NRAS_0.1           Genes  1.92976 -0.05434 0.37569  5.1366  1 2.80e-07 ***
## RAD21_0.1          Genes  1.75445 -0.22966 0.66215  2.6496  1 8.06e-03  **
## SF3B1_0.1          Genes  1.56640 -0.41770 0.99531  1.5738  1 1.16e-01
## SRSF2_0.1          Genes  1.51230 -0.47181 0.27893  5.4217  1 5.90e-08 ***
## TET2_0.1           Genes  1.31638 -0.66772 0.13659  9.6374  1 5.56e-22 ***
## TP53_0.1           Genes  4.92658  2.94248 0.92037  5.3528  1 8.66e-08 ***
## U2AF1_0.1          Genes  6.33456  4.35046 0.76145  8.3191  1 8.86e-17 ***
## age_10       Demographics  0.03788  0.03788 0.11866  0.3193  1 7.50e-01
## gender       Demographics -0.01411 -0.01411 0.10079 -0.1400  1 8.89e-01
## systol_100          Blood  0.01712  0.01712 0.04486  0.3816  1 7.03e-01
## diastol_100         Blood  0.03900  0.03900 0.02964  1.3156  1 1.88e-01
## bmi_10              Blood  0.15297  0.15297 0.08406  1.8198  1 6.88e-02   .
## cholestl_10         Blood  0.00238  0.00238 0.01544  0.1542  1 8.77e-01
## triglyc             Blood -0.03451 -0.03451 0.11758 -0.2935  1 7.69e-01
## hdl                 Blood -0.12128 -0.12128 0.08447 -1.4357  1 1.51e-01
## ldl                 Blood  0.13215  0.13215 0.11436  1.1555  1 2.48e-01
## lym                 Blood  0.07976  0.07976 0.10326  0.7724  1 4.40e-01
## mcv_100             Blood -0.02401 -0.02401 0.00786 -3.0529  1 2.27e-03  **
## rdw_10              Blood  0.06721  0.06721 0.01666  4.0355  1 5.45e-05 ***
## wbc_10              Blood  0.00757  0.00757 0.04834  0.1567  1 8.76e-01
## plt_100             Blood  0.08415  0.08415 0.09986  0.8427  1 3.99e-01
## hgb_10              Blood  0.03718  0.03718 0.02437  1.5255  1 1.27e-01
```

```
waldWeightedSanger$p.adj <- p.adjust(p=waldWeightedSanger$p.value, method = "bonfe
rroni")
#View(waldWeightedSanger)

survConcordance(sangerSurv ~ fitWeightedSanger$linear.predictors, weights=weights[
cohort=="Sanger"])
```

```
## Call:
## survConcordance(formula = sangerSurv ~ fitWeightedSanger$linear.predictors,
##     weights = weights[cohort == "Sanger"])
##
##   n= 445
## Concordance= 0.8351691 se= 0.05475847
## concordant discordant  tied.risk  tied.time   std(c-d)
##  218019.86   43028.90       0.00       0.00   28589.26
```

Uno's estimator of cumulative/dynamic AUC

```
w <- c(which(sangerSurv[,1]==0)[-1]-1, nrow(sangerSurv))  #get right censored surv
ival data for each individual
s <- Surv(sangerSurv[w,2], sangerSurv[w,3])  ##Adjust according to dimensions of s
urvival object
a <- AUC.uno(s, s, fitWeightedSanger$linear.predictors[w], times= seq(0, 22, 0.1))
round(a$iauc, digits = 3)
```

```
## [1] 0.82
```

```
png("./figures/VC.ajd.coxph.auc.uno.png", width = 9, height = 10, units = "cm", re
s = 500)
par(mar = c(3.2, 3.2, 4, 2) + 0.1, mgp=c(2,0.5,0), bty="L",  tcl =-0.2, las = 1, c
ex=1)
plot(a$times, a$auc, xlab="Time (years)", ylab="AUC", pch=16, col="grey80", ylim =
c(0,1.0))
lines(a$times, predict(loess(a$auc ~ a$times, span=0.25)))
abline(h=a$iauc, lty = 3, lwd = 1)
legend("bottomright", bty = "n", legend = paste("AUC = ",round(a$iauc,2)))
dev.off()
```

```
## pdf
##   2
```

Time-dependent ROC AUC

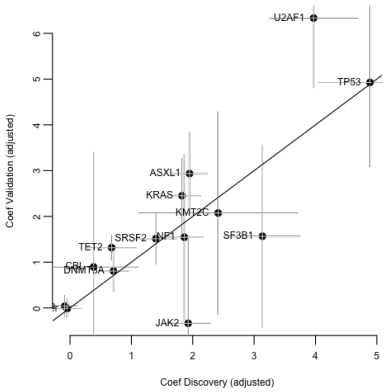
```
r <- survivalROC(Stime = s[,1], status=s[,2], marker=fitWeightedSanger$linear.pred
ictors[w]-colMeans(fitWeightedSanger$Z[w,]) %*% fitWeightedSanger$coefficients, pr
edict.time = 10, method="NNE", span=0.001)
round(r$AUC, digits = 3)
```

```
## [1] 0.737
```

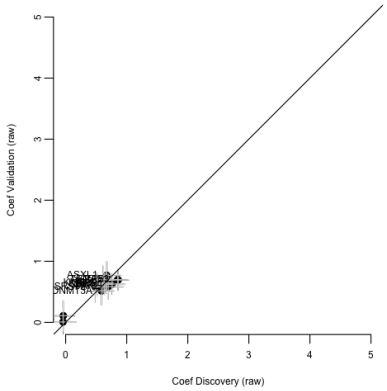
```
png("./figures/VC.ajd.coxph.roct.png", width = 9, height = 10, units = "cm", res =
500)
par(mar = c(3.2, 3.2, 4, 2) + 0.1, mgp=c(2,0.5,0), bty="L",  tcl =-0.2, las = 1, c
ex = 1)
plot(r$FP, r$TP, type='s',
     xlab="False Positive Rate", ylab="True Positive Rate",
     col = "black")
abline(a = 0, b = 1, col = "grey70", lty = 1, lwd = 1)
legend("bottomright", bty = "n", legend = paste("AUC = ",round(r$AUC,2)))
dev.off()
```

```
## pdf
##   2
```

```
i <- intersect(rownames(waldWeightedSanger), rownames(waldWeightedToronto))
plot( waldWeightedToronto[i,"coef"], waldWeightedSanger[i, "coef"], xlab="Coef Dis
covery (adjusted)", ylab="Coef Validation (adjusted)", pch=19, cex=1)
segments(waldWeightedToronto[i,"coef"]  - 2*waldWeightedToronto[i,"sd"], waldWeigh
tedSanger[i, "coef"], waldWeightedToronto[i,"coef"]  + 2*waldWeightedToronto[i,"sd
"], waldWeightedSanger[i, "coef"], col="grey" )
segments(waldWeightedToronto[i,"coef"]  , waldWeightedSanger[i, "coef"]-  2*waldWe
ightedSanger[i,"sd"], waldWeightedToronto[i,"coef"] , waldWeightedSanger[i, "coef"
] +2*waldWeightedSanger[i,"sd"], col="grey")
text(labels=sub("_.+","", i), waldWeightedToronto[i,"coef"], waldWeightedSanger[i,
"coef"], pos=2, adj=c(0,1))
abline(0,1)
```




```
plot( waldToronto[i,"coef"], waldSanger[i, "coef"], xlab="Coef Discovery (raw)", y
lab="Coef Validation (raw)", pch=19, cex=1, ylim=c(0,5),xlim=c(0,5))
segments(waldToronto[i,"coef"]  - 2*waldToronto[i,"sd"], waldSanger[i, "coef"], wa
ldToronto[i,"coef"]  + 2*waldToronto[i,"sd"], waldSanger[i, "coef"], col="grey" )
segments(waldToronto[i,"coef"]  , waldSanger[i, "coef"]-  2*waldSanger[i,"sd"], wa
ldToronto[i,"coef"] , waldSanger[i, "coef"] +2*waldSanger[i,"sd"], col="grey")
text(labels=sub("_.+","", i), waldToronto[i,"coef"], waldSanger[i, "coef"], pos=2,
adj=c(0,1))
abline(0,1)
```




# 7.3 Cross-validation

## 7.3.1 Non-adjusted

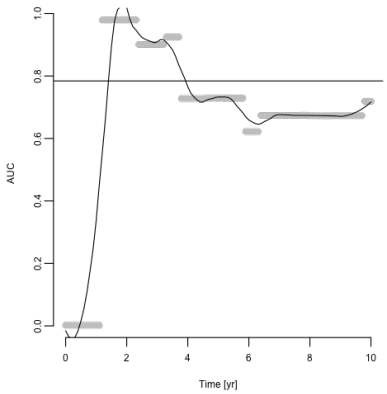
```
sangerImp <- torontoX[1:nrow(sangerX),]
sangerImp[,] <- NA
i <- intersect(names(sangerX),colnames(torontoX))
sangerImp[,i] <- sangerX[,i]
j <- setdiff(names(torontoX)[torontoGroups=="Genes"], names(sangerX))
sangerImp[,j] <- 0
```

DC fit, VC data

```
pS <- PredictRiskMissing(fitToronto, sangerImp)
survConcordance(sangerSurv ~ pS[,1])
```

```
## Call:
## survConcordance(formula = sangerSurv ~ pS[, 1])
##
##   n= 445
## Concordance= 0.7963548 se= 0.05514445
## concordant discordant  tied.risk  tied.time   std(c-d)
##   5545.000   1415.000      8.000      0.000    768.493
```

```
w <- c(which(sangerSurv[,1]==0)[-1]-1, nrow(sangerSurv))
s <- Surv(sangerSurv[w,2], sangerSurv[w,3])
t <- seq(0,10,0.1)
a <- AUC.uno(torontoSurv, s, pS[w,1], times=t)
plot(a$times, a$auc, xlab="Time [yr]", ylab="AUC", pch=16, col='grey')
lines(a$times, predict(loess(a$auc ~ a$times, span=0.25)))
abline(h=a$iauc)
```



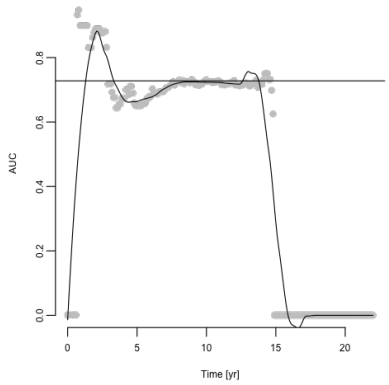

```
torontoImp <- sangerX[1:nrow(torontoX),]
torontoImp[,] <- NA
i <- intersect(names(sangerX),colnames(torontoX))
torontoImp[,i] <- torontoX[,i]
j <- setdiff(names(sangerX)[sangerGroups=="Genes"], names(torontoX))
torontoImp[,j] <- 0
```

VC fit, DC data

```
pT <- PredictRiskMissing(fitSanger, torontoImp)
survConcordance(torontoSurv ~ pT[,1])
```

```
## Call:
## survConcordance(formula = torontoSurv ~ pT[, 1])
##
##   n= 505
## Concordance= 0.6992477 se= 0.03079247
## concordant discordant  tied.risk  tied.time   std(c-d)
##  27235.000  11714.000      0.000      1.000   2398.672
```

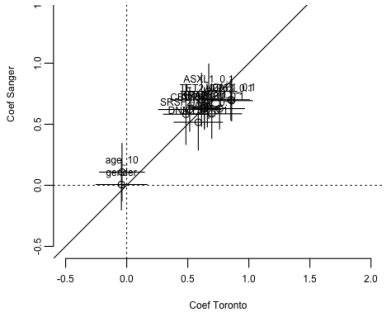
```
t <- seq(0,22,0.1)
a <- AUC.uno(s, torontoSurv, pT[,1], times=t)
plot(a$times, a$auc, xlab="Time [yr]", ylab="AUC", pch=16, col='grey')
lines(a$times, predict(loess(a$auc ~ a$times, span=0.25)))
abline(h=a$iauc)
```




```
sangerM <- sangerX
sangerM[,sangerGroups=="Blood"] <- NA
p <- PredictRiskMissing(fitSanger, sangerM)
survConcordance(sangerSurv ~ p[,1])
```

```
## Call:
## survConcordance(formula = sangerSurv ~ p[, 1])
##
##   n= 445
## Concordance= 0.8069747 se= 0.05514449
## concordant discordant  tied.risk  tied.time   std(c-d)
##  5619.0000  1341.0000     8.0000     0.0000   768.4936
```

```
plot(waldToronto[i,"coef"], waldSanger[i,"coef"], xlab="Coef Toronto", ylab="Coef
Sanger", xlim=c(-0.5,2), ylim=c(-0.5,2))
text(labels=i,waldToronto[i,"coef"], waldSanger[i,"coef"], pos=3)
segments(x0=waldToronto[i,"coef"], x1=waldToronto[i,"coef"], y0= waldSanger[i,"coe
f"]-1.96*waldSanger[i,"sd"], y1=waldSanger[i,"coef"]+1.96*waldSanger[i,"sd"])
segments(x0=waldToronto[i,"coef"]-1.96*waldToronto[i,"sd"], x1=waldToronto[i,"coef
"]+1.96*waldToronto[i,"sd"], y0= waldSanger[i,"coef"], y1=waldSanger[i,"coef"])
abline(0,1)
abline(h=0, lty=3)
abline(v=0, lty=3)
```



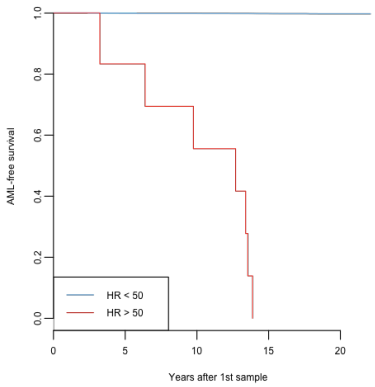

## 7.3.2 Adjusted

DC fit, VC data

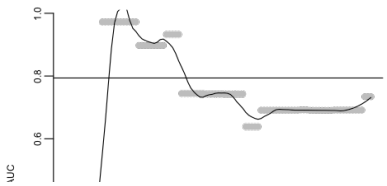
```
pS <- PredictRiskMissing(fitWeightedToronto, sangerImp)
survConcordance(sangerSurv ~ pS[,1], weights=weights[cohort=="Sanger"])
```

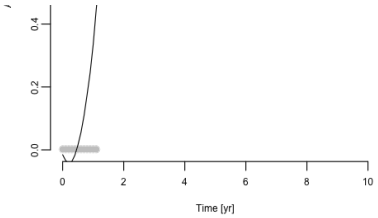
```
## Call:
## survConcordance(formula = sangerSurv ~ pS[, 1], weights = weights[cohort ==
##     "Sanger"])
##
##   n= 445
## Concordance= 0.821456 se= 0.05475772
##  concordant  discordant   tied.risk   tied.time    std(c-d)
## 214281.1753  46449.8206    317.7601      0.0000  28588.8682
```

```
m <- as.numeric(colSums(fitWeightedToronto$Z * weights[cohort=="Toronto"])/sum(wei
ghts[cohort=="Toronto"])) %*% coef(fitWeightedToronto)
plot(survfit(sangerSurv ~ exp(pS[,1]-as.numeric(m))>50, weights=weights[cohort=="S
anger"]), col=set1[2:1], ylab="AML-free survival", xlab='Years after 1st sample')
legend("bottomleft", c("HR < 50", "HR > 50"), lty=1, col=set1[2:1])
```




```
w <- c(which(sangerSurv[,1]==0)[-1]-1, nrow(sangerSurv))
s <- Surv(sangerSurv[w,2], sangerSurv[w,3])
t <- seq(0,10,0.1)
a <- AUC.uno(torontoSurv, s, pS[w,1], times=t)
plot(a$times, a$auc, xlab="Time [yr]", ylab="AUC", pch=16, col='grey')
lines(a$times, predict(loess(a$auc ~ a$times, span=0.25)))
abline(h=a$iauc)
```






```
png("./figures/DCfit.VCdata.adj.coxph.auc.uno.png", width = 14, height = 14, units
= "cm", res = 500)
par(mar = c(4, 4, 4, 2) + 0.1, mgp=c(2.7,0.7,0), bty="L",  tcl =-0.2, las = 1, cex
.lab = 1.1)
plot(a$times, a$auc, xlab="Time (years)", ylab="AUC", pch=16, col="grey80", ylim =
c(0,1.0))
lines(a$times, predict(loess(a$auc ~ a$times, span=0.25)))
abline(h=a$iauc, lty = 3, lwd = 1)
mtext("DC fit, VC data", font= 2, side = 3, cex = 1, line = 0.5)
legend("bottomright", bty = "n", cex = 1.2, legend = paste("AUC = ",round(a$iauc,2
)))
dev.off()
```

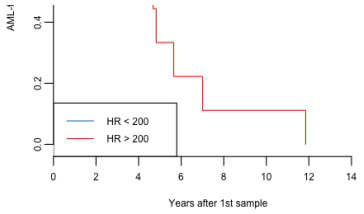
```
## pdf
##   2
```

VC fit, DC data

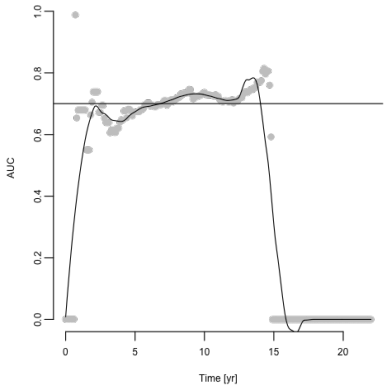
```
pT <- PredictRiskMissing(fitWeightedSanger, torontoImp)
survConcordance(torontoSurv ~ pT[,1], weights=weights[cohort=="Toronto"])
```

```
## Call:
## survConcordance(formula = torontoSurv ~ pT[, 1], weights = weights[cohort ==
##     "Toronto"])
##
##   n= 505
## Concordance= 0.7202544 se= 0.03055735
## concordant discordant  tied.risk  tied.time   std(c-d)
##  4391848.0  1705786.7        0.0        1.0   372655.1
```

```
m <- as.numeric(colSums(fitWeightedSanger$Z * weights[cohort=="Sanger"])/sum(weigh
ts[cohort=="Sanger"])) %*% coef(fitWeightedSanger)
plot(survfit(torontoSurv ~ exp(pT[,1]-as.numeric(m))>200, weights=weights[cohort==
"Toronto"]), col=set1[2:1], ylab="AML-free survival", xlab='Years after 1st sample
')
legend("bottomleft", c("HR < 200", "HR > 200"), lty=1, col=set1[2:1])
```




```
t <- seq(0,22,0.1)
a <- AUC.uno(s, torontoSurv, pT[,1], times=t)
plot(a$times, a$auc, xlab="Time [yr]", ylab="AUC", pch=16, col='grey')
lines(a$times, predict(loess(a$auc ~ a$times, span=0.25)))
abline(h=a$iauc)
```




```
png("./figures/VCfit.DCdata.adj.coxph.auc.uno.png", width = 14, height = 14, units
= "cm", res = 500)
par(mar = c(4, 4, 4, 2) + 0.1, mgp=c(2.7,0.7,0), bty="L",  tcl =-0.2, las = 1, cex
.lab = 1.1)
plot(a$times, a$auc, xlab="Time (years)", ylab="AUC", pch=16, col="grey80", ylim =
c(0,1.0))
lines(a$times, predict(loess(a$auc ~ a$times, span=0.25)))
abline(h=a$iauc, lty = 3, lwd = 1)
mtext("VC fit, DC data", font= 2, side = 3, cex = 1, line = 0.5)
legend("bottomright", bty = "n", cex = 1.2, legend = paste("AUC = ",round(a$iauc,2
)))#dev.off()
dev.off()
```

```
## pdf
##   2
```

# 7.4 Combined

## 7.4.1 Non-adjusted

```
fitAll <- CoxRFX(allX, allSurv, allGroups, which.mu=which.mu, sigma0=sigma0, nu=nu
)
fitAll
```

```
## Means:
##              mean    sd  z   p.val sig
## Genes        0.79 0.068 12 3.9e-31 ***
## Demographics 0.00 0.000  0      NA
##
## Variances - p-values only indicative:
##              sigma2 chisq  df   p.val sig
## Genes          0.19    25 9.2 2.7e-03  **
## Demographics   0.48    25 2.7 1.2e-05 ***
##
## Partial log hazard:
##              Cov[g,g] Sum(Cov[,g])   MSE
## Genes            0.40         0.41 0.012
## Demographics     0.45         0.46 0.032
## TOTAL             NaN         0.88 0.044
```

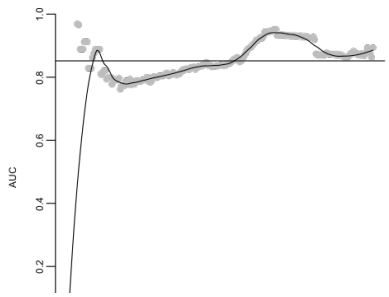
```
WaldTest(fitAll, uncentered=FALSE)
```

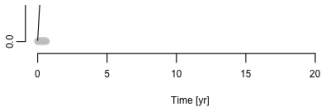
```
##                         group      coef coef-mu      sd       z df  p.value sig
## ASXL1_0.1               Genes -0.042129 -0.8326 0.12580 -0.3349  1 7.38e-01
## BCOR_0.1                Genes  0.018602 -0.7719 0.00792  2.3484  1 1.89e-02   *
## CBL_0.1                 Genes -0.313214 -1.1037 0.20346 -1.5394  1 1.24e-01
## DNMT3A_0.1              Genes -0.233727 -1.0242 0.10840 -2.1561  1 3.11e-02   *
## IDH1_0.1                Genes  0.021937 -0.7685 0.20020  0.1096  1 9.13e-01
## IDH2_0.1                Genes -0.278283 -1.0687 0.15309 -1.8177  1 6.91e-02   .
## JAK2_0.1                Genes -0.030573 -0.8210 0.14841 -0.2060  1 8.37e-01
## KDM6A_0.1               Genes  0.000538 -0.7899 0.00638  0.0843  1 9.33e-01
## KMT2C_0.1               Genes  0.068877 -0.7216 0.08598  0.8011  1 4.23e-01
## KMT2D_0.1               Genes -0.391241 -1.1817 0.20457 -1.9125  1 5.58e-02   .
## KRAS_0.1                Genes  0.006235 -0.7842 0.01271  0.4907  1 6.24e-01
## NF1_0.1                 Genes -0.020208 -0.8107 0.03223 -0.6270  1 5.31e-01
## NRAS_0.1                Genes  0.034555 -0.7559 0.01285  2.6887  1 7.17e-03  **
## PHF6_0.1                Genes  0.016466 -0.7740 0.01532  1.0749  1 2.82e-01
## PTPN11_0.1              Genes  0.360022 -0.4304 0.20817  1.7295  1 8.37e-02   .
## RAD21_0.1               Genes -0.006662 -0.7971 0.01823 -0.3654  1 7.15e-01
## RUNX1_0.1               Genes -0.399568 -1.1900 0.11410 -3.5019  1 4.62e-04 ***
## SF3B1_0.1               Genes  0.239576 -0.5509 0.20922  1.1451  1 2.52e-01
## SRSF2_0.1               Genes -0.290822 -1.0813 0.13577 -2.1420  1 3.22e-02   *
## TET2_0.1                Genes -0.158347 -0.9488 0.10442 -1.5165  1 1.29e-01
## TP53_0.1                Genes  0.686128 -0.1043 0.19933  3.4423  1 5.77e-04 ***
## U2AF1_0.1               Genes  0.711837 -0.0786 0.19998  3.5595  1 3.72e-04 ***
## age_10          Demographics -0.034319 -0.0343 0.10560 -0.3250  1 7.45e-01
## gender          Demographics -0.096757 -0.0968 0.18251 -0.5302  1 5.96e-01
## cohort          Demographics -1.297202 -1.2972 0.24120 -5.3781  1 7.53e-08 ***
## mu.Genes                  NA  0.790457      NA      NA      NA  1       NA
## mu.Demographics           NA  0.000000      NA      NA      NA  1       NA
```

```
survConcordance(allSurv ~ fitAll$linear.predictors)
```

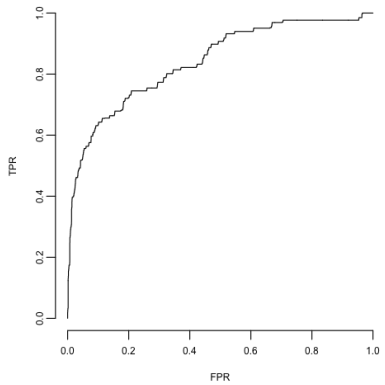
```
## Call:
## survConcordance(formula = allSurv ~ fitAll$linear.predictors)
##
##   n= 950
## Concordance= 0.8059859 se= 0.02746324
## concordant discordant  tied.risk  tied.time   std(c-d)
##  61799.000  14873.000      8.000      1.000   4211.763
```

```
w <- c(which(allSurv[,1]==0)[-1]-1, nrow(allSurv))
s <- Surv(allSurv[w,2], allSurv[w,3])
t <- seq(0,22,0.1)
a <- AUC.uno(s, s, fitAll$linear.predictors[w], times=t)
plot(a$times, a$auc, xlab="Time [yr]", ylab="AUC", pch=16, col='grey')
lines(a$times, predict(loess(a$auc ~ a$times, span=0.25)))
abline(h=a$iauc)
```






```
r <- survivalROC(Stime = s[,1], status=s[,2], marker=fitAll$linear.predictors[w]-c
olMeans(fitAll$Z[w,]) %*% fitAll$coefficients, predict.time = 10, method="NNE", sp
an=0.001)
plot(r$FP, r$TP, type='s', xlab="FPR", ylab="TPR")
```




```
round(r$AUC, 3)
```

```
## [1] 0.84
```

## 7.4.2 Adjusted

```
fitWeighted <- CoxRFX(allX, allSurv, allGroups, which.mu=which.mu, sigma0=sigma0,
nu=nu, weights=weights)
waldWeighted <- WaldTest(fitWeighted)
```

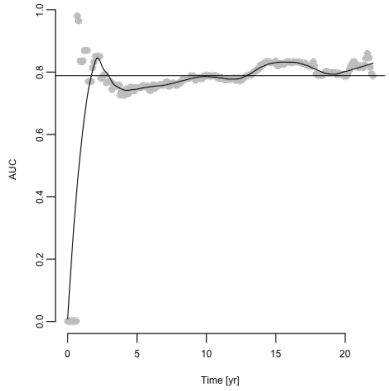
```
##                   group    coef coef-mu     sd      z df  p.value sig
## ASXL1_0.1         Genes  1.9907  0.0666 0.1328 14.985  1 9.18e-51 ***
## BCOR_0.1          Genes  2.1375  0.2134 0.1144 18.677  1 7.57e-78 ***
## CBL_0.1           Genes  0.3984 -1.5256 0.3634  1.096  1 2.73e-01
## DNMT3A_0.1        Genes  0.6589 -1.2652 0.1112  5.926  1 3.10e-09 ***
## IDH1_0.1          Genes  2.4306  0.5065 0.3313  7.337  1 2.18e-13 ***
## IDH2_0.1          Genes  0.8422 -1.0818 0.2181  3.862  1 1.13e-04 ***
## JAK2_0.1          Genes  1.8770 -0.0471 0.1954  9.607  1 7.44e-22 ***
## KDM6A_0.1         Genes  1.9370  0.0129 0.1241 15.607  1 6.51e-55 ***
## KMT2C_0.1         Genes  2.3674  0.4434 0.7114  3.328  1 8.75e-04 ***
## KMT2D_0.1         Genes  0.1632 -1.7609 0.4835  0.338  1 7.36e-01
## KRAS_0.1          Genes  1.9831  0.0590 0.1706 11.622  1 3.20e-31 ***
## NF1_0.1           Genes  1.5839 -0.3402 0.4410  3.592  1 3.29e-04 ***
## NRAS_0.1          Genes  2.3167  0.3926 0.1248 18.569  1 5.76e-77 ***
## PHF6_0.1          Genes  2.2266  0.3025 0.1241 17.937  1 6.04e-72 ***
## PTPN11_0.1        Genes  2.1631  0.2390 0.3107  6.962  1 3.35e-12 ***
## RAD21_0.1         Genes  1.8365 -0.0876 0.2512  7.311  1 2.65e-13 ***
## RUNX1_0.1         Genes  0.8106 -1.1134 0.1329  6.098  1 1.08e-09 ***
## SF3B1_0.1         Genes  3.1070  1.1829 0.3114  9.977  1 1.92e-23 ***
## SRSF2_0.1         Genes  1.3684 -0.5557 0.1491  9.176  1 4.47e-20 ***
## TET2_0.1          Genes  0.9527 -0.9714 0.1172  8.126  1 4.45e-16 ***
## TP53_0.1          Genes  5.0534  3.1293 0.3907 12.934  1 2.88e-38 ***
## U2AF1_0.1         Genes  4.1247  2.2006 0.3300 12.498  1 7.67e-36 ***
## age_10     Demographics -0.0962 -0.0962 0.0863 -1.114  1 2.65e-01
## gender     Demographics -0.0522 -0.0522 0.1044 -0.499  1 6.17e-01
## cohort     Demographics  0.0499  0.0499 0.0973  0.512  1 6.08e-01
```

```
survConcordance(fitWeighted$surv ~ fitWeighted$linear.predictor, weights=weights)
```

```
## Call:
## survConcordance(formula = fitWeighted$surv ~ fitWeighted$linear.predictor,
##     weights = weights)
##
##   n= 950
## Concordance= 0.7778849 se= 0.02802535
##   concordant   discordant    tied.risk    tied.time     std(c-d)
## 6313552.2348 1802641.1313     317.7601       1.0000  454936.0746
```

Dynamic/cumulative AUC

```
w <- c(which(allSurv[,1]==0)[-1]-1, nrow(allSurv))
survAll2 <- Surv(allSurv[w,2], allSurv[w,3])
t <- seq(0,22,0.1)
a <- AUC.uno(survAll2, survAll2, fitWeighted$linear.predictor[w], times=t)
plot(a$times, a$auc, xlab="Time [yr]", ylab="AUC", pch=16, col='grey')
lines(a$times, predict(loess(a$auc ~ a$times, span=0.25)))
abline(h=a$iauc)
```




```
round(a$iauc, 3)
```

```
## [1] 0.789
```

```
png("./figures/combined.ajd.coxph.auc.uno.png", width = 9, height = 10, units = "c
m", res = 500)
par(mar = c(3.2, 3.2, 4, 2) + 0.1, mgp=c(2,0.5,0), bty="L",  tcl =-0.2, las = 1, c
ex=1)
plot(a$times, a$auc, xlab="Time (years)", ylab="AUC", pch=16, col="grey80", ylim =
c(0,1.0))
lines(a$times, predict(loess(a$auc ~ a$times, span=0.25)))
abline(h=a$iauc, lty = 3, lwd = 1)
#mtext("Combined adjusted Cox PH", font= 2, side = 3, line = 0.5)
legend("bottomright", bty = "n", legend = paste("AUC = ",round(a$iauc,2)))
dev.off()
```

```
## pdf
##   2
```

Time-depenent ROC

```
r <- survivalROC(Stime = survAll2[,1], status=survAll2[,2], marker=fitWeighted$lin
ear.predictors[w]-colMeans(fitWeighted$Z[w,]) %*% fitWeighted$coefficients, predic
t.time = 10, method="NNE", span=0.001)
round(r$AUC, 3)
```

```
## [1] 0.791
```

```
png("./figures/Combined.adj.coxph.roct.png", width = 9, height = 10, units = "cm",
res = 500)
par(mar = c(3.2, 3.2, 4, 2) + 0.1, mgp=c(2,0.5,0), bty="L",  tcl =-0.2, las = 1, c
ex = 1)
plot(r$FP, r$TP, type='s',
     xlab="False Positive Rate", ylab="True Positive Rate",
     col = "black")
abline(a = 0, b = 1, col = "grey70", lty = 1, lwd = 1)
legend("bottomright", bty = "n", legend = paste("AUC = ",round(r$AUC,2)))
dev.off()
```

```
## pdf
##   2
```

## 7.4.3 Bootstrap

```
coefWeightedBoot <- sapply(1:100, function(foo){
            set.seed(foo)
            b <- unique(sample(1:nrow(allX), replace=TRUE))
            fitWeighted <- CoxRFX(allX[b,], allSurv[b,], allGroups, which.mu=which
.mu, sigma0=sigma0, nu=5, weights=weights[b])
            c(coef(fitWeighted), 'mu.Genes'=fitWeighted$mu["Genes"])
        })
```

```
concBoots <- sapply(1:100, function(foo){
            set.seed(foo)
            b <- unique(sample(1:nrow(allX), replace=TRUE))
            oob <- !1:nrow(allX) %in% b
            c(inb=as.numeric(survConcordance(allSurv[b,]~ as.matrix(allX)[b,] %*%
coefWeightedBoot[-26,foo], weights=weights[b])$concordance),
                    oob=as.numeric(survConcordance(allSurv[oob,]~ as.matrix(allX)[
oob,] %*% coefWeightedBoot[-26,foo],weights=weights[oob])$concordance),
                    auc = AUC.uno(survAll2[oob[w],], survAll2[oob[w],], as.matrix(
allX)[w,][oob[w],] %*% coefWeightedBoot[-26,foo], times=t)$iauc
            )
        })

apply(concBoots,1,quantile)
```

```
##            inb       oob       auc
## 0%   0.7127155 0.6414249 0.6163769
## 25%  0.7623231 0.7268340 0.7333587
## 50%  0.7757864 0.7643297 0.7833229
## 75%  0.7985773 0.7875492 0.8223659
## 100% 0.8519811 0.8713292 0.8805585
```

## 7.4.4 Forest plot

Figure 3

```
pal1 <- c("#C32B4A", "#3F76B4", "#57B2AB", "#5E4FA2", "#EB6046")
rownames(waldWeighted)
```

```
##  [1] "ASXL1_0.1"  "BCOR_0.1"   "CBL_0.1"    "DNMT3A_0.1" "IDH1_0.1"   "IDH2_0.1
"   "JAK2_0.1"   "KDM6A_0.1"
##  [9] "KMT2C_0.1"  "KMT2D_0.1"  "KRAS_0.1"   "NF1_0.1"    "NRAS_0.1"   "PHF6_0.1
"   "PTPN11_0.1" "RAD21_0.1"
## [17] "RUNX1_0.1"  "SF3B1_0.1"  "SRSF2_0.1"  "TET2_0.1"   "TP53_0.1"   "U2AF1_0.
1"  "age_10"     "gender"
## [25] "cohort"
```

```
png("./figures/Combined.adj.coxph.boostrapped.forest.png", width = 15.5, height =
17, units = "cm", res = 800)
par(bty="n", mar=c(3,6,3,15)+.5, mgp=c(2,0.5,0), xpd=FALSE, tcl=-.25, cex = 0.9)
c <- c(waldWeighted[-25,"coef"], "mu"=fitWeighted$mu["Genes"]); names(c)[1:24] <-
rownames(waldWeighted)[-25] #-25 removes 'cohort' variable
o <- c(23:24,1:22,25)
s <- c(rep(1,2), rep(.5, 23))
c <- exp(c*c(rep(0.5,22), c(1,1),0.5))
ci <- apply(coefWeightedBoot,1,quantile, c(0.025,0.975))[,-25] * rep(c(rep(0.5,22)
, c(1,1),0.5), each=2)
y <- rev(seq_along(c))
plot(c[o], y, xlab="Hazard ratio", log='x', ylab='', xaxt = "n", yaxt="n", pch=NA,
xlim=c(0.5,50))
atx <- axTicks(1)
axis(1,at=atx,labels=atx)
segments(x0=0.5, x1 = 50, y0=y, y1=y, col="#EEEEEE", lty=1)
abline(v=1, lty=1, col="grey")
abline(v=c["mu.Genes"], col=mg14::colTrans("#57B2AB"), lty=1)
segments(exp(ci[1,o]), y, exp(ci[2,o]),y)
points(c[o], y, xlab="",  bg=pal1[3], cex=2, pch=c(rep(21,24), 23))
m1 <- match(names(c)[o],rownames(waldWeightedToronto))[-25]
points(exp(c(waldWeightedToronto$coef[m1], fitWeightedToronto$mu["Genes"])*s), y,b
g=pal1[4], pch=c(rep(21,24), 23), cex=1)
m2 <- match(names(c)[o],rownames(waldWeightedSanger))[-25]
points(exp(c(waldWeightedSanger$coef[m2], fitWeightedSanger$mu["Genes"])*s), y,bg=
pal1[5], pch=c(rep(21,24), 23), cex=1)
mtext(side=2, sub("mu.Genes","Av. gene", sub("_.+","", sub("age", "Age", sub("gend
er", "Gender", names(c)[o])))), at=y, las=2, cex=0.85, font=c(1,1,rep(3,22),1))
r <- sapply(split(as.data.frame(allX>0), control), colMeans)
f <- sapply(split(allX, control), apply, 2, function(x) mean(x[x>0]))
par(xpd=NA)
points(rep(100,22),y[3:24], cex=sqrt(r[o[3:24],2]*10), pch=21, bg=pal1[2])
points(rep(100*1.5,22), y[3:24], cex=sqrt(r[o[3:24],1]*10), pch=21, bg=pal1[1])
points(rep(360,22),y[3:24], cex=sqrt(f[o[3:24],2]), pch=21, bg=set1[2])
points(rep(360*1.5,22), y[3:24], cex=sqrt(f[o[3:24],1]), pch=21, bg=pal1[1])
legend(x=0.8, y=27.8, pch=21, pt.bg=pal1[c(4,5,3)], c("DC","VC","Combined"), bty="
n", ncol=3, text.width=0.25)
text(y=24, x=100, "     Frequency", cex = 0.92)
text(y=24, x=360*1.5, "VAF    ", cex = 0.92)
axis(1, at=c(100,100*1.5), c("Control ","Pre-AML "), las=2, line=-1, cex = 0.89)
axis(1, at=c(360,360*1.5), c("Control ","Pre-AML "), las=2, line=-1, cex = 0.89)
dev.off()
```

```
## pdf
##   2
```

```
Fig3Data1 <- data.frame(Parameter = sapply(strsplit(names(c[o]), "_"), "[", 1),
                        CombinedModel.HR = round(c[o], 1),
                        CombinedModel.HR.CI2.5 = round(exp(ci[1,o]), 1),
                        CombinedModel.HR.CI97.5 = round(exp(ci[2,o]),1),
                        DC.HR = round(exp(c(waldWeightedToronto$coef[m1], fitWeigh
tedToronto$mu["Genes"])*s),1),
                        VC.HR = round(exp(c(waldWeightedSanger$coef[m2], fitWeight
edSanger$mu["Genes"])*s),1)
                        )
rownames(Fig3Data1) <- NULL
head(Fig3Data1)
```

| Parameter | CombinedModel.... | CombinedModel.HR.CI2.5 | CombinedModel.HR.CI97.5 | D |
|---|---|---|---|---|
| <fctr> | <dbl> | <dbl> | <dbl> | <d |
| 1 age | 0.9 | 0.8 | 1.0 | |
| 2 gender | 0.9 | 0.8 | 1.2 | |
| 3 ASXL1 | 2.7 | 2.5 | 6.6 | |

| | | | |
|---|---|---|---|
| 4 BCOR | 2.9 | 2.5 | 11.1 |
| 5 CBL | 1.2 | 1.0 | 5.1 |
| 6 DNMT3A | 1.4 | 1.2 | 1.8 |

6 rows

```
table(rownames(r)==rownames(f))
```

```
##
## TRUE
##   25
```

```
Fig3Data2 <- data.frame(Parameter = sapply(strsplit(rownames(r), "_"), "[", 1)[1:2
2],
                        Frequency_PreAML = round(r[1:22, 1],3),
                        Frequency_Controls = round(r[1:22, 2],3),
                        MeanVAF_PreAML = round(f[1:22, 1],3),
                        MeanVAF_Control = round(f[1:22, 2],3))
head(Fig3Data2)
```

| | Parameter<br><fctr> | Frequency_PreAML<br><dbl> | Frequency_Controls<br><dbl> | MeanVAF_Pre...<br><dbl> | MeanV |
|---|---|---|---|---|---|
| ASXL1_0.1 | ASXL1 | 0.090 | 0.021 | 1.262 | |
| BCOR_0.1 | BCOR | 0.008 | 0.001 | 0.117 | |
| CBL_0.1 | CBL | 0.030 | 0.011 | 0.414 | |
| DNMT3A_0.1 | DNMT3A | 0.391 | 0.212 | 0.950 | |
| IDH1_0.1 | IDH1 | 0.023 | 0.001 | 1.156 | |
| IDH2_0.1 | IDH2 | 0.038 | 0.001 | 1.848 | |

6 rows

```
rownames(Fig3Data2) <- NULL
Fig3Data <- left_join(x = Fig3Data1, y = Fig3Data2, by = 'Parameter')
```

```
## Warning: Column `Parameter` joining factors with different levels, coercing to
character vector
```

```
Fig3Data$Parameter <- ifelse(Fig3Data$Parameter == "mu.Genes", "Av.gene", Fig3Data
$Parameter)
#View(Fig3Data)
write_csv(Fig3Data, "./figures/Figure3_Data.csv")
```

## 7.4.5 Dichotomous variables

```
allXDich <- allX
allXDich[allGroups=="Genes"] <- (allXDich[allGroups=="Genes"] > 0) + 0
fitWeightedDich <- CoxRFX(allXDich, allSurv, allGroups, which.mu=which.mu, sigma0=
sigma0, nu=nu, weights=weights)

WaldTest(fitWeightedDich)
```

```
##                   group    coef coef-mu     sd       z df  p.value sig
## ASXL1_0.1         Genes  1.3797 -0.3942 0.3175  4.3456  1 1.39e-05 ***
## BCOR_0.1          Genes  2.5308  0.7570 0.8406  3.0106  1 2.61e-03  **
## CBL_0.1           Genes  0.3932 -1.3806 0.4991  0.7879  1 4.31e-01
## DNMT3A_0.1        Genes  0.7794 -0.9944 0.2049  3.8048  1 1.42e-04 ***
## IDH1_0.1          Genes  2.0403  0.2665 0.5817  3.5073  1 4.53e-04 ***
## IDH2_0.1          Genes  3.9907  2.2169 0.5363  7.4414  1 9.96e-14 ***
## JAK2_0.1          Genes  3.2315  1.4577 0.3911  8.2629  1 1.42e-16 ***
## KDM6A_0.1         Genes  0.7396 -1.0343 0.7822  0.9456  1 3.44e-01
## KMT2C_0.1         Genes -0.4630 -2.2368 0.5910 -0.7834  1 4.33e-01
## KMT2D_0.1         Genes  0.8142 -0.9597 0.9409  0.8653  1 3.87e-01
## KRAS_0.1          Genes -0.0209 -1.7948 0.7030 -0.0298  1 9.76e-01
## NF1_0.1           Genes -1.1385 -2.9124 0.8236 -1.3824  1 1.67e-01
## NRAS_0.1          Genes  1.6320 -0.1419 0.7812  2.0891  1 3.67e-02   *
## PHF6_0.1          Genes  4.0915  2.3176 0.7069  5.7883  1 7.11e-09 ***
## PTPN11_0.1        Genes  2.2597  0.4859 0.6548  3.4510  1 5.59e-04 ***
## RAD21_0.1         Genes  1.0923 -0.6816 0.9283  1.1767  1 2.39e-01
## RUNX1_0.1         Genes  2.6557  0.8818 0.5738  4.6284  1 3.69e-06 ***
## SF3B1_0.1         Genes  0.0815 -1.6924 0.6027  0.1352  1 8.92e-01
## SRSF2_0.1         Genes  4.2431  2.4693 0.3084 13.7566  1 4.65e-43 ***
## TET2_0.1          Genes  0.9715 -0.8023 0.2351  4.1328  1 3.58e-05 ***
## TP53_0.1          Genes  2.0033  0.2295 0.4168  4.8067  1 1.53e-06 ***
## U2AF1_0.1         Genes  5.7172  3.9433 0.4178 13.6831  1 1.28e-42 ***
## age_10     Demographics -0.3024 -0.3024 0.0958 -3.1571  1 1.59e-03  **
## gender     Demographics -0.0512 -0.0512 0.1362 -0.3759  1 7.07e-01
## cohort     Demographics  0.2569  0.2569 0.1435  1.7896  1 7.35e-02   .
```

```
survConcordance(allSurv ~ fitWeightedDich$linear.predictors, weights=weights)
```

```
## Call:
## survConcordance(formula = allSurv ~ fitWeightedDich$linear.predictors,
##     weights = weights)
##
##   n= 950
## Concordance= 0.764251 se= 0.02802535
##   concordant   discordant    tied.risk    tied.time     std(c-d)
## 6202805.3608 1913213.1798     492.5856       1.0000  454936.0734
```

## 7.4.6 Bootstrap adjustment

To compare to the weighted CoxRFX models

```
set.seed(42)

p <- c(rep(n_total_sanger, sum(cohort=="Sanger" & control)), rep(n_total_toronto,
sum(cohort=="Toronto" & control)))
b42 <- c(sample(which(control), size=round(n_total) - sum(!control), prob=p, repla
ce=TRUE), which(!control))

fitBoot <- CoxRFX(allX[b42,], allSurv[b42,], allGroups, which.mu=which.mu, sigma0=
sigma0, nu=nu)

set.seed(42)
b <- c(sample(which( sangerData$Diagnosis=="Control"), size=round(n_total_sanger)
- sum(sangerData$Diagnosis!="Control"), replace=TRUE), which(sangerData$Diagnosis!
="Control"))

fitBootSanger <- CoxRFX(sangerX[b,], sangerSurv[b,], sangerGroups, which.mu=which.
mu, sigma0=sigma0, nu=nu)

survConcordance(fitBootSanger$surv ~ fitBootSanger$linear.predictors)
```

```
## Call:
## survConcordance(formula = fitBootSanger$surv ~ fitBootSanger$linear.predictors)
##
```

```
##   n= 10407
## Concordance= 0.8334695 se= 0.05475909
## concordant discordant  tied.risk  tied.time   std(c-d)
##   140833.0    28139.0        0.0        0.0    18505.5
```

```
waldBootSanger <- WaldTest(fitBootSanger)
```

```
##                    group     coef  coef-mu      sd       z df  p.value sig
## ASXL1_0.1          Genes  2.75130  0.85036 0.44987  6.1157  1 9.61e-10 ***
## CBL_0.1            Genes  0.90179 -0.99914 1.17452  0.7678  1 4.43e-01
## DNMT3A_0.1         Genes  0.75840 -1.14254 0.22408  3.3845  1 7.13e-04 ***
## JAK2_0.1           Genes -0.20568 -2.10662 0.92220 -0.2230  1 8.24e-01
## KMT2C_0.1          Genes  2.16912  0.26819 0.96833  2.2401  1 2.51e-02   *
## KMT2D_0.1          Genes  0.06618 -1.83475 0.76576  0.0864  1 9.31e-01
## KRAS_0.1           Genes  2.31066  0.40972 0.38106  6.0638  1 1.33e-09 ***
## NF1_0.1            Genes  1.57512 -0.32581 0.77819  2.0241  1 4.30e-02   *
## NRAS_0.1           Genes  1.84937 -0.05157 0.35761  5.1715  1 2.32e-07 ***
## RAD21_0.1          Genes  1.70593 -0.19501 0.58727  2.9049  1 3.67e-03  **
## SF3B1_0.1          Genes  1.54550 -0.35544 0.87032  1.7758  1 7.58e-02   .
## SRSF2_0.1          Genes  1.40565 -0.49529 0.27962  5.0271  1 4.98e-07 ***
## TET2_0.1           Genes  1.25279 -0.64815 0.13571  9.2317  1 2.66e-20 ***
## TP53_0.1           Genes  4.63845  2.73751 0.89272  5.1959  1 2.04e-07 ***
## U2AF1_0.1          Genes  5.78946  3.88853 0.73724  7.8528  1 4.07e-15 ***
## age_10       Demographics  0.04278  0.04278 0.11873  0.3603  1 7.19e-01
## gender       Demographics -0.01852 -0.01852 0.10088 -0.1836  1 8.54e-01
## systol_100          Blood  0.02344  0.02344 0.04556  0.5145  1 6.07e-01
## diastol_100         Blood  0.04133  0.04133 0.03020  1.3686  1 1.71e-01
## bmi_10              Blood  0.14916  0.14916 0.08426  1.7702  1 7.67e-02   .
## cholestl_10         Blood  0.00303  0.00303 0.01547  0.1958  1 8.45e-01
## triglyc             Blood -0.02770 -0.02770 0.11803 -0.2347  1 8.14e-01
## hdl                 Blood -0.12117 -0.12117 0.08479 -1.4291  1 1.53e-01
## ldl                 Blood  0.13479  0.13479 0.11448  1.1775  1 2.39e-01
## lym                 Blood  0.08408  0.08408 0.10435  0.8057  1 4.20e-01
## mcv_100             Blood -0.02485 -0.02485 0.00798 -3.1160  1 1.83e-03  **
## rdw_10              Blood  0.06629  0.06629 0.01703  3.8934  1 9.88e-05 ***
## wbc_10              Blood  0.01199  0.01199 0.04735  0.2532  1 8.00e-01
## plt_100             Blood  0.09163  0.09163 0.10006  0.9158  1 3.60e-01
## hgb_10              Blood  0.03986  0.03986 0.02497  1.5960  1 1.10e-01
```

```
set.seed(42)
b <- c(sample(which( torontoData$Diagnosis=="Control"), size=round(n_total_toronto
) - sum(torontoData$Diagnosis!="Control"), replace=TRUE), which(torontoData$Diagno
sis!="Control"))

fitBootToronto <- CoxRFX(torontoX[b,], torontoSurv[b,], torontoGroups, which.mu=wh
ich.mu, sigma0=sigma0, nu=nu)
survConcordance(fitBootToronto$surv ~ fitBootToronto$linear.predictors)
```

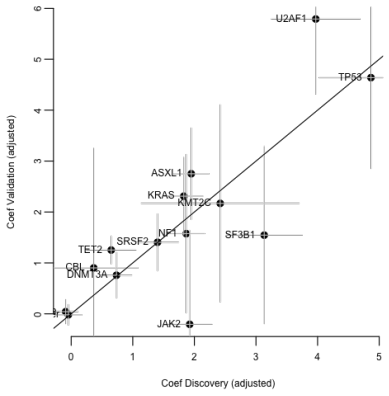
```
## Call:
## survConcordance(formula = fitBootToronto$surv ~ fitBootToronto$linear.predictor
s)
##
##   n= 72378
## Concordance= 0.7750173 se= 0.03055346
## concordant discordant  tied.risk  tied.time   std(c-d)
##  4722585.0  1370937.0        0.0        1.0   372356.4
```

```
waldWeightedToronto <- WaldTest(fitBootToronto)
```

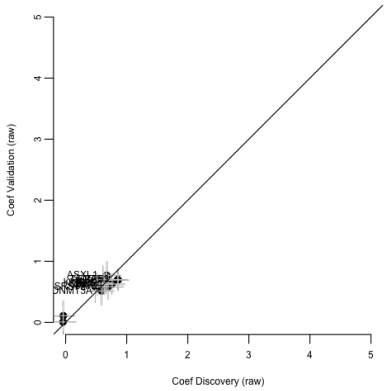
```
##                   group    coef  coef-mu     sd      z df  p.value sig
## ASXL1_0.1         Genes  1.9494  0.01801 0.1451 13.430  1 4.03e-41 ***
## CALR_0.1          Genes  0.9415 -0.98990 0.7233  1.302  1 1.93e-01
## CBL_0.1           Genes  0.3663 -1.56509 0.3604  1.016  1 3.09e-01
## DNMT3A_0.1        Genes  0.7358 -1.19559 0.1243  5.921  1 3.20e-09 ***
## IDH1_0.1          Genes  2.3973  0.46594 0.3355  7.145  1 8.98e-13 ***
## IDH2_0.1          Genes  0.8078 -1.12360 0.2283  3.538  1 4.03e-04 ***
## JAK2_0.1          Genes  1.9240 -0.00738 0.1822 10.562  1 4.49e-26 ***
## KDM6A_0.1         Genes  1.9436  0.01219 0.1340 14.506  1 1.12e-47 ***
## KMT2C_0.1         Genes  2.4194  0.48806 0.6410  3.774  1 1.60e-04 ***
## KRAS_0.1          Genes  1.8282 -0.10316 0.1559 11.725  1 9.46e-32 ***
## NF1_0.1           Genes  1.8677 -0.06366 0.1512 12.353  1 4.69e-35 ***
## PHF6_0.1          Genes  2.1755  0.24415 0.1302 16.711  1 1.08e-62 ***
## PTPN11_0.1        Genes  2.5369  0.60555 0.2217 11.445  1 2.49e-30 ***
## RUNX1_0.1         Genes  0.7795 -1.15181 0.1359  5.738  1 9.57e-09 ***
## SF3B1_0.1         Genes  3.1337  1.20231 0.3091 10.138  1 3.76e-24 ***
## SRSF2_0.1         Genes  1.4023 -0.52910 0.1703  8.235  1 1.80e-16 ***
## TET2_0.1          Genes  0.6503 -1.28104 0.2012  3.232  1 1.23e-03  **
## TP53_0.1          Genes  4.8664  2.93502 0.4220 11.532  1 9.14e-31 ***
## U2AF1_0.1         Genes  3.9705  2.03910 0.3601 11.025  1 2.89e-28 ***
## age_10     Demographics -0.0891 -0.08907 0.0998 -0.892  1 3.72e-01
## gender     Demographics -0.0449 -0.04493 0.1114 -0.403  1 6.87e-01
```

Compare results

```
i <- intersect(rownames(waldBootSanger), rownames(waldWeightedToronto))
plot( waldWeightedToronto[i,"coef"], waldBootSanger[i, "coef"], xlab="Coef Discove
ry (adjusted)", ylab="Coef Validation (adjusted)", pch=19, cex=1)#sqrt(colMeans(rb
ind(sangerX[,i], torontoX[,i])>0)*100))
segments(waldWeightedToronto[i,"coef"]  - 2*waldWeightedToronto[i,"sd"], waldBootS
anger[i, "coef"], waldWeightedToronto[i,"coef"]  + 2*waldWeightedToronto[i,"sd"],
waldBootSanger[i, "coef"], col="grey" )
segments(waldWeightedToronto[i,"coef"]  , waldBootSanger[i, "coef"]-  2*waldBootSa
nger[i,"sd"], waldWeightedToronto[i,"coef"] , waldBootSanger[i, "coef"] +2*waldBoo
tSanger[i,"sd"], col="grey")
text(labels=sub("_.+","", i), waldWeightedToronto[i,"coef"], waldBootSanger[i, "co
ef"], pos=2, adj=c(0,1))
abline(0,1)
```




```
plot( waldToronto[i,"coef"], waldSanger[i, "coef"], xlab="Coef Discovery (raw)", y
lab="Coef Validation (raw)", pch=19, cex=1, ylim=c(0,5),xlim=c(0,5))#sqrt(colMeans
(rbind(sangerX[,i], torontoX[,i])>0)*100))
segments(waldToronto[i,"coef"]  - 2*waldToronto[i,"sd"], waldSanger[i, "coef"], wa
ldToronto[i,"coef"]  + 2*waldToronto[i,"sd"], waldSanger[i, "coef"], col="grey" )
segments(waldToronto[i,"coef"]  , waldSanger[i, "coef"]-  2*waldSanger[i,"sd"], wa
ldToronto[i,"coef"] , waldSanger[i, "coef"] +2*waldSanger[i,"sd"], col="grey")
text(labels=sub("_.+","", i), waldToronto[i,"coef"], waldSanger[i, "coef"], pos=2,
adj=c(0,1))
abline(0,1)
```




## 7.4.7 LOOCV

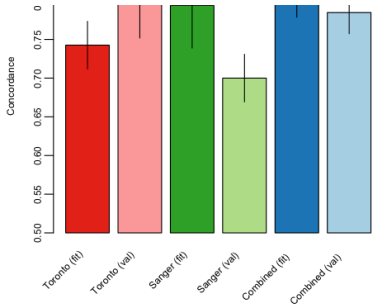
```
samples <- factor(c(as.character(sangerData$Individual), as.character(torontoData$
Sample)))
```

```
looAll <- do.call("rbind",mclapply(levels(samples), function(l){
                    i <- samples!=l
                    f <<- CoxRFX(allX[i,], allSurv[i,], allGroups, which.mu=which.
mu, sigma0=sigma0, nu=nu)
                    p <- as.matrix(allX[!i,,drop=FALSE]) %*% f$coefficients
                    r <- cbind(matrix(f$coefficients, nrow=length(p), ncol=length(
f$coefficients), byrow=TRUE), linear.predictor=p)
                    colnames(r) <- c(names(f$coefficients), "linear.predictor")
                    as.data.frame(r)
                }, mc.cores=4))
looAll <- looAll[order(order(samples)),]
pp <- looAll$linear.predictor

c <- rbind(
        `Toronto (fit)`=as.data.frame(survConcordance(torontoSurv ~ fitToronto$lin
ear.predictors)[c("concordance","std.err")]),
        `Toronto (val)`=as.data.frame(survConcordance(sangerSurv ~ pS[,1])[c("conc
ordance","std.err")]),
        `Sanger (fit)`=as.data.frame(survConcordance(sangerSurv ~ fitSanger$linear
.predictors)[c("concordance","std.err")]),
        `Sanger (val)`=as.data.frame(survConcordance(torontoSurv ~ pT[,1])[c("conc
ordance","std.err")]),
        `Combined (fit)`=as.data.frame(survConcordance(allSurv ~ fitAll$linear.pre
dictors)[c("concordance","std.err")]),
        `Combined (val)`=as.data.frame(survConcordance(allSurv ~ pp)[c("concordanc
e","std.err")]))

c
```

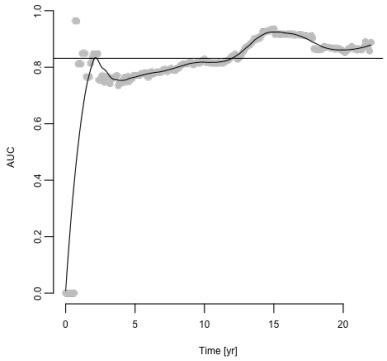
| | concordance<br><dbl> | std.err<br><dbl> |
|---|---|---|
| Toronto (fit) | 0.7426378 | 0.03079247 |
| Toronto (val) | 0.8069747 | 0.05514445 |
| Sanger (fit) | 0.7939150 | 0.05514512 |
| Sanger (val) | 0.7000180 | 0.03079247 |
| Combined (fit) | 0.8059859 | 0.02746324 |
| Combined (val) | 0.7847548 | 0.02746328 |

6 rows

```
par(mar=c(5,3,1,1), mgp=c(2,.5,0))
b <- barplot(c$concordance-0.5, ylab="Concordance", col=rev(RColorBrewer::brewer.p
al(6,"Paired")), ylim=c(0.5,0.88), offset=0.5)
mg14::rotatedLabel(x=b, labels=rownames(c))
segments(b,c$concordance+c$std.err,b,c$concordance-c$std.err)
```



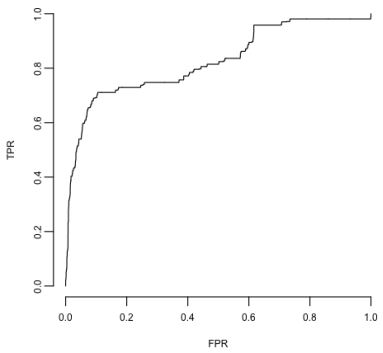

```
w <- c(which(allSurv[,1]==0)[-1]-1, nrow(allSurv))
survAll2 <- Surv(allSurv[w,2], allSurv[w,3])
t <- seq(0,22,0.1)
a <- AUC.uno(survAll2, survAll2, looAll$linear.predictor[w], times=t)
plot(a$times, a$auc, xlab="Time [yr]", ylab="AUC", pch=16, col='grey')
lines(a$times, predict(loess(a$auc ~ a$times, span=0.25)))
abline(h=a$iauc)
```




```
round(a$iauc, 3)
```

```
## [1] 0.832
```

```
r <- survivalROC(Stime = survAll2[,1], status=survAll2[,2], marker=looAll$linear.p
redictor[w], predict.time = 10, method="NNE", span=0.001)#0.25*nrow(s)^(-0.20))
plot(r$FP, r$TP, type='s', xlab="FPR", ylab="TPR")
```

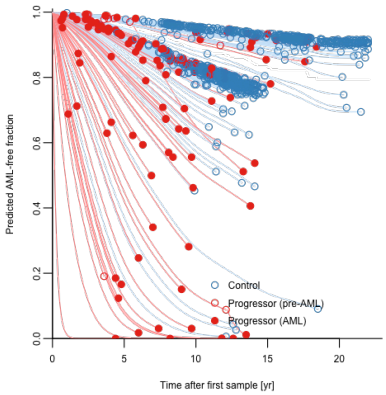



```
round(r$AUC, 3)
```

```
## [1] 0.825
```

#### 7.4.7.1 Individual Predictions (non-adjusted)

```
plot(survfit(allSurv~1), conf.int=FALSE, xlab='Time after first sample [yr]', ylab
='Predicted AML-free fraction', col='white', bty='L', yaxs='i', ylim=c(0,1.01))
d <- data.frame(t=NULL, s=NULL, pch=NULL, col=character())
for(i in unique(samples)){
    km <- exp(predict(smooth.spline(log(summary(survfit(allSurv[samples!=i,]~1), t
imes=t)$surv), df=10))$y)
    l0 <- colMeans(fitAll$Z[samples!=i,,drop=FALSE]) %*% as.numeric(looAll[samples
==i,][1,colnames(fitAll$Z)])
    kmi <- function(km, s, lp, l0){
        .kmi <- function(km, sj, lpj, l0) km[t >= sj[,1] & t <= sj[,2]]^exp(lpj-l0
)
        k0 <- 1
        for(j in 1:nrow(s)) {
            k <- .kmi(km, s[j,], lp[j], l0)
            k <- k * k0/k[1]
            w <- t >= s[j,1] & t <= s[j,2]
            k0 <- k[length(k)]
            c <- if(s[nrow(s),3]==1) set1[1] else set1[2]
            #if(c==set1[1]) next
            lines(t[w], k, col=mg14:::colTrans(c), type='l')
            p <- if(s[j,3]==1) 19 else 1
            #points(t[w][length(k)], k[length(k)], col=c, pch=p)
            d <<- rbind(d, data.frame(t=t[w][length(k)], s=k[length(k)], pch=p, co
l=c))
        }
    }
    kmi(km, allSurv[samples==i,], looAll$linear.predictor[samples==i], l0)
}
points(d$t, d$s, pch=d$pch, col=as.character(d$col))
legend("bottomright", pch=c(1,1,19), col=c(set1[2], set1[1], set1[1]), legend=c("C
ontrol", "Progressor (pre-AML)", "Progressor (AML)"), bty='n')
```




### 7.4.7.2 Jackknife variance

```
i <- !duplicated(samples)
coef.jack <- colMeans(looAll[i,-ncol(looAll)])
var.jack <- rowSums((t(looAll[i,-ncol(looAll)]) - coef.jack)^2) * (sum(i)-1)/sum(i
)

p.jack <- pchisq(coef.jack^2/var.jack,1, lower.tail=FALSE)
```

```
data.frame(coef.jack, p.jack, sig=mg14::sig2star(p.jack), n=colSums(allX[i,]>0))
```

| | coef.jack | p.jack | sig | n |
|---|---|---|---|---|
| | <dbl> | <dbl> | <fctr> | <dbl> |
| ASXL1_0.1 | 0.74835623 | 1.277998e-05 | *** | 26 |
| BCOR_0.1 | 0.80859507 | 2.311062e-04 | *** | 1 |
| CBL_0.1 | 0.47795378 | 3.123703e-01 | | 12 |
| DNMT3A_0.1 | 0.55685260 | 7.358773e-06 | *** | 194 |
| IDH1_0.1 | 0.81211760 | 5.586147e-10 | *** | 3 |
| IDH2_0.1 | 0.51251777 | 1.351015e-01 | | 6 |
| JAK2_0.1 | 0.75979214 | 3.181470e-08 | *** | 10 |
| KDM6A_0.1 | 0.79059980 | 7.666406e-05 | *** | 3 |
| KMT2C_0.1 | 0.85878619 | 5.304616e-04 | *** | 6 |
| KMT2D_0.1 | 0.40005469 | 3.584861e-01 | | 1 |

1-10 of 25 rows Previous **1** 2 3 Next

## 7.4.8 Multiple bootstraps

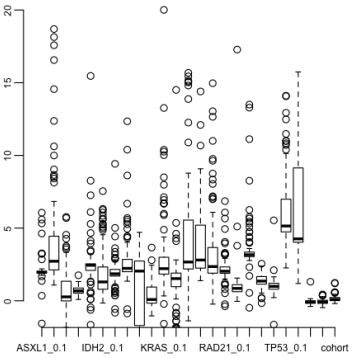
```
save(file="boot.RData", control, allX, allSurv, sigma0, nu, which.mu, allGroups, n
_total, cohort, p)
```

```
fitBoots <- simplify2array(mclapply(1:100, function(foo){
                    set.seed(foo)
                    w <- which(control)
                    s <- sample(seq_along(which(control)), replace=TRUE)
                    b <- c(sample(which(control)[s], size=round(n_total) - sum(!co
ntrol), prob=p[s], replace=TRUE), sample(which(!control), replace=TRUE))
                    fitBoot <- CoxRFX(allX[b,], allSurv[b,], allGroups, which.mu=w
hich.mu, sigma0=sigma0, nu=nu)
                    fitBoot$coefficients
                }, mc.cores=4))
save(fitBoots, file="fitBoots.RData")
```

```
load('fitBoots.RData')

WaldTest(fitBoot)
```

```
##                   group    coef coef-mu     sd      z df  p.value sig
## ASXL1_0.1         Genes  1.9782  0.0682 0.1330 14.873  1 4.90e-50 ***
## BCOR_0.1          Genes  2.1204  0.2104 0.1157 18.319  1 5.81e-75 ***
## CBL_0.1           Genes  0.3747 -1.5352 0.3614  1.037  1 3.00e-01
## DNMT3A_0.1        Genes  0.6499 -1.2600 0.1133  5.735  1 9.77e-09 ***
## IDH1_0.1          Genes  2.4215  0.5116 0.3299  7.341  1 2.12e-13 ***
## IDH2_0.1          Genes  0.8614 -1.0486 0.2191  3.931  1 8.47e-05 ***
## JAK2_0.1          Genes  1.8708 -0.0391 0.1956  9.562  1 1.15e-21 ***
## KDM6A_0.1         Genes  1.9211  0.0112 0.1251 15.363  1 2.92e-53 ***
## KMT2C_0.1         Genes  2.3935  0.4836 0.7067  3.387  1 7.07e-04 ***
## KMT2D_0.1         Genes  0.1309 -1.7790 0.4810  0.272  1 7.86e-01
## KRAS_0.1          Genes  1.9602  0.0503 0.1717 11.415  1 3.53e-30 ***
## NF1_0.1           Genes  1.5704 -0.3396 0.4386  3.580  1 3.43e-04 ***
## NRAS_0.1          Genes  2.3060  0.3960 0.1213 19.014  1 1.31e-80 ***
## PHF6_0.1          Genes  2.2127  0.3028 0.1241 17.835  1 3.80e-71 ***
## PTPN11_0.1        Genes  2.1333  0.2233 0.3110  6.860  1 6.86e-12 ***
## RAD21_0.1         Genes  1.8285 -0.0815 0.2524  7.244  1 4.36e-13 ***
## RUNX1_0.1         Genes  0.8075 -1.1025 0.1325  6.095  1 1.10e-09 ***
## SF3B1_0.1         Genes  3.0963  1.1863 0.3107  9.967  1 2.13e-23 ***
## SRSF2_0.1         Genes  1.3408 -0.5692 0.1503  8.923  1 4.55e-19 ***
## TET2_0.1          Genes  0.9202 -0.9897 0.1179  7.807  1 5.85e-15 ***
## TP53_0.1          Genes  5.0203  3.1104 0.3921 12.803  1 1.57e-37 ***
## U2AF1_0.1         Genes  4.0999  2.1900 0.3306 12.402  1 2.54e-35 ***
## age_10     Demographics -0.0761 -0.0761 0.0912 -0.835  1 4.04e-01
## gender     Demographics -0.0530 -0.0530 0.1157 -0.458  1 6.47e-01
## cohort     Demographics  0.1992  0.1992 0.1103  1.806  1 7.09e-02   .
```

```
boxplot(t(fitBoots), ylim=c(-1,20))
points(fitBoot$coefficiencts, pch="*", col='red')
```



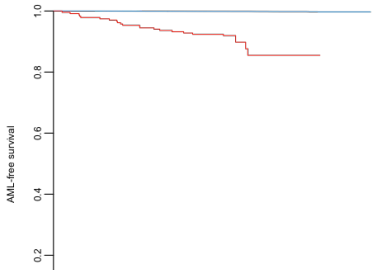

Concordance on out of bag samples

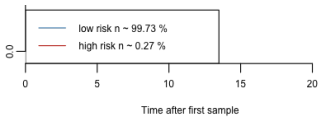
```
concBoots <- sapply(1:100, function(foo){
            set.seed(foo)
            w <- which(control)
            s <- sample(seq_along(which(control)), replace=TRUE)
            b <- c(sample(which(control)[s], size=round(n_total) - sum(!control),
prob=p[s], replace=TRUE), sample(which(!control), replace=TRUE))
            oob <- !1:nrow(allX) %in% b
            oos <- c(sample(which(oob & control), size=round(n_total) - sum(!contr
ol), replace=TRUE), sample(which(oob&!control), size=sum(!control), replace=TRUE))
            c(inb=as.numeric(survConcordance(allSurv[b,]~ as.matrix(allX)[b,] %*%
fitBoots[,foo])$concordance),
                    oob=as.numeric(survConcordance(allSurv[oob,]~ as.matrix(allX)[
oob,] %*% fitBoots[,foo])$concordance),
                    oos=as.numeric(survConcordance(allSurv[oos,]~ as.matrix(allX)[
oos,] %*% fitBoots[,foo])$concordance)
            )
        })
```

```
looAllWeighted <- do.call("rbind",mclapply(levels(samples), function(l){
                    i <- samples!=l
                    f <<- CoxRFX(allX[i,], allSurv[i,], allGroups, which.mu=which.
mu, sigma0=sigma0, nu=nu, weights=weights[i])
                    p <- as.matrix(allX[!i,,drop=FALSE]) %*% f$coefficients
                    r <- cbind(matrix(f$coefficients, nrow=length(p), ncol=length(
f$coefficients), byrow=TRUE), linear.predictor=p)
                    colnames(r) <- c(names(f$coefficients), "linear.predictor")
                    as.data.frame(r)
                }, mc.cores=4))
looAllWeighted <- looAllWeighted[order(order(samples)),]
pp <- looAllWeighted$linear.predictor
survConcordance(allSurv ~ pp, weights=weights)
```

```
## Call:
## survConcordance(formula = allSurv ~ pp, weights = weights)
##
##   n= 950
## Concordance= 0.7561883 se= 0.02802535
## concordant discordant  tied.risk  tied.time   std(c-d)
##  6137610.4  1978900.7        0.0        1.0   454936.2
```

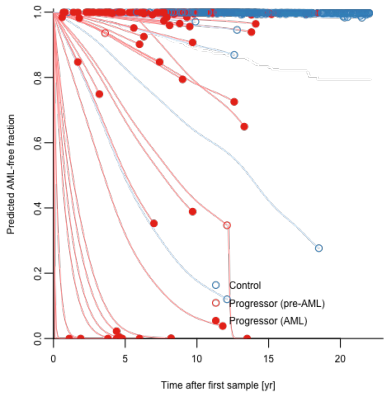
```
h <- exp(looAllWeighted$linear.predictor) > 100
plot(survfit(allSurv ~ h, weights=weights), col=set1[2:1], ylab="AML-free survival
", xlab="Time after first sample")
f <- sum(h*weights)/sum(weights) *100
legend("bottomleft", lty=1, col=set1[2:1], paste(c("low risk", "high risk"), "n ~"
, round(c( 100-f,f), 2),"%"))
```






## 7.4.9 Individual Predictions with corrected baseline

```
plot(survfit(allSurv~1), conf.int=FALSE, xlab='Time after first sample [yr]', ylab
='Predicted AML-free fraction', col='white', bty='L', yaxs='i', ylim=c(0,1.01))
d <- data.frame(t=NULL, s=NULL, pch=NULL, col=character())
for(i in unique(samples)){
    km <- exp(predict(smooth.spline(log(summary(survfit(allSurv[samples!=i,]~1, we
ights=weights[samples!=i]), times=t)$surv), df=10))$y)
    l0 <- colSums(fitAll$Z[samples!=i,,drop=FALSE] * weights[samples!=i]) %*% as.n
umeric(looAllWeighted[samples==i,][1,colnames(fitAll$Z)]) / sum(weights[samples!=i
])
    kmi <- function(km, s, lp, l0){
        .kmi <- function(km, sj, lpj, l0) km[t >= sj[,1] & t <= sj[,2]]^exp(lpj-l0
)
        k0 <- 1
        for(j in 1:nrow(s)) {
            k <- .kmi(km, s[j,], lp[j], l0)
            k <- k * k0/k[1]
            w <- t >= s[j,1] & t <= s[j,2]
            k0 <- k[length(k)]
            c <- if(s[nrow(s),3]==1) set1[1] else set1[2]
            lines(t[w], k, col=mg14:::colTrans(c), type='l')
            p <- if(s[j,3]==1) 19 else 1
            d <<- rbind(d, data.frame(t=t[w][length(k)], s=k[length(k)], pch=p, co
l=c))
        }
    }
    kmi(km, allSurv[samples==i,], looAllWeighted$linear.predictor[samples==i], l0)
}
points(d$t, d$s, pch=d$pch, col=as.character(d$col))
legend("bottomright", pch=c(1,1,19), col=c(set1[2], set1[1], set1[1]), legend=c("C
ontrol", "Progressor (pre-AML)", "Progressor (AML)"), bty='n')
```

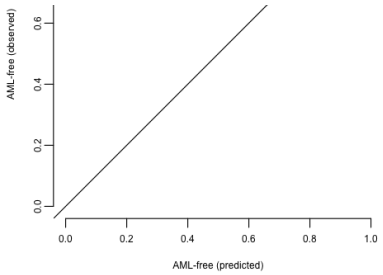



Callibration

```
p10 <- km[t==10]^exp(looAllWeighted$linear.predictor)
c <- cut(p10, c(0,0.4,0.95,0.99,1))
table(c)
```

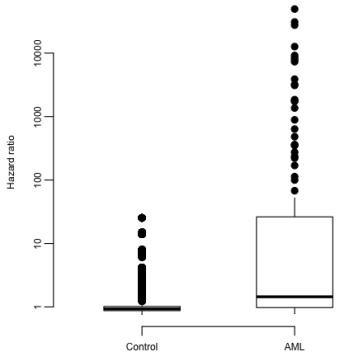
```
## c
##     (0,0.4]  (0.4,0.95] (0.95,0.99]    (0.99,1]
##          11          16          12         908
```

```
s <- summary(survfit(allSurv~c, weights=weights), times=10)
m <- sapply(split(p10,c), mean)
plot(m, s$surv, xlab="AML-free (predicted)", ylab="AML-free (observed)", xlim=c(0,
1), ylim=c(0,1))
segments(m,s$lower,m,s$upper)
abline(0,1)
```




Hazard

```
boxplot(exp(fitBoot$linear.predictors) ~ factor(1-control[b42], labels=c("Control"
,"AML")), log='y', ylab="Hazard ratio", pch=19, staplewex=0, lty=1, boxwex=0.5)
```




## 7.4.10 Some simulations

```
bX <- sapply(1:50, function(foo){
            set.seed(foo)
            X <- rbind(apply(allX[control,], 2, sample, n_total-sum(!control), rep
lace=TRUE), apply(allX[!control,], 2, sample) )
            lambda0 <- 5e-4
            r <- X%*%coef(fitBoot)
            t <- rexp(n_total, lambda0 * exp(r))
            tmax <- 13 + runif(n_total, 0,1)
            s <- Surv(pmin(t,tmax), t < tmax)
            cases <- which(s[,2]==1)
            controls1 <- sample(which(s[,2]==0), size=1*length(cases))
            controls4 <- sample(which(s[,2]==0), size=sum(control))
            cbind(controls_inc=colMeans(X[controls4,allGroups=="Genes"]>0), AML_in
c=colMeans(X[cases,allGroups=="Genes"]>0), controls_vaf=apply(X[controls4,allGroup
s=="Genes"], 2, function(x) mean(x[x>0])),AML_vaf=apply(X[cases,allGroups=="Genes"
], 2, function(x) mean(x[x>0])))
        }, simplify='array')
```

Expected vs observed driver frequency

```
graphics.off()
png("./figures/driver.freq.simulation.png", width = 15, height = 14, units = "cm",
res = 500)
par(mar = c(5, 4, 1.5, 0.5) + 0.1, mgp=c(2,0.4,0), las=1, tcl=-0.2, cex = 1)
plot(-rowMeans(bX[,'controls_inc',]), type='h', lend = 2, ylim=c(-.5,1)/2.5, lwd=8
, xaxt='n', yaxt = 'n',  ylab="Driver frequency (%)", xlab="", col=pal1[2])
atx <- axTicks(2)
axis(2,at=atx,labels= c(20, 10, 0, 10, 20, 30, 40))
points(x=1:22+.5,-colMeans(allX[control,allGroups=="Genes"]>0), type='h', lend = 2
, lwd=8, col=pal1[1])
points(rowMeans(bX[,"AML_inc",]), type='h', lend = 2, lwd=8, col=pal1[2])
points(x=1:22+.5,colMeans(allX[!control,allGroups=="Genes"]>0), type='h', lend = 2
, lwd=8, col=pal1[1])
mtext(side=1, at=1:22,sub("_.+","",colnames(allX)[allGroups=="Genes"]), las=2, fon
t=3, line=0.7)
```

```
mtext(text = "Pre-AML", side=3, at = 12, las=1, font=1, line=-1.5, cex = 1.1)
mtext(text = "Controls", side=1, at = 12, las=1, font=1, line=-1.5, cex = 1.1)
legend("bottomright", fill=pal1[2:1], c("Expected","Observed"), cex = 0.8)
abline(h=0)
dev.off()
```

```
## null device
##           1
```

Expected vs observed driver VAF

```
avgVaf <- function(x) mean(x[x>0])

png("./figures/driver.vaf.simulation.png", width = 15, height = 14, units = "cm",
res = 500)
par(mar = c(5, 4, 1.5, 0.5) + 0.1, mgp=c(2,0.4,0), las=1, tcl=-0.2, cex=1)
plot(-apply(bX[,'controls_vaf',],1,avgVaf)*10, type='h', lend = 2, ylim=c(-40,50),
lwd=8, xaxt='n', yaxt = 'n', ylab="Driver VAF (%)", xlab="", col=pal1[2])
atx <- axTicks(2)
axis(2,at=atx,labels= c(40, 20,0, 20, 40))
points(x=1:22+.5,-apply(allX[control,allGroups=="Genes"],2,avgVaf)*10, type='h', l
end = 2, lwd=8, col=pal1[1])
points(apply(bX[,"AML_vaf",],1,avgVaf)*10, type='h', lend = 2, lwd=8, col=pal1[2])
points(x=1:22+.5,apply(allX[!control,allGroups=="Genes"],2,avgVaf)*10, type='h', l
end = 2, lwd=8, col=pal1[1])
mtext(side=1, at=1:22,sub("_.+","",colnames(allX)[allGroups=="Genes"]), las=2, fon
t=3, line = 0.7)
mtext(text = "Pre-AML", side=3, at = 12, las=1, font=1, line=-1.5, cex = 1.1)
mtext(text = "Controls", side=1, at = 12, las=1, font=1, line=-1.5, cex = 1.1)
legend("bottomright", fill=pal1[2:1], c("Expected","Observed"), cex = 0.8)
abline(h=0)
dev.off()
```

```
## pdf
##   2
```

## 7.4.11 Simple models

```
samples <- factor(c(as.character(sangerData$Individual), as.character(torontoData$
Sample)))
```

max vaf:

```
v <- apply(allX[,allGroups=="Genes"], 1, max)*10
```

cumulative vaf

```
c <- apply(allX[,allGroups=="Genes"], 1, sum)*10
```

number of mutations

```
m <- rowSums(allX[,allGroups=="Genes"]>0)
```

any mutation

```
a <- as.integer(m>0)
```

### 7.4.11.1 Presence of any mutation

```
d <- data.frame(a)
summary(f <- coxph(allSurv ~ ., data=d ))
```

```
## Call:
## coxph(formula = allSurv ~ ., data = d)
##
##   n= 950, number of events= 120
##
##     coef exp(coef) se(coef)     z Pr(>|z|)
## a 1.5144    4.5468   0.2046 7.402 1.35e-13 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##   exp(coef) exp(-coef) lower .95 upper .95
## a     4.547     0.2199     3.045      6.79
##
## Concordance= 0.672  (se = 0.023 )
## Rsquare= 0.064   (max possible= 0.801 )
## Likelihood ratio test= 63.31  on 1 df   p=2e-15
```

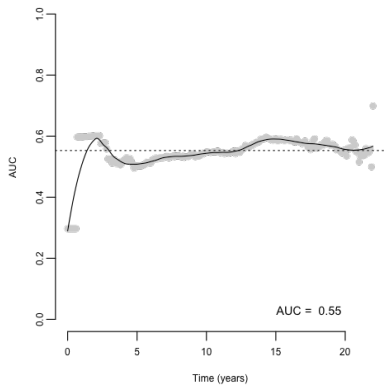
```
## Likelihood ratio test= 65.91  on 1 df,   p=2e-15
## Wald test            = 54.78  on 1 df,   p=1e-13
## Score (logrank) test = 66.02  on 1 df,   p=4e-16
```

```
los <- do.call("rbind",mclapply(levels(samples), function(l){
  i <- samples!=l
  f <<- coxph(allSurv ~ ., data=d, subset=i)
  p <- as.matrix(d[!i,]) %*% f$coefficients
  r <- cbind(matrix(f$coefficients, nrow=length(p), ncol=length(f$coefficients), b
yrow=TRUE), linear.predictor=p)
  colnames(r) <- c(names(f$coefficients), "linear.predictor")
  as.data.frame(r)
}, mc.cores=4))
psAnyMt <- los[order(order(samples)),]

survConcordance(allSurv ~ psAnyMt$linear.predictor)
```

```
## Call:
## survConcordance(formula = allSurv ~ psAnyMt$linear.predictor)
##
##   n= 950
## Concordance= 0.5431925 se= 0.02388586
## concordant discordant  tied.risk  tied.time   std(c-d)
##  34829.000  28205.000  13646.000      1.000   3663.136
```

Dynamic/cumulative AUC

```
w <- c(which(allSurv[,1]==0)[-1]-1, nrow(allSurv))
survAll2 <- Surv(allSurv[w,2], allSurv[w,3])
t <- seq(0,22,0.1)
allX2 <- allX[w, ]

auc.uno <- AUC.uno(survAll2, survAll2, psAnyMt$linear.predictor[w], times=t)

plot(auc.uno$times, auc.uno$auc, xlab="Time (years)", ylab="AUC", pch=16, col="gre
y80", ylim = c(0,1.0))
lines(auc.uno$times, predict(loess(auc.uno$auc ~ auc.uno$times, span=0.25)))
abline(h=auc.uno$iauc, lty = 3, lwd = 1)
legend("bottomright", bty = "n", cex = 1.2, legend = paste("AUC = ",round(auc.uno$
iauc,2)))
```




```
AnyMt.a <- auc.uno
```

Presence of any mutation + vaf

Presence of any mutation + vaf

```
d <- data.frame(a,v)
summary(f <- coxph(allSurv ~ ., data=d ))
```

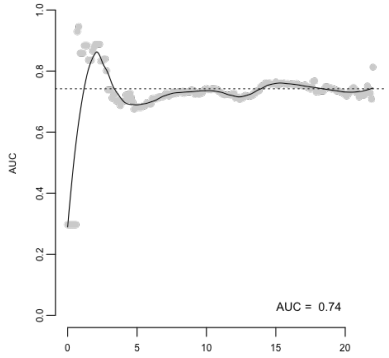
```
## Call:
## coxph(formula = allSurv ~ ., data = d)
##
##   n= 950, number of events= 120
##
##       coef exp(coef) se(coef)     z Pr(>|z|)
## a 1.025548  2.788622 0.223677 4.585 4.54e-06 ***
## v 0.050613  1.051915 0.005605 9.030  < 2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##   exp(coef) exp(-coef) lower .95 upper .95
## a     2.789     0.3586     1.799     4.323
## v     1.052     0.9506     1.040     1.064
##
## Concordance= 0.737  (se = 0.024 )
## Rsquare= 0.119   (max possible= 0.801 )
## Likelihood ratio test= 120.5  on 2 df,   p=<2e-16
## Wald test            = 161.8  on 2 df,   p=<2e-16
## Score (logrank) test = 263.9  on 2 df,   p=<2e-16
```

```
los <- do.call("rbind",mclapply(levels(samples), function(l){
  i <- samples!=l
  f <<- coxph(allSurv ~ ., data=d, subset=i)
  p <- as.matrix(d[!i,]) %*% f$coefficients
  r <- cbind(matrix(f$coefficients, nrow=length(p), ncol=length(f$coefficients), b
yrow=TRUE), linear.predictor=p)
  colnames(r) <- c(names(f$coefficients), "linear.predictor")
  as.data.frame(r)
}, mc.cores=4))
psAnyMtVaf <- los[order(order(samples)),]

survConcordance(allSurv ~ psAnyMtVaf$linear.predictor)
```

```
## Call:
## survConcordance(formula = allSurv ~ psAnyMtVaf$linear.predictor)
##
##   n= 950
## Concordance= 0.7287559 se= 0.0238873
## concordant discordant  tied.risk  tied.time   std(c-d)
##  49091.000  14009.000  13580.000      1.000   3663.356
```

Dynamic/cumulative AUC

```
auc.uno <- AUC.uno(survAll2, survAll2, psAnyMtVaf$linear.predictor[w], times=t)

plot(auc.uno$times, auc.uno$auc, xlab="Time (years)", ylab="AUC", pch=16, col="gre
y80", ylim = c(0,1.0))
lines(auc.uno$times, predict(loess(auc.uno$auc ~ auc.uno$times, span=0.25)))
abline(h=auc.uno$iauc, lty = 3, lwd = 1)
legend("bottomright", bty = "n", cex = 1.2, legend = paste("AUC = ",round(auc.uno$
iauc,2)))
```



Time (years)

```
AnyMtVaf.a <- auc.uno
```

### 7.4.11.2 Number of mutations + vaf

```
d <- data.frame(m,v)
summary(f <- coxph(allSurv ~ ., data=d ))
```

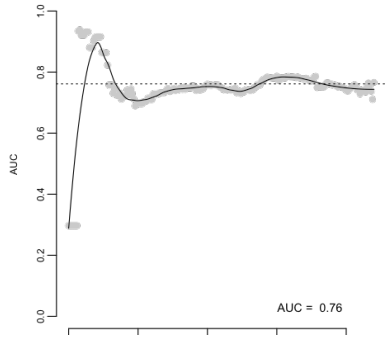
```
## Call:
## coxph(formula = allSurv ~ ., data = d)
##
##   n= 950, number of events= 120
##
##       coef exp(coef) se(coef)     z Pr(>|z|)
## m 0.653487  1.922231 0.088287 7.402 1.34e-13 ***
## v 0.040976  1.041827 0.006562 6.245 4.25e-10 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##   exp(coef) exp(-coef) lower .95 upper .95
## m     1.922     0.5202     1.617     2.285
## v     1.042     0.9599     1.029     1.055
##
## Concordance= 0.744  (se = 0.024 )
## Rsquare= 0.142   (max possible= 0.801 )
## Likelihood ratio test= 145.3  on 2 df,   p=<2e-16
## Wald test            = 213.3  on 2 df,   p=<2e-16
## Score (logrank) test = 302.9  on 2 df,   p=<2e-16
```

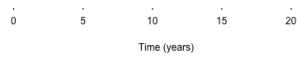
```
los <- do.call("rbind",mclapply(levels(samples), function(l){
  i <- samples!=l
  f <<- coxph(allSurv ~ ., data=d, subset=i)
  p <- as.matrix(d[!i,]) %*% f$coefficients
  r <- cbind(matrix(f$coefficients, nrow=length(p), ncol=length(f$coefficients), b
yrow=TRUE), linear.predictor=p)
  colnames(r) <- c(names(f$coefficients), "linear.predictor")
  as.data.frame(r)
}, mc.cores=4))
psNMtVaf <- los[order(order(samples)),]

survConcordance(allSurv ~ psNMtVaf$linear.predictor)
```

```
## Call:
## survConcordance(formula = allSurv ~ psNMtVaf$linear.predictor)
##
##   n= 950
## Concordance= 0.7431403 se= 0.0238873
## concordant discordant  tied.risk  tied.time   std(c-d)
##  50194.000  12906.000  13580.000      1.000   3663.356
```

Dynamic/cumulative AUC

```
auc.uno <- AUC.uno(survAll2, survAll2, psNMtVaf$linear.predictor[w], times=t)

plot(auc.uno$times, auc.uno$auc, xlab="Time (years)", ylab="AUC", pch=16, col="gre
y80", ylim = c(0,1.0))
lines(auc.uno$times, predict(loess(auc.uno$auc ~ auc.uno$times, span=0.25)))
abline(h=auc.uno$iauc, lty = 3, lwd = 1)
legend("bottomright", bty = "n", cex = 1.2, legend = paste("AUC = ",round(auc.uno$
iauc,2)))
```






```
NMtVaf.a <- auc.uno
```

### 7.4.11.3 Number of mutations + cumulative vaf

```
d <- data.frame(m,c)
summary(f <- coxph(allSurv ~ ., data=d ))
```

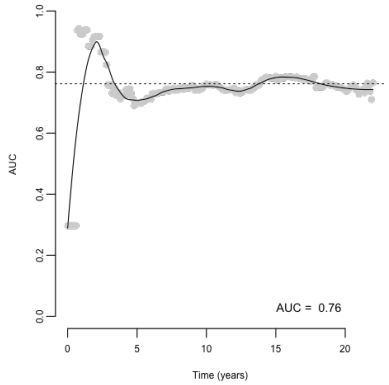
```
## Call:
## coxph(formula = allSurv ~ ., data = d)
##
##   n= 950, number of events= 120
##
##       coef exp(coef) se(coef)     z Pr(>|z|)
## m 0.613264  1.846449 0.090393 6.784 1.17e-11 ***
## c 0.033648  1.034220 0.005036 6.681 2.38e-11 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##   exp(coef) exp(-coef) lower .95 upper .95
## m     1.846     0.5416     1.547     2.204
## c     1.034     0.9669     1.024     1.044
##
## Concordance= 0.744  (se = 0.024 )
## Rsquare= 0.144   (max possible= 0.801 )
## Likelihood ratio test= 148.2  on 2 df,   p=<2e-16
## Wald test            = 223.3  on 2 df,   p=<2e-16
## Score (logrank) test = 350.7  on 2 df,   p=<2e-16
```

```
los <- do.call("rbind",mclapply(levels(samples), function(l){
  i <- samples!=l
  f <<- coxph(allSurv ~ ., data=d, subset=i)
  p <- as.matrix(d[!i,]) %*% f$coefficients
  r <- cbind(matrix(f$coefficients, nrow=length(p), ncol=length(f$coefficients), b
yrow=TRUE), linear.predictor=p)
  colnames(r) <- c(names(f$coefficients), "linear.predictor")
  as.data.frame(r)
}, mc.cores=4))
psNMtCumVaf <- los[order(order(samples)),]

survConcordance(allSurv ~ psNMtCumVaf$linear.predictor)
```

```
## Call:
## survConcordance(formula = allSurv ~ psNMtCumVaf$linear.predictor)
##
##   n= 950
## Concordance= 0.743362 se= 0.0238873
## concordant discordant  tied.risk  tied.time   std(c-d)
##  50211.000  12889.000  13580.000      1.000   3663.356
```

Dynamic/cumulative AUC

```
auc.uno <- AUC.uno(survAll2, survAll2, psNMtCumVaf$linear.predictor[w], times=t)

plot(auc.uno$times, auc.uno$auc, xlab="Time (years)", ylab="AUC", pch=16, col="gre
y80", ylim = c(0,1.0))
lines(auc.uno$times, predict(loess(auc.uno$auc ~ auc.uno$times, span=0.25)))
abline(h=auc.uno$iauc, lty = 3, lwd = 1)
legend("bottomright", bty = "n", cex = 1.2, legend = paste("AUC = ",round(auc.uno$
iauc,2)))
```




```
NMtCumVaf.a <- auc.uno
```

Gene-level risks

```
d <- allX
summary(f <- coxph(allSurv ~ ., data=d))
```

```
## Call:
## coxph(formula = allSurv ~ ., data = d)
##
##   n= 950, number of events= 120
##
##                   coef  exp(coef)   se(coef)      z Pr(>|z|)
## ASXL1_0.1      0.45410    1.57475    0.25483  1.782   0.0748 .
## BCOR_0.1       4.53517   93.23942   15.29850  0.296   0.7669
## CBL_0.1        0.02418    1.02448    0.74288  0.033   0.9740
## DNMT3A_0.1     0.13468    1.14417    0.18286  0.737   0.4614
## IDH1_0.1       0.39412    1.48307    0.63231  0.623   0.5331
## IDH2_0.1       0.51163    1.66800    0.29079  1.759   0.0785 .
## JAK2_0.1       0.59064    1.80514    0.39331  1.502   0.1332
## KDM6A_0.1      0.15988    1.17337   32.12704  0.005   0.9960
## KMT2C_0.1     -0.50258    0.60497    1.77003 -0.284   0.7765
## KMT2D_0.1     -0.01333    0.98676    0.58364 -0.023   0.9818
## KRAS_0.1       0.54336    1.72178   12.36468  0.044   0.9649
## NF1_0.1       -0.76668    0.46455    5.94275 -0.129   0.8973
## NRAS_0.1       7.40428 1643.00852    6.01855  1.230   0.2186
## PHF6_0.1       4.31340   74.69375   15.42773  0.280   0.7798
## PTPN11_0.1     4.49429   89.50474    6.18432  0.727   0.4674
## RAD21_0.1      0.07319    1.07594    6.89358  0.011   0.9915
## RUNX1_0.1      0.17980    1.19698    0.24611  0.731   0.4650
## SF3B1_0.1      1.10331    3.01414    0.52063  2.119   0.0341 *
## SRSF2_0.1      0.34535    1.41248    0.21771  1.586   0.1127
## TET2_0.1       0.17179    1.18743    0.20206  0.850   0.3952
## TP53_0.1       2.17381    8.79176    0.55321  3.929 8.51e-05 ***
## U2AF1_0.1      2.74012   15.48884    0.35246  7.774 7.58e-15 ***
## age_10        -0.01189    0.98818    0.10907 -0.109   0.9132
## gender        -0.01138    0.98868    0.19862 -0.057   0.9543
## cohort        -0.13561    0.87318    0.23791 -0.570   0.5687
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##             exp(coef) exp(-coef) lower .95 upper .95
## ASXL1_0.1      1.5747  0.6350222 9.557e-01 2.595e+00
## BCOR_0.1      93.2394  0.0107251 8.861e-12 9.811e+14
## CBL_0.1        1.0245  0.9761095 2.389e-01 4.394e+00
## DNMT3A_0.1     1.1442  0.8739972 7.995e-01 1.637e+00
## IDH1_0.1       1.4831  0.6742750 4.295e-01 5.121e+00
## IDH2_0.1       1.6680  0.5995195 9.434e-01 2.949e+00
## JAK2_0.1       1.8051  0.5539734 8.351e-01 3.902e+00
## KDM6A_0.1      1.1734  0.8522477 5.283e-28 2.606e+27
## KMT2C_0.1      0.6050  1.6529815 1.884e-02 1.943e+01
## KMT2D_0.1      0.9868  1.0134221 3.144e-01 3.097e+00
## KRAS_0.1       1.7218  0.5807959 5.142e-11 5.765e+10
## NF1_0.1        0.4646  2.1526020 4.060e-06 5.315e+04
```

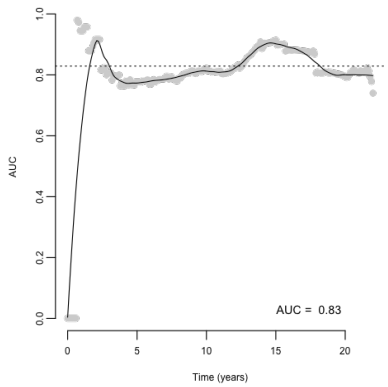
```
## NRAS_0.1   1643.0085  0.0006086 1.238e-02 2.181e+08
## PHF6_0.1     74.6937  0.0133880 5.510e-12 1.012e+15
## PTPN11_0.1   89.5047  0.0111726 4.872e-04 1.644e+07
## RAD21_0.1     1.0759  0.9294227 1.459e-06 7.936e+05
## RUNX1_0.1     1.1970  0.8354364 7.389e-01 1.939e+00
## SF3B1_0.1     3.0141  0.3317696 1.086e+00 8.362e+00
## SRSF2_0.1     1.4125  0.7079756 9.219e-01 2.164e+00
## TET2_0.1      1.1874  0.8421566 7.991e-01 1.764e+00
## TP53_0.1      8.7918  0.1137429 2.973e+00 2.600e+01
## U2AF1_0.1    15.4888  0.0645626 7.763e+00 3.091e+01
## age_10        0.9882  1.0119578 7.980e-01 1.224e+00
## gender        0.9887  1.0114489 6.699e-01 1.459e+00
## cohort        0.8732  1.1452345 5.478e-01 1.392e+00
##
## Concordance= 0.81  (se = 0.027 )
## Rsquare= 0.069   (max possible= 0.801 )
## Likelihood ratio test= 67.53  on 25 df,   p=9e-06
## Wald test            = 110.8  on 25 df,   p=9e-13
## Score (logrank) test = 782.6  on 25 df,   p=<2e-16
```

```
los <- do.call("rbind",mclapply(levels(samples), function(l){
  i <- samples!=l
  f <<- coxph(allSurv ~ ., data=d, subset=i)
  p <- as.matrix(d[!i,]) %*% f$coefficients
  r <- cbind(matrix(f$coefficients, nrow=length(p), ncol=length(f$coefficients), b
yrow=TRUE), linear.predictor=p)
  colnames(r) <- c(names(f$coefficients), "linear.predictor")
  as.data.frame(r)
}, mc.cores=4))
psGenes <- los[order(order(samples)),]

survConcordance(allSurv ~ psGenes$linear.predictor)
```

```
## Call:
## survConcordance(formula = allSurv ~ psGenes$linear.predictor)
##
##   n= 950
## Concordance= 0.7799296 se= 0.02746327
## concordant discordant  tied.risk  tied.time   std(c-d)
##  59805.000  16875.000      0.000      1.000   4211.768
```

Dynamic/cumulative AUC

```
auc.uno <- AUC.uno(survAll2, survAll2, psGenes$linear.predictor[w], times=t)

plot(auc.uno$times, auc.uno$auc, xlab="Time (years)", ylab="AUC", pch=16, col="gre
y80", ylim = c(0,1.0))
lines(auc.uno$times, predict(loess(auc.uno$auc ~ auc.uno$times, span=0.25)))
abline(h=auc.uno$iauc, lty = 3, lwd = 1)
legend("bottomright", bty = "n", cex = 1.2, legend = paste("AUC = ",round(auc.uno$
iauc,2)))
```



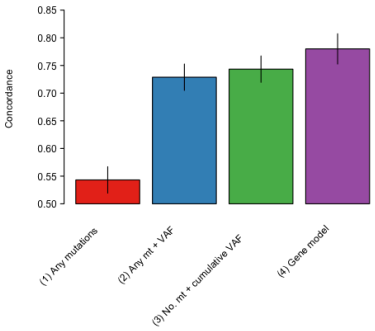

```
Genes.a <- auc.uno
```

```
# Concordance summary
c <- rbind(
  `(1) Any mutations`=as.data.frame(survConcordance(allSurv ~ psAnyMt$linear.predi
ctor)[c("concordance","std.err")]),
  `(2) Any mt + VAF`=as.data.frame(survConcordance(allSurv ~ psAnyMtVaf$linear.pre
dictor)[c("concordance","std.err")]),
  `(3) No. mt + cumulative VAF`=as.data.frame(survConcordance(allSurv ~ psNMtCumVa
f$linear.predictor)[c("concordance","std.err")]),
  `(4) Gene model`=as.data.frame(survConcordance(allSurv ~ psGenes$linear.predicto
r)[c("concordance","std.err")]))

c
```

| | concordance <dbl> | std.err <dbl> |
|---|---|---|
| (1) Any mutations | 0.5431925 | 0.02388586 |
| (2) Any mt + VAF | 0.7287559 | 0.02388730 |
| (3) No. mt + cumulative VAF | 0.7433620 | 0.02388730 |
| (4) Gene model | 0.7799296 | 0.02746327 |

4 rows

```
set1 <- RColorBrewer::brewer.pal(6,"Set1")

par(mar = c(9, 4, 1.5, 0.5) + 0.1, mgp=c(2.7,0.4,0), las=1, tcl=-0.2)
b <- barplot(c$concordance-0.5, ylab="Concordance", col=set1, ylim=c(0.5,0.88), of
fset=0.5)
mg14::rotatedLabel(x=b, labels=rownames(c))
segments(b,c$concordance+c$std.err,b,c$concordance-c$std.err)
```



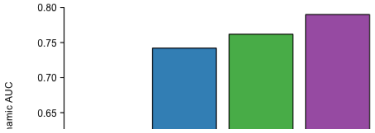

Dynamic/cumulative AUC summary

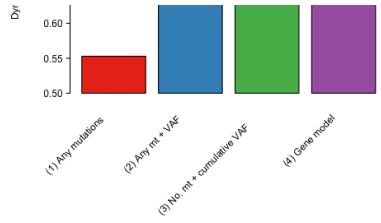
```
d.auc <- data.frame(iauc = c(AnyMt.a$iauc, AnyMtVaf.a$iauc, NMtCumVaf.a$iauc, 0.79
))
rownames(d.auc) <- c("(1) Any mutations", "(2) Any mt + VAF", "(3) No. mt + cumula
tive VAF", "(4) Gene model")

d.auc
```

| | iauc <dbl> |
|---|---|
| (1) Any mutations | 0.5528776 |
| (2) Any mt + VAF | 0.7420613 |
| (3) No. mt + cumulative VAF | 0.7618961 |
| (4) Gene model | 0.7900000 |

4 rows

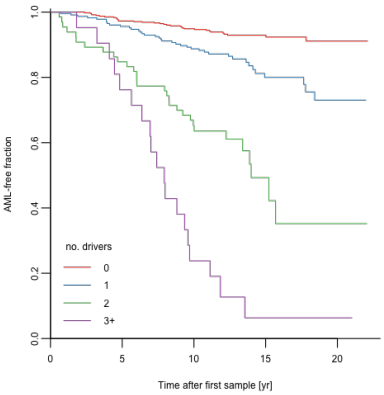
```
par(mar = c(9, 4, 1.5, 0.5) + 0.1, mgp=c(2.7,0.4,0), las=1, tcl=-0.2)
b <- barplot(d.auc$iauc-0.5, ylab="Dynamic AUC", col=set1, ylim=c(0.5,0.80), offse
t=0.5)
mg14::rotatedLabel(x=b, labels=rownames(d.auc))
```





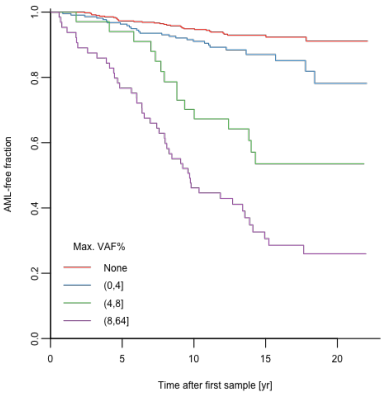

AML-free survival by number of drivers

```
nonc <- rowSums(allX[,allGroups=="Genes"]>0)
nonc <- cut(nonc, c(-1,0,1,2,max(nonc)))
plot(survfit(allSurv~nonc), col=set1, xlab='Time after first sample [yr]', ylab='A
ML-free fraction', bty='L', yaxs='i', ylim=c(0,1.01))
legend("bottomleft", c(0,1,2,"3+"), col=set1, lty=1, bty='n', title="no. drivers")
```




AML-free survival by max VAF

```
mvaf <- apply(allX[,allGroups=="Genes"], 1, max)*10
mvaf <- cut(mvaf, c(-1,0,4,8,max(mvaf)))
plot(survfit(allSurv~mvaf), col=set1, xlab='Time after first sample [yr]', ylab='A
ML-free fraction', bty='L', yaxs='i', ylim=c(0,1.01))
levels(mvaf)[1] <- "None"
legend("bottomleft", levels(mvaf), col=set1, lty=1, bty='n', title="Max. VAF%")
```



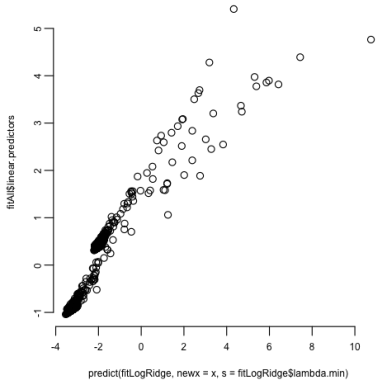

# 8 Logistic regression

```
library(glmnet)
library(ROCR)
```

## 8.1 Combined

```
set.seed(42)
y <- allSurv[,3]
x <- allX
x <- as.matrix(cbind(x, mu.Genes=rowSums(x[,allGroups=="Genes"])))
fitLogRidge <- cv.glmnet(x, y, alpha=0, standardize=FALSE, penalty.factor=c(allGro
ups=="Genes",FALSE), family="binomial", lambda=10^seq(-5,5,0.1)/nrow(x))
```

```
fitLog <- glm(y ~ x[,-ncol(x)], family= binomial )
coefLogRidge <- coef(fitLogRidge, s=fitLogRidge$lambda.min)[-1,1]
w <- names(coefLogRidge) %in% colnames(allX)[allGroups=="Genes"]
coefLogRidge[w] <- coefLogRidge[w] + coefLogRidge["mu.Genes"]
names(coefLogRidge) <- colnames(x)
s <- summary(survfit(allSurv ~1))

plot(predict(fitLogRidge, newx=x, s=fitLogRidge$lambda.min),fitAll$linear.predicto
rs)
```




```
cor(predict(fitLogRidge, newx=x, s=fitLogRidge$lambda.min),fitAll$linear.predictor
s)
```

```
##        [,1]
## 1 0.9325608
```

# 8.2 Discovery cohort

```
set.seed(42)
x <- cbind(as.matrix(torontoX), mu.Genes=rowSums(torontoX[torontoGroups=="Genes"])
)
fitLogRidgeToronto <- cv.glmnet(x, torontoSurv[,2], alpha=0, standardize=FALSE, pe
nalty.factor=c(torontoGroups=="Genes",FALSE), family="binomial", lambda=10^seq(-5,
5,0.1)/nrow(x))
l <- max(which(abs(fitLogRidgeToronto$cvm- min(fitLogRidgeToronto$cvm)) < 0.01))
coefFitLogRidgeToronto <- coef(fitLogRidgeToronto, s=fitLogRidge$lambda.min *nrow(
allX)/nrow(torontoX))[-1,1]
w <- names(coefFitLogRidgeToronto) %in% colnames(torontoX)[torontoGroups=="Genes"]
coefFitLogRidgeToronto[w] <- coefFitLogRidgeToronto[w] + coefFitLogRidgeToronto["m
u.Genes"]
```

# 8.3 Validation cohort

```
set.seed(42)
x <- cbind(as.matrix(sangerX), mu.Genes=rowSums(sangerX[sangerGroups=="Genes"]))
y <- sangerSurv[,3]
fitLogRidgeSanger <- glmnet(x, y, alpha=0, standardize=FALSE, penalty.factor=c(san
gerGroups%in%c("Genes","Blood"),1e-2) , family="binomial",lambda=10^seq(-5,5,0.1)/
nrow(x))
coefFitLogRidgeSanger <- coef(fitLogRidgeSanger, s=fitLogRidge$lambda.min*nrow(all
X)/nrow(sangerX)/4)[-1,1]
w <- names(coefFitLogRidgeSanger) %in% colnames(sangerX)[sangerGroups=="Genes"]
coefFitLogRidgeSanger[w] <- coefFitLogRidgeSanger[w] + coefFitLogRidgeSanger["mu.G
enes"]
coefFitLogRidgeSanger
```

```
##   ASXL1_0.1     CBL_0.1  DNMT3A_0.1    JAK2_0.1   KMT2C_0.1   KMT2D_0.1    KRAS
_0.1     NF1_0.1    NRAS_0.1   RAD21_0.1
##  1.61735484  0.62402794  0.60690505  1.21223108  1.28664688  0.38990853  1.3057
9768  1.05008349  1.12131863  1.08384807
##   SF3B1_0.1   SRSF2_0.1    TET2_0.1    TP53_0.1   U2AF1_0.1      age_10      ge
```

```
nder  systol_100 diastol_100      bmi_10
##  0.95795153  0.76775960  0.87432787  2.09849607  2.46513749  0.15915519 -0.1710
4884 -0.26674155  0.40623412  0.78151214
## cholestl_10     triglyc         hdl         ldl         lym     mcv_100      rd
w_10      wbc_10     plt_100      hgb_10
##  0.02221735 -0.02231645 -0.60655423  0.08051073  0.02388812 -0.48424380  1.4392
5261 -0.13343432  0.28531137  0.80105113
##    mu.Genes
##  1.16143798
```

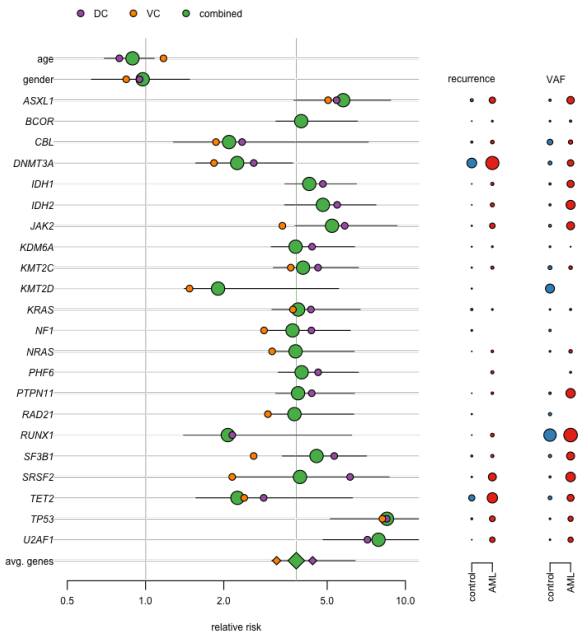
# 8.4 Bootstrap CIs

```
coefLogRidgeBoot <- sapply(1:100, function(foo){
            set.seed(foo)
            y <- allSurv[,3]
            x <- allX
            x <- as.matrix(cbind(x, mu.Genes=rowSums(x[,allGroups=="Genes"])))
            b <- sample(1:nrow(x), replace=TRUE)
            fitLogRidgeBoot <- glmnet(x[b,], y[b], alpha=0, standardize=FALSE, pen
alty.factor=c(allGroups=="Genes",FALSE, FALSE), family="binomial", lambda=10^seq(-
5,5,0.1)/nrow(x))
            coefLogRidgeBoot <- coef(fitLogRidgeBoot, s=fitLogRidge$lambda.min)[-1
,1]
            w <- names(coefLogRidgeBoot) %in% colnames(allX)[allGroups=="Genes"]
            coefLogRidgeBoot[w] <- coefLogRidgeBoot[w] + coefLogRidgeBoot["mu.Gene
s"]
            names(coefLogRidgeBoot) <- colnames(x)
            coefLogRidgeBoot
        })
```

# 8.5 Forest plot

```
par(bty="n", mar=c(3,6,3,10)+.5, mgp=c(2,0.5,0), xpd=FALSE)
c <- exp(coefLogRidge[-25])
o <- c(23:24,1:22,25)
ci <- apply(coefLogRidgeBoot,1,quantile, c(0.025,0.975))[,-25]
y <- rev(seq_along(c))
plot(c[o], y, xlab="relative risk", log='x', ylab='', yaxt="n", pch=NA, xlim=c(0.5
,10))
abline(h=y, col="#EEEEEE", lty=1)
abline(v=1, lty=1, col="grey")
abline(v=c["mu.Genes"], col=mg14::colTrans(set1[3]), lty=1)
segments(exp(ci[1,o]), y, exp(ci[2,o]),y)
```

```
segments(exp(ci[1,o]), y, exp(ci[2,o]),y)
points(c[o], y, xlab="relative risk",  bg=set1[3], cex=2, pch=c(rep(21,24), 23))
m <- match(names(c)[o],names(coefFitLogRidgeToronto))
points(exp(coefFitLogRidgeToronto[m]), y,bg=set1[4], pch=c(rep(21,24), 23), cex=1)
m <- match(names(c)[o],names(coefFitLogRidgeSanger))
points(exp(coefFitLogRidgeSanger[m]), y,bg=set1[5], pch=c(rep(21,24), 23), cex=1)
mtext(side=2, sub("mu.Genes","avg. genes",sub("_.+","",names(c)[o])), at=y, las=2,
font=c(1,1,rep(3,22),1))

r <- sapply(split(as.data.frame(allX>0), control), colMeans)
f <- sapply(split(allX, control), apply, 2, function(x) mean(x[x>0]))
par(xpd=NA)
points(rep(18,22),y[3:24], cex=sqrt(r[o[3:24],2]*10), pch=21, bg=set1[2])
points(rep(18*1.2,22), y[3:24], cex=sqrt(r[o[3:24],1]*10), pch=21, bg=set1[1])
points(rep(36,22),y[3:24], cex=sqrt(f[o[3:24],2]), pch=21, bg=set1[2])
points(rep(36*1.2,22), y[3:24], cex=sqrt(f[o[3:24],1]), pch=21, bg=set1[1])
legend(x=0.5, y=28, pch=21, pt.bg=set1[c(4,5,3)], c("DC","VC","combined"), bty="n"
, ncol=3, text.width=0.1)

text(y=24, x=18, "recurrence")
text(y=24, x=38, "VAF")

axis(1, at=c(18,18*1.2), c("control","AML"), las=2, line=-1)
axis(1, at=c(36,36*1.2), c("control","AML"), las=2, line=-1)
```




# 8.6 AUC

```
aucLogRidgeBoot <- t(sapply(1:100, function(foo){
                    set.seed(foo)
                    y <- allSurv[,3]
                    x <- allX
                    x <- as.matrix(cbind(x, mu.Genes=rowSums(x[,allGroups=="Genes"
]})))
                    b <- sample(1:nrow(x), replace=TRUE)
                    oob <- setdiff(1:nrow(x),b)
                    c(inb=performance(prediction(x[b,] %*% coefLogRidgeBoot[,foo],
y[b]), "auc")@y.values[[1]],
```

```
y[b]), auc ,y.values[[1]],
                          oob=performance(prediction(x[oob,] %*% coefLogRidgeBoo
t[,foo], y[oob]),"auc")@y.values[[1]])
                })

apply(aucLogRidgeBoot, 2, quantile)
```

```
##            inb       oob
## 0%   0.7600825 0.7331746
## 25%  0.7981192 0.7814137
## 50%  0.8107881 0.8058353
## 75%  0.8228798 0.8254089
## 100% 0.8616209 0.8650056
```

```
performance(prediction(as.matrix(torontoX) %*% coefFitLogRidgeToronto[-22], toront
oSurv[,2]),"auc")@y.values[[1]]
```

```
## [1] 0.7649573
```

```
performance(prediction(as.matrix(sangerImp) %*% coefFitLogRidgeToronto[-22], sange
rSurv[,3]),"auc")@y.values[[1]]
```

```
## [1] 0.806366
```

```
performance(prediction(as.matrix(sangerX) %*% coefFitLogRidgeSanger[-31], sangerSu
rv[,3]),"auc")@y.values[[1]]
```

```
## [1] 0.8479775
```

```
performance(prediction(ImputeMissing(sangerX, as.matrix(torontoImp)) %*% coefFitLo
gRidgeSanger[-31], torontoSurv[,2]),"auc")@y.values[[1]]
```

```
## [1] 0.6885916
```

# 9 Tabulate results

```
# library(xlsx)
# wb <- createWorkbook("xlsx")
# sheet  <- createSheet(wb, sheetName="Cox PH adjusted (combined)")
# addDataFrame(waldWeighted,
#       sheet,
#       colnamesStyle = CellStyle(wb) + Font(wb, isBold=TRUE) + Border(),
#       rownamesStyle = CellStyle(wb) + Font(wb, isBold=TRUE)
# )
# sheet  <- createSheet(wb, sheetName="Cox PH adjusted (DC)")
# addDataFrame(waldWeightedToronto,
#       sheet,
#       colnamesStyle = CellStyle(wb) + Font(wb, isBold=TRUE) + Border(),
#       rownamesStyle = CellStyle(wb) + Font(wb, isBold=TRUE)
# )
#
```

```
# sheet  <- createSheet(wb, sheetName="Cox PH adjusted (VC)")
# addDataFrame(waldWeightedSanger,
#       sheet,
#       colnamesStyle = CellStyle(wb) + Font(wb, isBold=TRUE) + Border(),
#       rownamesStyle = CellStyle(wb) + Font(wb, isBold=TRUE)
# )
#
# sheet  <- createSheet(wb, sheetName="Logistic regression (combined)")
# addDataFrame(data.frame(`Coef combined`=coefLogRidge, CI=t(apply(coefLogRidgeBoo
t, 1, quantile, c(0.025,0.975))),
#               check.names=FALSE),
#       sheet,
#       colnamesStyle = CellStyle(wb) + Font(wb, isBold=TRUE) + Border(),
#       rownamesStyle = CellStyle(wb) + Font(wb, isBold=TRUE)
# )
#
# sheet  <- createSheet(wb, sheetName="Logistic regression (DC)")
# addDataFrame(data.frame(`Coef combined`=coefFitLogRidgeToronto,
#               check.names=FALSE),
#       sheet,
#       colnamesStyle = CellStyle(wb) + Font(wb, isBold=TRUE) + Border(),
#       rownamesStyle = CellStyle(wb) + Font(wb, isBold=TRUE)
# )
# sheet  <- createSheet(wb, sheetName="Logistic regression (Sanger)")
# addDataFrame(data.frame(`Coef combined`=coefFitLogRidgeSanger,
#               check.names=FALSE),
#       sheet,
#       colnamesStyle = CellStyle(wb) + Font(wb, isBold=TRUE) + Border(),
#       rownamesStyle = CellStyle(wb) + Font(wb, isBold=TRUE)
# )
# saveWorkbook(wb, file="SupplementaryTables.xlsx")
```

# 10 Clinical/Demographic model

Necessary to reconstruct matrices and survival objects to use data from VC for all 8 samples sequenced in both cohorts ## Discovery cohort Data 83 pre-AML (keeping duplicates with validation cohort)

```
f = "data/DC_vaf_matrix_no_duplicates_414ctrl_83aml.csv"
torontoData <- read.csv(f)

torontoData$gender <- ifelse(torontoData$Sex == "male", 1,
                             ifelse(torontoData$Sex == "female", 0, torontoData$Se
x))
table(torontoData$gender)
```

```
##
##   0   1
## 293 204
```

```
torontoData$gender <- as.numeric(torontoData$gender)
colnames(torontoData)
```

```
##  [1] "Sample"     "ASXL1"      "BCOR"       "CALR"       "CBL"        "DNMT3A"
"IDH1"       "IDH2"
##  [9] "JAK2"       "KDM6A"      "KIT"        "KMT2C"      "KRAS"       "NF1"
"NRAS"       "PHF6"
## [17] "PTPN11"     "RUNX1"      "SF3B1"      "SRSF2"      "TET2"       "TP53"
"U2AF1"      "Diagnosis"
## [25] "fu_years"   "age"        "Sex"        "no_drivers" "gender"
```

Manually standardize magnitudes

```
torontoData <- torontoData[!duplicated(torontoData),]

gene_vars <- c("CALR", "NRAS", "DNMT3A", "SF3B1", "IDH1", "KIT", "TET2", "RAD21",
"JAK2", "CBL", "KRAS", "PTPN11", "IDH2", "TP53", "NF1", "SRSF2", "CEBPA", "ASXL1",
"RUNX1", "U2AF1", "BCOR", "KDM6A", "PHF6", "KMT2C", "KMT2D")

torontoX <- torontoData[, colnames(torontoData) %in% c(gene_vars, "age", "gender")
]

torontoX <- as.data.frame(torontoX)
```

Only include genes in model if mutated in >2 samples

```
thr <- 2
torontoX <- torontoX[,colSums(torontoX != 0)>=thr]
```

```
torontoGroups <- factor(names(torontoX) %in% c("age","gender")+1, level=1:2, label
s=c("Genes","Demographics"))
colnames(torontoX)
```

```
##  [1] "ASXL1"  "CALR"   "CBL"    "DNMT3A" "IDH1"   "IDH2"   "JAK2"   "KDM6A"  "K
MT2C"  "KRAS"   "NF1"    "PHF6"
## [13] "PTPN11" "RUNX1"  "SF3B1"  "SRSF2"  "TET2"   "TP53"   "U2AF1"  "age"    "g
ender"
```

```
torontoGroups
```

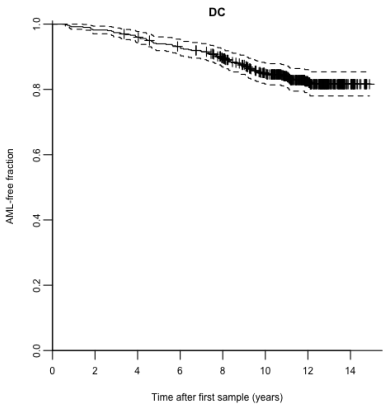
```
##  [1] Genes        Genes        Genes        Genes        Genes        Genes
Genes        Genes
##  [9] Genes        Genes        Genes        Genes        Genes        Genes
Genes        Genes
## [17] Genes        Genes        Genes        Demographics Demographics
## Levels: Genes Demographics
```

Manually standardize age and mutation VAFs

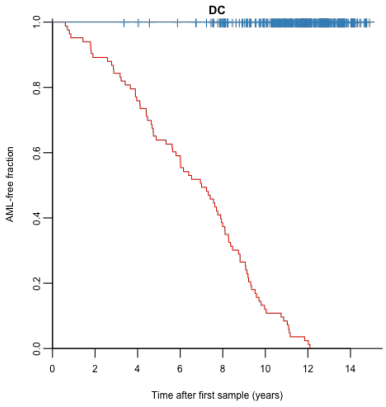
```
torontoX$age <- torontoX$age/10
names(torontoX)[which(names(torontoX)=="age")] <- "age_10"
g <- torontoGroups == "Genes"
torontoX[,g] <- torontoX[,g]*10
names(torontoX)[g] <- paste(names(torontoX)[g], "0.1",sep="_")
colnames(torontoX)
```

```
##  [1] "ASXL1_0.1"  "CALR_0.1"   "CBL_0.1"    "DNMT3A_0.1" "IDH1_0.1"   "IDH2_0.1
"   "JAK2_0.1"   "KDM6A_0.1"
##  [9] "KMT2C_0.1"  "KRAS_0.1"   "NF1_0.1"    "PHF6_0.1"   "PTPN11_0.1" "RUNX1_0.
1"  "SF3B1_0.1"  "SRSF2_0.1"
## [17] "TET2_0.1"   "TP53_0.1"   "U2AF1_0.1"  "age_10"     "gender"
```

```
torontoSurv <- Surv(torontoData$fu_years, torontoData$Diagnosis=="AML")
plot(survfit(torontoSurv~ 1), col= "black", main = "DC", xlab='Time after first sa
mple (years)', ylab='AML-free fraction', bty='L', yaxs='i', ylim=c(0,1.01), mark.t
ime = T)
```




```
plot(survfit(torontoSurv ~ torontoData$Diagnosis), xlab='Time after first sample (
years)', main = "DC", ylab='AML-free fraction', bty='L', yaxs='i', ylim=c(0,1.01),
mark.time = T, col = set1[1:2])
```




# 10.1 Validation cohort

all 37 pre-AML samples including overlap with DC

```
f = "data/VC_vaf_matrix_262ctrl_37aml_nodates.csv"
sangerData <- read.csv(f)

sangerData$hcdate <- as.Date(sangerData$hcdate)
sangerData$dodx <- as.Date(sangerData$dodx)

sangerPatients <- sub("[a-z]+$","", sangerData$Sample)
o <- order(sangerPatients, as.numeric(sangerData$hcdate))

sangerData <- sangerData[o,]
sangerPatients <- sangerPatients[o]

clinical_vars <- c("systol", "diastol", "bmi", "cholestl", "triglyc", "hdl", "ldl"
, "lym", "mcv", "rdw", "wbc", "plt", "hgb")
sangerX <- sangerData[, colnames(sangerData) %in% c(gene_vars, "age","gender",clin
ical_vars)]
sangerX <- as.data.frame(sangerX)

sangerX <- sangerX[,colSums(sangerX != 0,na.rm=TRUE)>=thr]
sangerGroups <- factor(grepl("^[a-z]", colnames(sangerX))*2, levels=0:2, labels=c(
"Genes", "Demographics", "Blood"))
sangerGroups[names(sangerX) %in% c("age","gender")] <- "Demographics"
table(sangerGroups)
```

```
## sangerGroups
##        Genes Demographics        Blood
##           15            2           13
```

```
colnames(sangerX)
```

```
##  [1] "ASXL1"    "CBL"      "DNMT3A"   "JAK2"     "KMT2C"    "KMT2D"    "KRAS"
"NF1"      "NRAS"     "RAD21"
## [11] "SF3B1"    "SRSF2"    "TET2"     "TP53"     "U2AF1"    "age"      "gender"
"systol"   "diastol"  "bmi"
## [21] "cholestl" "triglyc"  "hdl"      "ldl"      "lym"      "mcv"      "rdw"
"wbc"      "plt"      "hgb"
```

```
sangerGroups
```

```
##  [1] Genes        Genes        Genes        Genes        Genes        Genes
Genes        Genes
##  [9] Genes        Genes        Genes        Genes        Genes        Genes
Genes        Demographics
## [17] Demographics Blood        Blood        Blood        Blood        Blood
Blood        Blood
## [25] Blood        Blood        Blood        Blood        Blood        Blood
## Levels: Genes Demographics Blood
```

```
poorMansImpute <- function(x) {x[is.na(x)] <- mean(x, na.rm=TRUE); return(x)}
sangerX <- as.data.frame(sapply(sangerX, poorMansImpute))

foo <- split(sangerData[,c("Diagnosis","hcdate","dodx")], sangerPatients)

bar <- do.call("rbind",lapply(foo, function(x){
  y <- x
  n <- nrow(y)
  y[-n,"Diagnosis"] <- "Control"
  start <- as.numeric(y$hcdate - y$hcdate[1])/365.25
  end <- c(as.numeric(y$hcdate - y$hcdate[1])[-1]/365.25, as.numeric(y$dodx[n] - y
$hcdate[1])/365.25)
  return(data.frame(Diagnosis=y[,"Diagnosis"], start=start, end=end))
}))

bar[1:10, ]
```

| | **Diagnosis**<br><fctr> | **start**<br><dbl> | **end**<br><dbl> |
|---|---|---|---|
| PD29762 | AML | 0.000000 | 9.754962 |
| PD29764 | AML | 0.000000 | 10.360027 |
| PD29792 | AML | 0.000000 | 14.108145 |
| PD29804 | Control | 0.000000 | 5.138946 |
| PD29810 | Control | 0.000000 | 18.573580 |

| | | | |
|---|---|---|---|
| PD29810 | Control | 0.000000 | 18.573580 |
| PD29836.1 | Control | 0.000000 | 2.414784 |
| PD29836.2 | AML | 2.414784 | 10.023272 |
| | | | |
| PD29851.1 | Control | 0.000000 | 4.599589 |
| PD29851.2 | AML | 4.599589 | 12.205339 |
| PD29856.1 | Control | 0.000000 | 4.331280 |

1-10 of 10 rows

```
sangerPatientsSplit <- unlist(sapply(names(foo), function(n) rep(n, nrow(foo[[n]])
)))

sangerSurv <- Surv(time = bar$start, time2 = bar$end, event = bar$Diagnosis!="Cont
rol", origin = 0)

plot(survfit(sangerSurv~ 1), col= "black", main = "VC", xlab='Time after first sam
ple (years)', ylab='AML-free fraction', bty='L', yaxs='i', ylim=c(0,1.01), mark.ti
me = T) #mark = 1
```

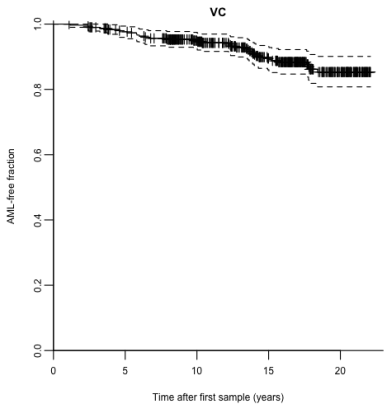



Figure 3 c-e

```
summary(sangerX$rdw)
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   11.40   13.10   13.42   13.42   13.42   22.00
```

```
rdw <- cut(sangerX$rdw, c(11, 14, max(sangerX$rdw)))
levels(rdw) <- c("11-14", "14+")
table(rdw)
```

```
## rdw
## 11-14   14+
##   400    59
```

```
selected_genes <- c("DNMT3A", "TET2", "TP53", "U2AF1")

png("./figures/CombinedCohorts.KM.selected.genes.png", width = 8.5, height = 17.5,
units = "cm", res = 800)
par(mfrow=c(4,2), mar = c(1.9, 1.9, 1.7, 0.7) + 0.1, mgp=c(2.2,0.4,0), bty="L", xp
d=TRUE, las=1, tcl=-0.15, cex.axis=1.15, cex.lab = 1)
for (i in 1:length(selected_genes)) {
  #i <- 1
  gene <- selected_genes[i]
  plot(survfit(surv ~ X[[gene]] == 0), col= pal1, bty='L', yaxs='i', ylim=c(0,1.01
), mark.time = T, conf.int = F)
  mtext(gene, font=3, side = 3, line = 0.2, cex = 0.83)
  legend("bottomleft", col=pal1[1:2], lty=1, c("MT","WT"), lwd = 1.5, bty="n", nco
l = 1, cex = 0.9, seg.len=0.7)
}
plot(survfit(surv ~ n_drivers), col=rev(pal1[1:3]), conf.int = F, mark.time = T, b
ty='L', yaxs='i', ylim=c(0,1.01))
mtext("Number of drivers", font=1, side = 3, line = 0.7, cex = 0.83)
legend("bottomleft", legend = levels(n_drivers), col= rev(pal1[1:3]), lty=1, lwd =
1.5, bty='n', title="", cex = 1, seg.len=0.7)
plot(survfit(surv ~ mvaf), col= rev(pal1[1:4]), conf.int = F, mark.time = T, bty='
L', yaxs='i', ylim=c(0,1.01))
mtext("Maximum VAF (%)", font=1, side = 3, line = 0.7, cex = 0.83)
```

```
legend("bottomleft", levels(mvaf), col=rev(pal1[1:4]), lty=1, lwd = 1.5, bty='n',
title="", cex = 1, seg.len=0.7)
plot(survfit(sangerSurv ~ rdw), col= rev(pal1[1:2]), conf.int = F, mark.time = T,
bty='L', yaxs='i', ylim=c(0,1.01))
mtext("RDW", font=1, side = 3, line = 0.2, cex = 0.83)
legend("bottomleft", levels(rdw), col=rev(pal1[1:2]), lty=1, lwd = 1.5, bty='n', t
itle="", cex = 1, seg.len=0.7)
dev.off()
```

```
## pdf
##   2
```

Standardise magnitudes

```
g <- sangerGroups=="Genes"
sangerX[g] <- sangerX[g] * 10
names(sangerX)[g] <- paste(names(sangerX[g]),"0.1", sep="_")
y <- StandardizeMagnitude(sangerX[!g])
sangerX <- cbind(sangerX[g],y)
```

# 10.2 Expected AML incidence

Validation cohort

```
w <- c(which(sangerSurv[,1]==0)[-1]-1, nrow(sangerSurv))
sangerSurv2 <- Surv(sangerSurv[w,2], sangerSurv[w,3])

expected_rate_sanger_cr <- mean(aml_inc_cr(sangerX[w,"gender"],sangerX[w,"age_10"]
*10, sangerX[w,"age_10"]*10+ pmax(1,sangerSurv2[,1]))[!sangerSurv2[,2]])

n_total_sanger <- sum(sangerSurv2[,2])/expected_rate_sanger_cr
n_total_sanger
```

```
## [1] 13277.44
```

Discovery cohort only

```
expected_rate_toronto_cr <- mean(aml_inc_cr(torontoX[,"gender"],torontoX[,"age_10"
]*10, torontoX[,"age_10"]*10+ pmax(1,torontoSurv[,1]))[!torontoSurv[,2]])

n_total_toronto <- sum(torontoSurv[,2])/expected_rate_toronto_cr
n_total_toronto
```

```
## [1] 66014.85
```

# 10.3 Combined data

Survival

```
allSurv <- rbind(sangerSurv, Surv(rep(0, nrow(torontoSurv)), torontoSurv[,1], toro
ntoSurv[,2]))
allSurv <- Surv(allSurv[,1], allSurv[,2], allSurv[,3])
```

Data matrix

```
cohort <- c(rep("Sanger", nrow(sangerX)), rep("Toronto", nrow(torontoX)))
i <- c(sort(setdiff(gene_vars,"CALR")),"age","gender")
allX <- rbind(superSet(sangerData,i,fill=0), superSet(torontoData,i,fill=0))
allX <- allX[,colSums(allX>0)>=thr]
allX <- cbind(allX, cohort=cohort=="Sanger") + 0
allGroups <- factor(grepl("^[A-Z]",colnames(allX))+0, levels=1:0, labels=c("Genes"
,"Demographics"))

g <- allGroups=="Genes"
allX <- cbind(10*allX[,g], StandardizeMagnitude(allX[,!g]))
colnames(allX)[g] <- paste(colnames(allX)[g],"0.1",sep="_")
control <- c(sangerData$Diagnosis=="Control", torontoData$Diagnosis=="Control")
```

Weights

```
weights <- rep(1, nrow(allX))
weights[cohort=="Sanger" & control] <- n_total_sanger/sum(cohort=="Sanger" & contr
ol & allSurv[,1]==0)
weights[cohort=="Toronto" & control] <- n_total_toronto/sum(cohort=="Toronto" & co
ntrol)

n_total <- n_total_sanger + n_total_toronto
n_total
```

```
## [1] 79292.3
```

# 10.4 Coxph model fits

```
sigma0 <- 0.1
nu <- 1
which.mu <- "Genes"
```

## 10.4.1 Discovery cohort

### 10.4.1.1 Raw

```
fitToronto <- CoxRFX(torontoX, torontoSurv, groups=torontoGroups, which.mu=which.m
u, nu=nu, sigma0=sigma0)
waldToronto <- WaldTest(fitToronto)
```

```
##                   group    coef   coef-mu     sd      z df  p.value sig
## ASXL1_0.1         Genes  0.6922  0.049613 0.1172  5.908  1 3.47e-09 ***
## CALR_0.1          Genes  0.6239 -0.018696 0.0710  8.784  1 1.58e-18 ***
## CBL_0.1           Genes  0.5335 -0.109028 0.1293  4.126  1 3.70e-05 ***
## DNMT3A_0.1        Genes  0.5843 -0.058207 0.1059  5.517  1 3.44e-08 ***
## IDH1_0.1          Genes  0.6912  0.048657 0.1245  5.550  1 2.86e-08 ***
## IDH2_0.1          Genes  0.5136 -0.128999 0.1151  4.460  1 8.19e-06 ***
## JAK2_0.1          Genes  0.7120  0.069470 0.1243  5.730  1 1.00e-08 ***
## KDM6A_0.1         Genes  0.6419 -0.000647 0.0590 10.887  1 1.32e-27 ***
## KMT2C_0.1         Genes  0.6658  0.023265 0.0621 10.725  1 7.79e-27 ***
## KRAS_0.1          Genes  0.6403 -0.002210 0.0590 10.855  1 1.89e-27 ***
## NF1_0.1           Genes  0.6412 -0.001393 0.0590 10.870  1 1.61e-27 ***
## PHF6_0.1          Genes  0.6475  0.004993 0.0595 10.891  1 1.27e-27 ***
## PTPN11_0.1        Genes  0.6595  0.016950 0.0592 11.145  1 7.57e-29 ***
## RUNX1_0.1         Genes  0.4100 -0.232587 0.0923  4.443  1 8.89e-06 ***
## SF3B1_0.1         Genes  0.7728  0.130235 0.1019  7.585  1 3.33e-14 ***
## SRSF2_0.1         Genes  0.4783 -0.164235 0.0945  5.062  1 4.16e-07 ***
## TET2_0.1          Genes  0.6389 -0.003667 0.1295  4.932  1 8.13e-07 ***
## TP53_0.1          Genes  0.8079  0.165351 0.0673 12.009  1 3.19e-33 ***
## U2AF1_0.1         Genes  0.8537  0.211135 0.0773 11.048  1 2.23e-28 ***
## age_10     Demographics -0.0836 -0.083628 0.0975 -0.858  1 3.91e-01
## gender     Demographics  0.0113  0.011327 0.1091  0.104  1 9.17e-01
```

```
survConcordance(fitToronto$surv ~ fitToronto$linear.predictors)
```

```
## Call:
## survConcordance(formula = fitToronto$surv ~ fitToronto$linear.predictors)
##
##   n= 497
## Concordance= 0.7538671 se= 0.03218546
## concordant discordant  tied.risk  tied.time   std(c-d)
##   26561.00    8672.00       0.00       1.00    2267.98
```

## 10.4.2 Validation cohort

### 10.4.2.1 Raw

```
fitSanger <- CoxRFX(sangerX, sangerSurv, groups=sangerGroups, which.mu=which.mu, n
u=nu, sigma0=sigma0)
waldSanger <- WaldTest(fitSanger)
```

```
##                   group     coef   coef-mu      sd      z df  p.value sig
## ASXL1_0.1         Genes  0.64051  0.105357 0.11285  5.676  1 1.38e-08 ***
## CBL_0.1           Genes  0.52291 -0.012246 0.08720  5.997  1 2.01e-09 ***
## DNMT3A_0.1        Genes  0.43301 -0.102144 0.11026  3.927  1 8.60e-05 ***
## JAK2_0.1          Genes  0.52046 -0.014699 0.09655  5.391  1 7.02e-08 ***
## KMT2C_0.1         Genes  0.54634  0.011184 0.08151  6.703  1 2.05e-11 ***
## KMT2D_0.1         Genes  0.42573 -0.109421 0.14122  3.015  1 2.57e-03  **
```

```
## KRAS_0.1           Genes  0.53897  0.003816 0.08013  6.726  1 1.74e-11 ***
## NF1_0.1            Genes  0.52911 -0.006044 0.08135  6.504  1 7.80e-11 ***
## NRAS_0.1           Genes  0.53431 -0.000849 0.08011  6.670  1 2.56e-11 ***
## RAD21_0.1          Genes  0.53226 -0.002897 0.08049  6.613  1 3.77e-11 ***
## SF3B1_0.1          Genes  0.53076 -0.004391 0.08104  6.550  1 5.76e-11 ***
## SRSF2_0.1          Genes  0.50357 -0.031583 0.11851  4.249  1 2.14e-05 ***
## TET2_0.1           Genes  0.58716  0.052000 0.10482  5.602  1 2.12e-08 ***
## TP53_0.1           Genes  0.58827  0.053119 0.08077  7.283  1 3.25e-13 ***
## U2AF1_0.1          Genes  0.59395  0.058796 0.08084  7.347  1 2.03e-13 ***
## age_10       Demographics  0.08031  0.080306 0.11847  0.678  1 4.98e-01
## gender       Demographics -0.11803 -0.118029 0.11360 -1.039  1 2.99e-01
## systol_100          Blood  0.01074  0.010736 0.04230  0.254  1 8.00e-01
## diastol_100         Blood  0.02297  0.022974 0.02697  0.852  1 3.94e-01
## bmi_10              Blood  0.09128  0.091285 0.07510  1.215  1 2.24e-01
## cholestl_10         Blood  0.00934  0.009343 0.01381  0.676  1 4.99e-01
## triglyc             Blood  0.02435  0.024354 0.09637  0.253  1 8.00e-01
## hdl                 Blood -0.07521 -0.075205 0.07691 -0.978  1 3.28e-01
## ldl                 Blood  0.12764  0.127641 0.09931  1.285  1 1.99e-01
## lym                 Blood  0.07714  0.077135 0.09427  0.818  1 4.13e-01
## mcv_100             Blood -0.00987 -0.009867 0.00826 -1.195  1 2.32e-01
## rdw_10              Blood  0.06196  0.061956 0.02072  2.990  1 2.79e-03  **
## wbc_10              Blood  0.01894  0.018939 0.03734  0.507  1 6.12e-01
## plt_100             Blood  0.05344  0.053435 0.09405  0.568  1 5.70e-01
## hgb_10              Blood  0.05198  0.051979 0.02446  2.125  1 3.36e-02   *
```

```
survConcordance(sangerSurv ~ fitSanger$linear.predictors)
```

```
## Call:
## survConcordance(formula = sangerSurv ~ fitSanger$linear.predictors)
##
##   n= 459
## Concordance= 0.7224015 se= 0.04865039
## concordant discordant  tied.risk  tied.time   std(c-d)
##  6714.0000  2580.0000     0.0000     0.0000   904.3134
```

#### 10.4.2.2 Adjusted

```
fitWeightedSanger <- CoxRFX(sangerX, sangerSurv, sangerGroups, which.mu=which.mu,
sigma0=sigma0, nu=nu, weights=weights[cohort=="Sanger"])
waldWeightedSanger <- WaldTest(fitWeightedSanger)
```

```
##                    group      coef   coef-mu      sd        z df  p.value sig
## ASXL1_0.1          Genes  2.634306  0.838861 0.43502  6.05558  1 1.40e-09 ***
## CBL_0.1            Genes  0.630557 -1.164888 1.13502  0.55555  1 5.79e-01
## DNMT3A_0.1         Genes  0.698827 -1.096619 0.22597  3.09251  1 1.98e-03  **
## JAK2_0.1           Genes  0.049363 -1.746082 0.90486  0.05455  1 9.56e-01
## KMT2C_0.1          Genes  1.829655  0.034210 1.05055  1.74162  1 8.16e-02   .
## KMT2D_0.1          Genes -0.004783 -1.800228 0.75790 -0.00631  1 9.95e-01
## KRAS_0.1           Genes  2.139544  0.344099 0.40749  5.25049  1 1.52e-07 ***
## NF1_0.1            Genes  1.252510 -0.542935 0.89204  1.40410  1 1.60e-01
## NRAS_0.1           Genes  1.730987 -0.064459 0.36379  4.75820  1 1.95e-06 ***
## RAD21_0.1          Genes  1.487062 -0.308383 0.68933  2.15726  1 3.10e-02   *
## SF3B1_0.1          Genes  1.309652 -0.485793 0.96376  1.35890  1 1.74e-01
## SRSF2_0.1          Genes  1.451418 -0.344027 0.27015  5.37269  1 7.76e-08 ***
## TET2_0.1           Genes  1.222954 -0.572491 0.12864  9.50695  1 1.96e-21 ***
## TP53_0.1           Genes  4.699561  2.904116 0.91319  5.14632  1 2.66e-07 ***
## U2AF1_0.1          Genes  5.800067  4.004622 0.74776  7.75664  1 8.72e-15 ***
## age_10       Demographics  0.024711  0.024711 0.12062  0.20487  1 8.38e-01
## gender       Demographics -0.140352 -0.140352 0.11358 -1.23575  1 2.17e-01
## systol_100          Blood -0.000324 -0.000324 0.04456 -0.00726  1 9.94e-01
## diastol_100         Blood  0.019654  0.019654 0.02894  0.67907  1 4.97e-01
## bmi_10              Blood  0.101555  0.101555 0.08137  1.24811  1 2.12e-01
## cholestl_10         Blood  0.007469  0.007469 0.01457  0.51275  1 6.08e-01
## triglyc             Blood  0.007316  0.007316 0.10707  0.06832  1 9.46e-01
## hdl                 Blood -0.108973 -0.108973 0.08295 -1.31365  1 1.89e-01
## ldl                 Blood  0.149658  0.149658 0.10397  1.43938  1 1.50e-01
## lym                 Blood  0.066987  0.066987 0.09901  0.67660  1 4.99e-01
## mcv_100             Blood -0.015964 -0.015964 0.00832 -1.91787  1 5.51e-02   .
## rdw_10              Blood  0.073201  0.073201 0.01789  4.09058  1 4.30e-05 ***
## wbc_10              Blood  0.020190  0.020190 0.04345  0.46465  1 6.42e-01
## plt_100             Blood  0.077199  0.077199 0.10027  0.76987  1 4.41e-01
## hgb_10              Blood  0.044376  0.044376 0.02513  1.76558  1 7.75e-02   .
```

```
survConcordance(sangerSurv ~ fitWeightedSanger$linear.predictors, weights=weights[
cohort=="Sanger"])
```

```
## Call:
## survConcordance(formula = sangerSurv ~ fitWeightedSanger$linear.predictors,
```

```
##     weights = weights[cohort == "Sanger"])
##
##   n= 459
## Concordance= 0.7639423 se= 0.04828991
## concordant discordant  tied.risk  tied.time   std(c-d)
##  334537.56  103371.88       0.00       0.00   42293.22
```

Uno's estimator of cumulative/dynamic AUC

```
w <- c(which(sangerSurv[,1]==0)[-1]-1, nrow(sangerSurv))
s <- Surv(sangerSurv[w,2], sangerSurv[w,3])
a <- AUC.uno(s, s, fitWeightedSanger$linear.predictors[w], times= c(0, 22, 0.1))
round(a$iauc, digits = 3)
```

```
## [1] 0.761
```

# 11 Model excluding controls without mutations

Include only controls with ARCH & all pre-AML (regardless of mutation status) ## Discovery cohort (Toronto) Data

```
f = "data/DC_vaf_matrix_no_duplicates_414ctrl_83aml.csv"
torontoData <- read.csv(f)

gene_vars <- c("CALR", "NRAS", "DNMT3A", "SF3B1", "IDH1", "KIT", "TET2", "RAD21",
"JAK2", "CBL", "KRAS", "PTPN11", "IDH2", "TP53", "NF1", "SRSF2", "CEBPA", "ASXL1",
"RUNX1", "U2AF1", "BCOR", "KDM6A", "PHF6", "KMT2C", "KMT2D")

table(torontoData$Diagnosis)
```

```
##
##     AML Control
##      83     414
```

```
torontoData$gender <- ifelse(torontoData$Sex == "male", 1,
                             ifelse(torontoData$Sex == "female", 0, torontoData$Se
x))
dim(torontoData)
```

```
## [1] 497  29
```

```
torontoData <- torontoData[rowSums(torontoData[, colnames(torontoData) %in% gene_v
ars])>0 | torontoData$Diagnosis == "AML", ]
dim(torontoData)
```

```
## [1] 240  29
```

```
table(torontoData$gender)
```

```
##
##   0   1
## 135 105
```

```
torontoData$gender <- as.numeric(torontoData$gender)
colnames(torontoData)
```

```
##  [1] "Sample"     "ASXL1"      "BCOR"       "CALR"       "CBL"        "DNMT3A"
"IDH1"       "IDH2"
##  [9] "JAK2"       "KDM6A"      "KIT"        "KMT2C"      "KRAS"       "NF1"
"NRAS"       "PHF6"
## [17] "PTPN11"     "RUNX1"      "SF3B1"      "SRSF2"      "TET2"       "TP53"
"U2AF1"      "Diagnosis"
## [25] "fu_years"   "age"        "Sex"        "no_drivers" "gender"
```

Manually standardize magnitudes

```
torontoData <- torontoData[!duplicated(torontoData),]
```

```
torontoX <- torontoData[, colnames(torontoData) %in% c(gene_vars, "age", "gender")
]

torontoX <- as.data.frame(torontoX)
thr <- 2
torontoX <- torontoX[,colSums(torontoX != 0)>=thr]

torontoGroups <- factor(names(torontoX) %in% c("age","gender")+1, level=1:2, label
s=c("Genes","Demographics"))
colnames(torontoX)
```

```
##  [1] "ASXL1"  "CALR"   "CBL"    "DNMT3A" "IDH1"   "IDH2"   "JAK2"   "KDM6A"  "K
MT2C"  "KRAS"   "NF1"    "PHF6"
## [13] "PTPN11" "RUNX1"  "SF3B1"  "SRSF2"  "TET2"   "TP53"   "U2AF1"  "age"    "g
ender"
```

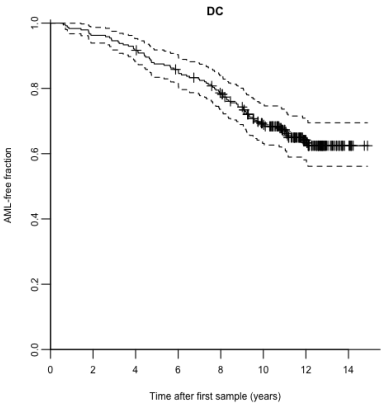
```
torontoGroups
```

```
##  [1] Genes        Genes        Genes        Genes        Genes        Genes
Genes        Genes
##  [9] Genes        Genes        Genes        Genes        Genes        Genes
Genes        Genes
## [17] Genes        Genes        Genes        Demographics Demographics
## Levels: Genes Demographics
```

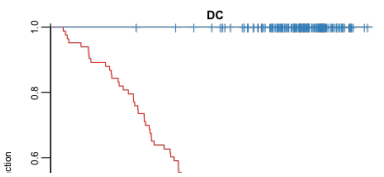
```
# Manually standardize age and mutation VAFs
torontoX$age <- torontoX$age/10
names(torontoX)[which(names(torontoX)=="age")] <- "age_10"
g <- torontoGroups == "Genes"
torontoX[,g] <- torontoX[,g]*10
names(torontoX)[g] <- paste(names(torontoX)[g], "0.1",sep="_")
colnames(torontoX)
```

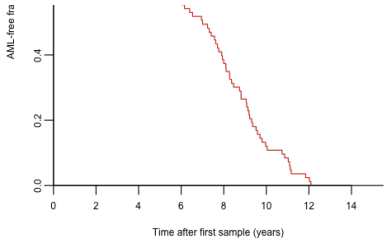
```
##  [1] "ASXL1_0.1"  "CALR_0.1"   "CBL_0.1"    "DNMT3A_0.1" "IDH1_0.1"   "IDH2_0.1
"   "JAK2_0.1"   "KDM6A_0.1"
##  [9] "KMT2C_0.1"  "KRAS_0.1"   "NF1_0.1"    "PHF6_0.1"   "PTPN11_0.1" "RUNX1_0.
1"  "SF3B1_0.1"  "SRSF2_0.1"
## [17] "TET2_0.1"   "TP53_0.1"   "U2AF1_0.1"  "age_10"     "gender"
```

```
torontoSurv <- Surv(torontoData$fu_years, torontoData$Diagnosis=="AML")
plot(survfit(torontoSurv~ 1), col= "black", main = "DC", xlab='Time after first sa
mple (years)', ylab='AML-free fraction', bty='L', yaxs='i', ylim=c(0,1.01), mark.t
ime = T)
```




```
plot(survfit(torontoSurv ~ torontoData$Diagnosis), xlab='Time after first sample (
years)', main = "DC", ylab='AML-free fraction', bty='L', yaxs='i', ylim=c(0,1.01),
mark.time = T, col = set1[1:2])
```






# 11.1 Validation cohort

```
f = "data/VC_vaf_matrix_262ctrl_37aml_nodates.csv"
sangerData <- read.csv(f)
dim(sangerData)
```

```
## [1] 459  43
```

```
sangerData <- sangerData[rowSums(sangerData[, colnames(sangerData) %in% gene_vars]
)>0 | sangerData$Diagnosis == "AML", ]
dim(sangerData)
```

```
## [1] 173  43
```

```
length(unique(sangerData$Individual))
```

```
## [1] 128
```

```
sangerData$hcdate <- as.Date(sangerData$hcdate)
sangerData$dodx <- as.Date(sangerData$dodx)

sangerPatients <- sub("[a-z]+$","", sangerData$Sample)
o <- order(sangerPatients, as.numeric(sangerData$hcdate))

sangerData <- sangerData[o,]
sangerPatients <- sangerPatients[o]

clinical_vars <- c("systol", "diastol", "bmi", "cholestl", "triglyc", "hdl", "ldl"
, "lym", "mcv", "rdw", "wbc", "plt", "hgb")
sangerX <- sangerData[, colnames(sangerData) %in% c(gene_vars, "age","gender",clin
ical_vars)]
sangerX <- as.data.frame(sangerX)

sangerX <- sangerX[,colSums(sangerX != 0,na.rm=TRUE)>=thr]
sangerGroups <- factor(grepl("^[a-z]", colnames(sangerX))*2, levels=0:2, labels=c(
"Genes", "Demographics", "Blood"))
sangerGroups[names(sangerX) %in% c("age","gender")] <- "Demographics"
table(sangerGroups)
```

```
## sangerGroups
##        Genes Demographics        Blood
##           15            2           13
```

```
colnames(sangerX)
```

```
##  [1] "ASXL1"    "CBL"      "DNMT3A"   "JAK2"     "KMT2C"    "KMT2D"    "KRAS"
"NF1"      "NRAS"     "RAD21"
## [11] "SF3B1"    "SRSF2"    "TET2"     "TP53"     "U2AF1"    "age"      "gender"
"systol"   "diastol"  "bmi"
## [21] "cholestl" "triglyc"  "hdl"      "ldl"      "lym"      "mcv"      "rdw"
"wbc"      "plt"      "hgb"
```

```
sangerGroups
```

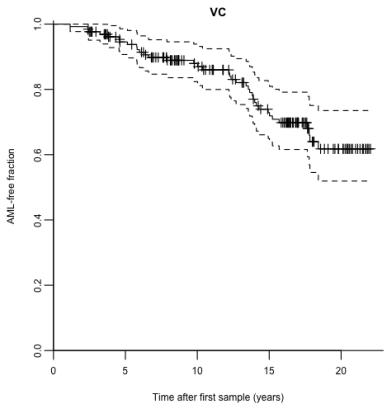
```
##  [1] Genes        Genes        Genes        Genes        Genes        Genes
Genes        Genes
##  [9] Genes        Genes        Genes        Genes        Genes        Genes
Genes        Demographics
## [17] Demographics Blood        Blood        Blood        Blood        Blood
Blood        Blood
## [25] Blood        Blood        Blood        Blood        Blood        Blood
## Levels: Genes Demographics Blood
```

```
g <- sangerGroups=="Genes"
sangerX[g] <- sangerX[g] * 10
names(sangerX)[g] <- paste(names(sangerX[g]),"0.1", sep="_")
y <- StandardizeMagnitude(sangerX[!g])
sangerX <- cbind(sangerX[g],y)

poorMansImpute <- function(x) {x[is.na(x)] <- mean(x, na.rm=TRUE); return(x)}
sangerX <- as.data.frame(sapply(sangerX, poorMansImpute))

foo <- split(sangerData[,c("Diagnosis","hcdate","dodx")], sangerPatients)

bar <- do.call("rbind",lapply(foo, function(x){
  y <- x
  n <- nrow(y)
  y[-n,"Diagnosis"] <- "Control"
  start <- as.numeric(y$hcdate - y$hcdate[1])/365.25
  end <- c(as.numeric(y$hcdate - y$hcdate[1])[-1]/365.25, as.numeric(y$dodx[n] - y
$hcdate[1])/365.25)
  return(data.frame(Diagnosis=y[,"Diagnosis"], start=start, end=end))
}))

bar[1:10, ]
```

| | **Diagnosis**<br><fctr> | **start**<br><dbl> | **end**<br><dbl> |
|---|---|---|---|
| PD29762 | AML | 0.000000 | 9.754962 |
| PD29764 | AML | 0.000000 | 10.360027 |
| PD29792 | AML | 0.000000 | 14.108145 |
| PD29810 | Control | 0.000000 | 18.573580 |
| PD29836.1 | Control | 0.000000 | 2.414784 |
| PD29836.2 | AML | 2.414784 | 10.023272 |
| PD29851.1 | Control | 0.000000 | 4.599589 |
| PD29851.2 | AML | 4.599589 | 12.205339 |
| PD29856.1 | Control | 0.000000 | 4.331280 |
| PD29856.2 | AML | 4.331280 | 17.828884 |

1-10 of 10 rows

```
sangerPatientsSplit <- unlist(sapply(names(foo), function(n) rep(n, nrow(foo[[n]])
)))

sangerSurv <- Surv(time = bar$start, time2 = bar$end, event = bar$Diagnosis!="Cont
rol", origin = 0)

plot(survfit(sangerSurv~ 1), col= "black", main = "VC", xlab='Time after first sam
ple (years)', ylab='AML-free fraction', bty='L', yaxs='i', ylim=c(0,1.01), mark.ti
me = T) #mark = 1
```




# 11.2 Expected AML incidence

Validation cohort

```
w <- c(which(sangerSurv[,1]==0)[-1]-1, nrow(sangerSurv))
sangerSurv2 <- Surv(sangerSurv[w,2], sangerSurv[w,3]) ## Unique individuals

expected_rate_sanger_cr <- mean(aml_inc_cr(sangerX[w,"gender"],sangerX[w,"age_10"]
*10, sangerX[w,"age_10"]*10+ pmax(1,sangerSurv2[,1]))[!sangerSurv2[,2]])

n_total_sanger <- sum(sangerSurv2[,2])/expected_rate_sanger_cr
n_total_sanger
```

```
## [1] 14208.3
```

Discovery cohort

```
expected_rate_toronto_cr <- mean(aml_inc_cr(torontoX[,"gender"],torontoX[,"age_10"
]*10, torontoX[,"age_10"]*10+ pmax(1,torontoSurv[,1]))[!torontoSurv[,2]])

n_total_toronto <- sum(torontoSurv[,2])/expected_rate_toronto_cr
n_total_toronto
```

```
## [1] 55688.66
```

# 11.3 Combined data

Survival

```
allSurv <- rbind(sangerSurv, Surv(rep(0, nrow(torontoSurv)), torontoSurv[,1], toro
ntoSurv[,2]))
allSurv <- Surv(allSurv[,1], allSurv[,2], allSurv[,3])
```

Data matrix

```
cohort <- c(rep("Sanger", nrow(sangerX)), rep("Toronto", nrow(torontoX)))
i <- c(sort(setdiff(gene_vars,"CALR")),"age","gender")
allX <- rbind(superSet(sangerData,i,fill=0), superSet(torontoData,i,fill=0))
allX <- allX[,colSums(allX>0)>=thr]
allX <- cbind(allX, cohort=cohort=="Sanger") + 0
allGroups <- factor(grepl("^[A-Z]",colnames(allX))+0, levels=1:0, labels=c("Genes"
,"Demographics"))

g <- allGroups=="Genes"
allX <- cbind(10*allX[,g], StandardizeMagnitude(allX[,!g]))
colnames(allX)[g] <- paste(colnames(allX)[g],"0.1",sep="_")
control <- c(sangerData$Diagnosis=="Control", torontoData$Diagnosis=="Control")
```

Weights

```
weights <- rep(1, nrow(allX))
weights[cohort=="Sanger" & control] <- n_total_sanger/sum(cohort=="Sanger" & contr
ol & allSurv[,1]==0)
weights[cohort=="Toronto" & control] <- n_total_toronto/sum(cohort=="Toronto" & co
ntrol)

n_total <- n_total_sanger + n_total_toronto
n_total
```

```
## [1] 69896.97
```

```
## [1] 69896.97
```

# 11.4 Coxph model fits

```
sigma0 <- 0.1
nu <- 1
which.mu <- "Genes"
```

## 11.4.1 DC

### 11.4.1.1 Raw

```
fitToronto <- CoxRFX(torontoX, torontoSurv, groups=torontoGroups, which.mu=which.m
u, nu=nu, sigma0=sigma0)
waldToronto <- WaldTest(fitToronto)
```

```
##                   group    coef   coef-mu     sd      z df  p.value sig
## ASXL1_0.1         Genes  0.4801  0.050389 0.1108  4.335  1 1.46e-05 ***
## CALR_0.1          Genes  0.4076 -0.022055 0.0700  5.824  1 5.76e-09 ***
## CBL_0.1           Genes  0.3119 -0.117817 0.1151  2.710  1 6.72e-03  **
## DNMT3A_0.1        Genes  0.3010 -0.128687 0.1054  2.857  1 4.28e-03  **
## IDH1_0.1          Genes  0.4535  0.023828 0.1092  4.152  1 3.29e-05 ***
## IDH2_0.1          Genes  0.3789 -0.050806 0.1052  3.602  1 3.15e-04 ***
## JAK2_0.1          Genes  0.4956  0.065922 0.1136  4.364  1 1.28e-05 ***
## KDM6A_0.1         Genes  0.4288 -0.000932 0.0594  7.214  1 5.45e-13 ***
## KMT2C_0.1         Genes  0.4450  0.015284 0.0619  7.194  1 6.28e-13 ***
## KRAS_0.1          Genes  0.4257 -0.004039 0.0595  7.156  1 8.31e-13 ***
## NF1_0.1           Genes  0.4272 -0.002451 0.0595  7.183  1 6.80e-13 ***
## PHF6_0.1          Genes  0.4321  0.002404 0.0598  7.230  1 4.83e-13 ***
## PTPN11_0.1        Genes  0.4414  0.011735 0.0596  7.407  1 1.29e-13 ***
## RUNX1_0.1         Genes  0.2761 -0.153642 0.0890  3.102  1 1.92e-03  **
## SF3B1_0.1         Genes  0.5346  0.104912 0.0892  5.993  1 2.06e-09 ***
## SRSF2_0.1         Genes  0.3772 -0.052539 0.0883  4.274  1 1.92e-05 ***
## TET2_0.1          Genes  0.4247 -0.005040 0.1174  3.617  1 2.98e-04 ***
## TP53_0.1          Genes  0.5441  0.114421 0.0665  8.181  1 2.81e-16 ***
## U2AF1_0.1         Genes  0.5788  0.149112 0.0722  8.015  1 1.10e-15 ***
## age_10     Demographics -0.3093 -0.309301 0.1116 -2.771  1 5.59e-03  **
## gender     Demographics -0.0253 -0.025329 0.1385 -0.183  1 8.55e-01
```

```
survConcordance(fitToronto$surv ~ fitToronto$linear.predictors, weights = weights[
cohort=="Toronto"])
```

```
## Call:
## survConcordance(formula = fitToronto$surv ~ fitToronto$linear.predictors,
##     weights = weights[cohort == "Toronto"])
##
##   n= 240
## Concordance= 0.7539084 se= 0.03193557
## concordant discordant  tied.risk  tied.time   std(c-d)
##  3255935.4  1062805.9        0.0        1.0   275842.9
```

### 11.4.1.2 Adjusted

```
fitWeightedToronto <- CoxRFX(torontoX, torontoSurv, torontoGroups, which.mu=which.
mu, sigma0=sigma0, nu=nu, weights=weights[cohort=="Toronto"])
waldWeightedToronto <- WaldTest(fitWeightedToronto)
```

```
##                   group    coef coef-mu    sd       z df  p.value sig
## ASXL1_0.1         Genes  1.9719  0.1365 0.150 13.1816  1 1.12e-39 ***
## CALR_0.1          Genes -0.0794 -1.9147 1.174 -0.0676  1 9.46e-01
## CBL_0.1           Genes  0.0165 -1.8188 0.426  0.0388  1 9.69e-01
## DNMT3A_0.1        Genes  0.3722 -1.4631 0.153  2.4301  1 1.51e-02   *
## IDH1_0.1          Genes  2.3375  0.5022 0.350  6.6815  1 2.36e-11 ***
## IDH2_0.1          Genes  0.5915 -1.2438 0.240  2.4621  1 1.38e-02   *
## JAK2_0.1          Genes  1.7762 -0.0592 0.193  9.2213  1 2.94e-20 ***
## KDM6A_0.1         Genes  1.6689 -0.1664 0.362  4.6081  1 4.06e-06 ***
## KMT2C_0.1         Genes -1.2330 -3.0683 1.191 -1.0356  1 3.00e-01
## KRAS_0.1          Genes  0.9875 -0.8478 0.555  1.7785  1 7.53e-02   .
## NF1_0.1           Genes  1.3623 -0.4730 0.501  2.7193  1 6.54e-03  **
## PHF6_0.1          Genes  2.6990  0.8636 0.255 10.5887  1 3.36e-26 ***
## PTPN11_0.1        Genes  3.6339  1.7986 0.723  5.0228  1 5.09e-07 ***
```

```
## RUNX1_0.1         Genes  0.6233 -1.2120 0.136  4.5906  1 4.42e-06 ***
## SF3B1_0.1         Genes  3.1088  1.2735 0.305 10.1981  1 2.02e-24 ***
## SRSF2_0.1         Genes  1.4956 -0.3397 0.172  8.6791  1 3.99e-18 ***
## TET2_0.1          Genes  0.5772 -1.2581 0.232  2.4920  1 1.27e-02   *
## TP53_0.1          Genes  8.9422  7.1069 0.823 10.8665  1 1.66e-27 ***
## U2AF1_0.1         Genes  4.0190  2.1836 0.384 10.4738  1 1.14e-25 ***
## age_10      Demographics -0.5274 -0.5274 0.135 -3.9171  1 8.96e-05 ***
## gender      Demographics  0.0323  0.0323 0.175  0.1842  1 8.54e-01
```

```
survConcordance(fitWeightedToronto$surv ~ fitWeightedToronto$linear.predictors, we
ights=weights[cohort=="Toronto"])
```

```
## Call:
## survConcordance(formula = fitWeightedToronto$surv ~ fitWeightedToronto$linear.p
redictors,
##     weights = weights[cohort == "Toronto"])
##
##   n= 240
## Concordance= 0.7701663 se= 0.03193557
## concordant discordant  tied.risk  tied.time   std(c-d)
##  3326148.9   992592.4        0.0        1.0   275842.9
```

```
#Uno's estimator of cumulative/dynamic AUC
a <- AUC.uno(torontoSurv, torontoSurv, fitWeightedToronto$linear.predictors, times
= seq(0,12, 0.1))
round(a$iauc, digits = 3)
```

```
## [1] 0.756
```

## 11.4.2 Validation cohort

### 11.4.2.1 Raw

```
fitSanger <- CoxRFX(sangerX, sangerSurv, groups=sangerGroups, which.mu=which.mu, n
u=nu, sigma0=sigma0)
waldSanger <- WaldTest(fitSanger)
```

```
##                    group     coef   coef-mu      sd       z df  p.value sig
## ASXL1_0.1          Genes  0.41389  1.04e-01 0.13253  3.1229  1 1.79e-03  **
## CBL_0.1            Genes  0.27978 -3.01e-02 0.10678  2.6202  1 8.79e-03  **
## DNMT3A_0.1         Genes  0.15476 -1.55e-01 0.12703  1.2183  1 2.23e-01
## JAK2_0.1           Genes  0.33012  2.02e-02 0.10874  3.0359  1 2.40e-03  **
## KMT2C_0.1          Genes  0.30175 -8.17e-03 0.09722  3.1037  1 1.91e-03  **
## KMT2D_0.1          Genes  0.14350 -1.66e-01 0.15722  0.9127  1 3.61e-01
## KRAS_0.1           Genes  0.30998  5.67e-05 0.09168  3.3811  1 7.22e-04 ***
## NF1_0.1            Genes  0.29225 -1.77e-02 0.09499  3.0768  1 2.09e-03  **
## NRAS_0.1           Genes  0.30685 -3.07e-03 0.09158  3.3507  1 8.06e-04 ***
## RAD21_0.1          Genes  0.29301 -1.69e-02 0.09373  3.1261  1 1.77e-03  **
## SF3B1_0.1          Genes  0.29894 -1.10e-02 0.09393  3.1825  1 1.46e-03  **
## SRSF2_0.1          Genes  0.40493  9.50e-02 0.13441  3.0125  1 2.59e-03  **
## TET2_0.1           Genes  0.37910  6.92e-02 0.11275  3.3624  1 7.73e-04 ***
## TP53_0.1           Genes  0.36746  5.75e-02 0.09308  3.9479  1 7.88e-05 ***
## U2AF1_0.1          Genes  0.37254  6.26e-02 0.09357  3.9813  1 6.85e-05 ***
## age_10       Demographics -0.01773 -1.77e-02 0.11451 -0.1548  1 8.77e-01
## gender       Demographics -0.03369 -3.37e-02 0.10501 -0.3208  1 7.48e-01
## systol_100         Blood  0.00145  1.45e-03 0.03839  0.0377  1 9.70e-01
## diastol_100        Blood  0.00773  7.73e-03 0.02329  0.3321  1 7.40e-01
## bmi_10             Blood  0.06828  6.83e-02 0.07091  0.9628  1 3.36e-01
## cholestl_10        Blood  0.01797  1.80e-02 0.01274  1.4109  1 1.58e-01
## triglyc            Blood  0.00471  4.71e-03 0.09569  0.0492  1 9.61e-01
## hdl                Blood -0.00891 -8.91e-03 0.07257 -0.1227  1 9.02e-01
## ldl                Blood  0.16056  1.61e-01 0.09725  1.6510  1 9.87e-02   .
## lym                Blood -0.02015 -2.01e-02 0.08835 -0.2280  1 8.20e-01
## mcv_100            Blood -0.00369 -3.69e-03 0.00786 -0.4694  1 6.39e-01
## rdw_10             Blood  0.05420  5.42e-02 0.02080  2.6056  1 9.17e-03  **
## wbc_10             Blood  0.00379  3.79e-03 0.03521  0.1077  1 9.14e-01
## plt_100            Blood  0.03410  3.41e-02 0.09166  0.3720  1 7.10e-01
## hgb_10             Blood  0.03314  3.31e-02 0.02245  1.4763  1 1.40e-01
```

```
survConcordance(sangerSurv ~ fitSanger$linear.predictors)
```

```
## Call:
## survConcordance(formula = sangerSurv ~ fitSanger$linear.predictors)
##
```

```
##   n= 173
## Concordance= 0.6611972 se= 0.05025086
## concordant discordant  tied.risk  tied.time   std(c-d)
##  2176.0000  1115.0000     0.0000     0.0000   330.7512
```

#### 11.4.2.2 Adjusted

```
fitWeightedSanger <- CoxRFX(sangerX, sangerSurv, sangerGroups, which.mu=which.mu,
sigma0=sigma0, nu=nu, weights=weights[cohort=="Sanger"])
waldWeightedSanger <- WaldTest(fitWeightedSanger)
```

```
##                   group      coef   coef-mu      sd         z df  p.value sig
## ASXL1_0.1         Genes  2.580959  1.414558 0.47618  5.42008  1 5.96e-08 ***
## CBL_0.1           Genes -0.660213 -1.826614 1.39628 -0.47284  1 6.36e-01
## DNMT3A_0.1        Genes  0.223151 -0.943251 0.24504  0.91066  1 3.62e-01
## JAK2_0.1          Genes  0.705927 -0.460474 1.04486  0.67562  1 4.99e-01
## KMT2C_0.1         Genes -0.385529 -1.551931 1.44435 -0.26692  1 7.90e-01
## KMT2D_0.1         Genes -0.627231 -1.793633 1.03607 -0.60539  1 5.45e-01
## KRAS_0.1          Genes  1.299133  0.132731 0.78999  1.64450  1 1.00e-01
## NF1_0.1           Genes -0.815764 -1.982166 1.46470 -0.55695  1 5.78e-01
## NRAS_0.1          Genes  0.728314 -0.438088 0.64251  1.13355  1 2.57e-01
## RAD21_0.1         Genes -0.678392 -1.844793 1.44210 -0.47042  1 6.38e-01
## SF3B1_0.1         Genes  0.072745 -1.093657 1.47708  0.04925  1 9.61e-01
## SRSF2_0.1         Genes  1.726024  0.559622 0.23912  7.21826  1 5.27e-13 ***
## TET2_0.1          Genes  1.101278 -0.065124 0.15079  7.30320  1 2.81e-13 ***
## TP53_0.1          Genes  4.694801  3.528400 1.13074  4.15198  1 3.30e-05 ***
## U2AF1_0.1         Genes  7.530821  6.364419 1.06931  7.04270  1 1.89e-12 ***
## age_10      Demographics -0.190256 -0.190256 0.13151 -1.44666  1 1.48e-01
## gender      Demographics -0.029742 -0.029742 0.12174 -0.24430  1 8.07e-01
## systol_100         Blood -0.032537 -0.032537 0.04764 -0.68293  1 4.95e-01
## diastol_100        Blood  0.000105  0.000105 0.02958  0.00356  1 9.97e-01
## bmi_10             Blood  0.098774  0.098774 0.08970  1.10111  1 2.71e-01
## cholestl_10        Blood  0.024226  0.024226 0.01553  1.55989  1 1.19e-01
## triglyc            Blood  0.051097  0.051097 0.11392  0.44854  1 6.54e-01
## hdl                Blood -0.082426 -0.082426 0.09326 -0.88380  1 3.77e-01
## ldl                Blood  0.248075  0.248075 0.11127  2.22950  1 2.58e-02   *
## lym                Blood -0.054414 -0.054414 0.10621 -0.51234  1 6.08e-01
## mcv_100            Blood -0.010783 -0.010783 0.00915 -1.17903  1 2.38e-01
## rdw_10             Blood  0.095279  0.095279 0.01797  5.30078  1 1.15e-07 ***
## wbc_10             Blood  0.011314  0.011314 0.04898  0.23099  1 8.17e-01
## plt_100            Blood  0.057755  0.057755 0.11248  0.51347  1 6.08e-01
## hgb_10             Blood  0.016212  0.016212 0.02615  0.62004  1 5.35e-01
```

```
waldWeightedSanger$p.adj <- p.adjust(p = waldWeightedSanger$p.value, method = "bon
ferroni")
#View(waldWeightedSanger)

survConcordance(sangerSurv ~ fitWeightedSanger$linear.predictors, weights=weights[
cohort=="Sanger"])
```

```
## Call:
## survConcordance(formula = sangerSurv ~ fitWeightedSanger$linear.predictors,
##     weights = weights[cohort == "Sanger"])
##
##   n= 173
## Concordance= 0.7231124 se= 0.0489519
## concordant discordant  tied.risk  tied.time   std(c-d)
##  296852.77  113668.16       0.00       0.00   40191.56
```

```
#Uno's estimator of cumulative/dynamic AUC
w <- c(which(sangerSurv[,1]==0)[-1]-1, nrow(sangerSurv))
s <- Surv(sangerSurv[w,2], sangerSurv[w,3])
a <- AUC.uno(s, s, fitWeightedSanger$linear.predictors[w], times= c(0, 22, 0.1))
round(a$iauc, digits = 3)
```

```
## [1] 0.403
```

# 12 CoxPH model excluding all samples without ARCH-PD

## 12.1 Discovery cohort

Data

```
f = "data/DC_vaf_matrix_414ctrl_91aml.csv"
torontoData <- read.csv(f)

gene_vars <- c("CALR", "NRAS", "DNMT3A", "SF3B1", "IDH1", "KIT", "TET2", "RAD21",
"JAK2", "CBL", "KRAS", "PTPN11", "IDH2", "TP53", "NF1", "SRSF2", "CEBPA", "ASXL1",
"RUNX1", "U2AF1", "BCOR", "KDM6A", "PHF6", "KMT2C", "KMT2D")

table(torontoData$Diagnosis)
```

```
##
##     AML Control
##      91     414
```

```
torontoData$gender <- ifelse(torontoData$Sex == "male", 1,
                             ifelse(torontoData$Sex == "female", 0, torontoData$Se
x))
dim(torontoData)
```

```
## [1] 505  29
```

```
torontoData <- torontoData[rowSums(torontoData[, colnames(torontoData) %in% gene_v
ars])>0, ]
dim(torontoData)
```

```
## [1] 221  29
```

```
table(torontoData$gender)
```

```
##
##   0   1
## 126  95
```

```
torontoData$gender <- as.numeric(torontoData$gender)
colnames(torontoData)
```

```
##  [1] "Sample"     "ASXL1"      "BCOR"       "CALR"       "CBL"        "DNMT3A"
"IDH1"       "IDH2"
##  [9] "JAK2"       "KDM6A"      "KIT"        "KMT2C"      "KRAS"       "NF1"
"NRAS"       "PHF6"
## [17] "PTPN11"     "RUNX1"      "SF3B1"      "SRSF2"      "TET2"       "TP53"
"U2AF1"      "Diagnosis"
## [25] "fu_years"   "age"        "Sex"        "no_drivers" "gender"
```

Manually standardize magnitudes

```
torontoData <- torontoData[!duplicated(torontoData),]

torontoX <- torontoData[, colnames(torontoData) %in% c(gene_vars, "age", "gender")
]

torontoX <- as.data.frame(torontoX)
thr <- 2
torontoX <- torontoX[,colSums(torontoX != 0)>=thr]

torontoGroups <- factor(names(torontoX) %in% c("age","gender")+1, level=1:2, label
s=c("Genes","Demographics"))
colnames(torontoX)
```

```
##  [1] "ASXL1"  "CALR"   "CBL"    "DNMT3A" "IDH1"   "IDH2"   "JAK2"   "KDM6A"  "K
MT2C"  "KRAS"   "NF1"    "PHF6"
## [13] "PTPN11" "RUNX1"  "SF3B1"  "SRSF2"  "TET2"   "TP53"   "U2AF1"  "age"    "g
ender"
```

```
torontoGroups
```

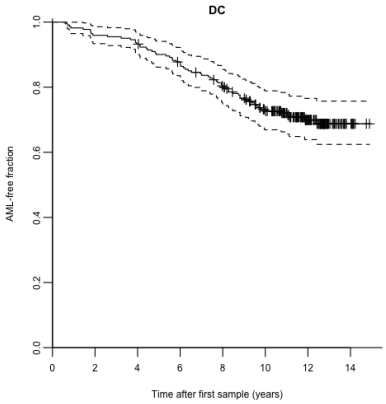
```
##  [1] Genes        Genes        Genes        Genes        Genes        Genes
Genes        Genes
##  [9] Genes        Genes        Genes        Genes        Genes        Genes
Genes        Genes
## [17] Genes        Genes        Genes        Demographics Demographics
## Levels: Genes Demographics
```

Manually standardize age and mutation VAFs

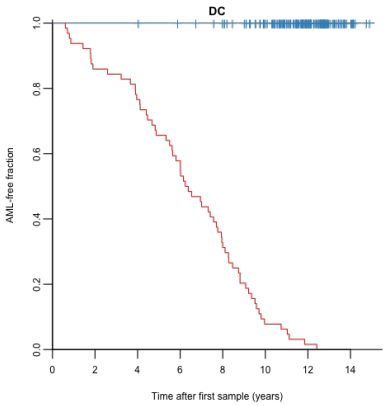
```
torontoX$age <- torontoX$age/10
names(torontoX)[which(names(torontoX)=="age")] <- "age_10"
g <- torontoGroups == "Genes"
torontoX[,g] <- torontoX[,g]*10
names(torontoX)[g] <- paste(names(torontoX)[g], "0.1",sep="_")
colnames(torontoX)
```

```
##  [1] "ASXL1_0.1"  "CALR_0.1"   "CBL_0.1"    "DNMT3A_0.1" "IDH1_0.1"   "IDH2_0.1
"   "JAK2_0.1"   "KDM6A_0.1"
##  [9] "KMT2C_0.1"  "KRAS_0.1"   "NF1_0.1"    "PHF6_0.1"   "PTPN11_0.1" "RUNX1_0.
1"  "SF3B1_0.1"  "SRSF2_0.1"
## [17] "TET2_0.1"   "TP53_0.1"   "U2AF1_0.1"  "age_10"     "gender"
```

```
torontoSurv <- Surv(torontoData$fu_years, torontoData$Diagnosis=="AML")
plot(survfit(torontoSurv~ 1), col= "black", main = "DC", xlab='Time after first sa
mple (years)', ylab='AML-free fraction', bty='L', yaxs='i', ylim=c(0,1.01), mark.t
ime = T)
```




```
plot(survfit(torontoSurv ~ torontoData$Diagnosis), xlab='Time after first sample (
years)', main = "DC", ylab='AML-free fraction', bty='L', yaxs='i', ylim=c(0,1.01),
mark.time = T, col = set1[1:2])
```




# 12.2 Validation cohort

```
f = "data/VC_vaf_matrix_no_duplicates_262ctrl_29aml_nodates.csv"
sangerData <- read.csv(f)
dim(sangerData)
```

```
## [1] 445  43
```

```
sangerData <- sangerData[rowSums(sangerData[, colnames(sangerData) %in% gene_vars]
)>0, ]
dim(sangerData)
```

```
## [1] 149  43
```

```
sangerData$hcdate <- as.Date(sangerData$hcdate)
sangerData$dodx <- as.Date(sangerData$dodx)

sangerPatients <- sub("[a-z]+$","", sangerData$Sample)
o <- order(sangerPatients, as.numeric(sangerData$hcdate))

sangerData <- sangerData[o,]
sangerPatients <- sangerPatients[o]

clinical_vars <- c("systol", "diastol", "bmi", "cholestl", "triglyc", "hdl", "ldl"
, "lym", "mcv", "rdw", "wbc", "plt", "hgb")
sangerX <- sangerData[, colnames(sangerData) %in% c(gene_vars, "age","gender",clin
ical_vars)]
sangerX <- as.data.frame(sangerX)

sangerX <- sangerX[,colSums(sangerX != 0,na.rm=TRUE)>=thr]
sangerGroups <- factor(grepl("^[a-z]", colnames(sangerX))*2, levels=0:2, labels=c(
"Genes", "Demographics", "Blood"))
sangerGroups[names(sangerX) %in% c("age","gender")] <- "Demographics"
table(sangerGroups)
```

```
## sangerGroups
##        Genes Demographics        Blood
##           15            2           13
```

```
colnames(sangerX)
```

```
##  [1] "ASXL1"    "CBL"      "DNMT3A"   "JAK2"     "KMT2C"    "KMT2D"    "KRAS"
"NF1"      "NRAS"     "RAD21"
## [11] "SF3B1"    "SRSF2"    "TET2"     "TP53"     "U2AF1"    "age"      "gender"
"systol"   "diastol"  "bmi"
## [21] "cholestl" "triglyc"  "hdl"      "ldl"      "lym"      "mcv"      "rdw"
"wbc"      "plt"      "hgb"
```

```
sangerGroups
```

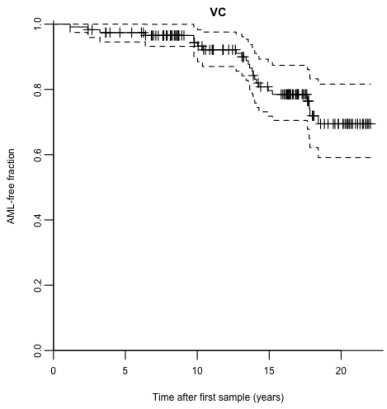
```
##  [1] Genes        Genes        Genes        Genes        Genes        Genes
Genes        Genes
##  [9] Genes        Genes        Genes        Genes        Genes        Genes
Genes        Demographics
## [17] Demographics Blood        Blood        Blood        Blood        Blood
Blood        Blood
## [25] Blood        Blood        Blood        Blood        Blood        Blood
## Levels: Genes Demographics Blood
```

```
g <- sangerGroups=="Genes"
sangerX[g] <- sangerX[g] * 10
names(sangerX)[g] <- paste(names(sangerX[g]),"0.1", sep="_")
y <- StandardizeMagnitude(sangerX[!g])
sangerX <- cbind(sangerX[g],y)

poorMansImpute <- function(x) {x[is.na(x)] <- mean(x, na.rm=TRUE); return(x)}
sangerX <- as.data.frame(sapply(sangerX, poorMansImpute))

foo <- split(sangerData[,c("Diagnosis","hcdate","dodx")], sangerPatients)

bar <- do.call("rbind",lapply(foo, function(x){
  y <- x
  n <- nrow(y)
  y[-n,"Diagnosis"] <- "Control"
  start <- as.numeric(y$hcdate - y$hcdate[1])/365.25
  end <- c(as.numeric(y$hcdate - y$hcdate[1])[-1]/365.25, as.numeric(y$dodx[n] - y
$hcdate[1])/365.25)
  return(data.frame(Diagnosis=y[,"Diagnosis"], start=start, end=end))
}))

bar[1:10, ]
```

| | **Diagnosis**<br><fctr> | **start**<br><dbl> | **end**<br><dbl> |
|---|---|---|---|
| PD29762 | AML | 0.000000 | 9.754962 |
| PD29764 | AML | 0.000000 | 10.360027 |
| PD29792 | AML | 0.000000 | 14.108145 |
| PD29810 | Control | 0.000000 | 18.573580 |
| PD29836.1 | Control | 0.000000 | 2.414784 |
| PD29836.2 | AML | 2.414784 | 10.023272 |
| PD29856 | AML | 0.000000 | 17.828884 |
| PD29896 | AML | 0.000000 | 6.387406 |
| PD29918.1 | Control | 0.000000 | 5.442847 |
| PD29918.2 | AML | 5.442847 | 13.396304 |

1-10 of 10 rows

```
sangerPatientsSplit <- unlist(sapply(names(foo), function(n) rep(n, nrow(foo[[n]])
)))

sangerSurv <- Surv(time = bar$start, time2 = bar$end, event = bar$Diagnosis!="Cont
rol", origin = 0)

plot(survfit(sangerSurv~ 1), col= "black", main = "VC", xlab='Time after first sam
ple (years)', ylab='AML-free fraction', bty='L', yaxs='i', ylim=c(0,1.01), mark.ti
me = T) #mark = 1
```



# 12.3 Expected AML incidence

Validation cohort

```
w <- c(which(sangerSurv[,1]==0)[-1]-1, nrow(sangerSurv))
sangerSurv2 <- Surv(sangerSurv[w,2], sangerSurv[w,3])

expected_rate_sanger_cr <- mean(aml_inc_cr(sangerX[w,"gender"],sangerX[w,"age_10"]
*10, sangerX[w,"age_10"]*10+ pmax(1,sangerSurv2[,1]))[!sangerSurv2[,2]])

n_total_sanger <- sum(sangerSurv2[,2])/expected_rate_sanger_cr
n_total_sanger
```

```
## [1] 9216.197
```

Discovery cohort

```
expected_rate_toronto_cr <- mean(aml_inc_cr(torontoX[,"gender"],torontoX[,"age_10"
]*10, torontoX[,"age_10"]*10+ pmax(1,torontoSurv[,1]))[!torontoSurv[,2]])

n_total_toronto <- sum(torontoSurv[,2])/expected_rate_toronto_cr
n_total_toronto
```

```
## [1] 42940.66
```

# 12.4 Combined data

Survival

```
allSurv <- rbind(sangerSurv, Surv(rep(0, nrow(torontoSurv)), torontoSurv[,1], toro
ntoSurv[,2]))
allSurv <- Surv(allSurv[,1], allSurv[,2], allSurv[,3])
```

Data matrix

```
cohort <- c(rep("Sanger", nrow(sangerX)), rep("Toronto", nrow(torontoX)))
i <- c(sort(setdiff(gene_vars,"CALR")),"age","gender")
allX <- rbind(superSet(sangerData,i,fill=0), superSet(torontoData,i,fill=0))
allX <- allX[,colSums(allX>0)>=thr]
allX <- cbind(allX, cohort=cohort=="Sanger") + 0
allGroups <- factor(grepl("^[A-Z]",colnames(allX))+0, levels=1:0, labels=c("Genes"
,"Demographics"))

g <- allGroups=="Genes"
allX <- cbind(10*allX[,g], StandardizeMagnitude(allX[,!g]))
colnames(allX)[g] <- paste(colnames(allX)[g],"0.1",sep="_")
control <- c(sangerData$Diagnosis=="Control", torontoData$Diagnosis=="Control")
```

Weights

```
weights <- rep(1, nrow(allX))
weights[cohort=="Sanger" & control] <- n_total_sanger/sum(cohort=="Sanger" & contr
ol & allSurv[,1]==0)
weights[cohort=="Toronto" & control] <- n_total_toronto/sum(cohort=="Toronto" & co
ntrol)

n_total <- n_total_sanger + n_total_toronto
n_total
```

```
## [1] 52156.85
```

# 12.5 Coxph model fits

```
sigma0 <- 0.1
nu <- 1
which.mu <- "Genes"
```

## 12.5.1 Toronto

### 12.5.1.1 Raw

```
fitToronto <- CoxRFX(torontoX, torontoSurv, groups=torontoGroups, which.mu=which.m
u, nu=nu, sigma0=sigma0)
```

```
d, nu=nu, sigma0=sigma0)
waldToronto <- WaldTest(fitToronto)
```

```
##                  group    coef   coef-mu     sd      z df  p.value sig
## ASXL1_0.1         Genes  0.5750  0.032700 0.1158  4.964  1 6.91e-07 ***
## CALR_0.1          Genes  0.5200 -0.022339 0.0744  6.990  1 2.74e-12 ***
## CBL_0.1           Genes  0.4268 -0.115522 0.1231  3.469  1 5.23e-04 ***
## DNMT3A_0.1        Genes  0.4724 -0.069936 0.1062  4.448  1 8.66e-06 ***
## IDH1_0.1          Genes  0.5730  0.030722 0.1188  4.822  1 1.42e-06 ***
## IDH2_0.1          Genes  0.4711 -0.071177 0.1126  4.184  1 2.86e-05 ***
## JAK2_0.1          Genes  0.6084  0.066072 0.1214  5.011  1 5.43e-07 ***
## KDM6A_0.1         Genes  0.5420 -0.000284 0.0628  8.629  1 6.17e-18 ***
## KMT2C_0.1         Genes  0.5603  0.017953 0.0656  8.545  1 1.29e-17 ***
## KRAS_0.1          Genes  0.5394 -0.002952 0.0628  8.583  1 9.20e-18 ***
## NF1_0.1           Genes  0.5404 -0.001954 0.0628  8.599  1 8.07e-18 ***
## PHF6_0.1          Genes  0.5469  0.004542 0.0632  8.655  1 4.91e-18 ***
## PTPN11_0.1        Genes  0.5556  0.013243 0.0631  8.810  1 1.25e-18 ***
## RUNX1_0.1         Genes  0.3347 -0.207621 0.0917  3.650  1 2.62e-04 ***
## SF3B1_0.1         Genes  0.6532  0.110858 0.0963  6.781  1 1.19e-11 ***
## SRSF2_0.1         Genes  0.4370 -0.105330 0.0920  4.750  1 2.03e-06 ***
## TET2_0.1          Genes  0.5053 -0.037059 0.1248  4.050  1 5.12e-05 ***
## TP53_0.1          Genes  0.7280  0.185639 0.0825  8.828  1 1.07e-18 ***
## U2AF1_0.1         Genes  0.7148  0.172443 0.0805  8.879  1 6.76e-19 ***
## age_10     Demographics -0.0236 -0.023625 0.1092 -0.216  1 8.29e-01
## gender     Demographics -0.0832 -0.083228 0.1113 -0.748  1 4.55e-01
```

```
survConcordance(fitToronto$surv ~ fitToronto$linear.predictors)
```

```
## Call:
## survConcordance(formula = fitToronto$surv ~ fitToronto$linear.predictors)
##
##   n= 221
## Concordance= 0.7806171 se= 0.03687602
## concordant discordant  tied.risk  tied.time   std(c-d)
##  8981.0000  2524.0000     0.0000     1.0000   848.5173
```

#### 12.5.1.2 Adjusted

```
fitWeightedToronto <- CoxRFX(torontoX, torontoSurv, torontoGroups, which.mu=which.
mu, sigma0=sigma0, nu=nu, weights=weights[cohort=="Toronto"])
waldWeightedToronto <- WaldTest(fitWeightedToronto)
```

```
##                  group    coef  coef-mu    sd      z df  p.value sig
## ASXL1_0.1         Genes  1.9878  0.06756 0.150 13.267  1 3.60e-40 ***
## CALR_0.1          Genes  0.6189 -1.30126 0.758  0.817  1 4.14e-01
## CBL_0.1           Genes  0.2531 -1.66705 0.379  0.668  1 5.04e-01
## DNMT3A_0.1        Genes  0.5859 -1.33434 0.136  4.313  1 1.61e-05 ***
## IDH1_0.1          Genes  2.4124  0.49218 0.341  7.083  1 1.41e-12 ***
## IDH2_0.1          Genes  0.8067 -1.11352 0.231  3.498  1 4.70e-04 ***
## JAK2_0.1          Genes  1.9535  0.03333 0.193 10.131  1 4.01e-24 ***
## KDM6A_0.1         Genes  1.9181 -0.00209 0.163 11.792  1 4.31e-32 ***
## KMT2C_0.1         Genes  2.3735  0.45328 0.730  3.250  1 1.16e-03  **
## KRAS_0.1          Genes  1.7434 -0.17684 0.195  8.955  1 3.38e-19 ***
## NF1_0.1           Genes  1.8059 -0.11434 0.190  9.518  1 1.77e-21 ***
## PHF6_0.1          Genes  2.2276  0.30741 0.144 15.462  1 6.24e-54 ***
## PTPN11_0.1        Genes  2.5970  0.67679 0.277  9.366  1 7.52e-21 ***
## RUNX1_0.1         Genes  0.7172 -1.20303 0.137  5.235  1 1.65e-07 ***
## SF3B1_0.1         Genes  3.2528  1.33260 0.321 10.149  1 3.36e-24 ***
## SRSF2_0.1         Genes  1.4698 -0.45035 0.170  8.656  1 4.91e-18 ***
## TET2_0.1          Genes  0.5707 -1.34952 0.211  2.699  1 6.96e-03  **
## TP53_0.1          Genes  5.2413  3.32111 0.440 11.916  1 9.82e-33 ***
## U2AF1_0.1         Genes  3.9483  2.02809 0.365 10.817  1 2.87e-27 ***
## age_10     Demographics -0.0820 -0.08201 0.117 -0.700  1 4.84e-01
## gender     Demographics -0.0899 -0.08989 0.117 -0.771  1 4.41e-01
```

```
survConcordance(fitWeightedToronto$surv ~ fitWeightedToronto$linear.predictors, we
ights=weights[cohort=="Toronto"])
```

```
## Call:
## survConcordance(formula = fitWeightedToronto$surv ~ fitWeightedToronto$linear.p
redictors,
```

```
##     weights = weights[cohort == "Toronto"])
##
##   n= 221
## Concordance= 0.8454794 se= 0.03633541
## concordant discordant  tied.risk  tied.time   std(c-d)
##  2196217.1   401382.8        0.0        1.0   188769.7
```

Uno's estimator of cumulative/dynamic AUC

```
a <- AUC.uno(torontoSurv, torontoSurv, fitWeightedToronto$linear.predictors, times
= seq(0,12, 0.1))
round(a$iauc, digits = 3)
```

```
## [1] 0.791
```

## 12.5.2 Validation cohort

### 12.5.2.1 Raw

```
fitSanger <- CoxRFX(sangerX, sangerSurv, groups=sangerGroups, which.mu=which.mu, n
u=nu, sigma0=sigma0)
waldSanger <- WaldTest(fitSanger)
```

```
##                    group      coef   coef-mu      sd        z df  p.value sig
## ASXL1_0.1          Genes  0.673478  0.158950 0.12882  5.22794  1 1.71e-07 ***
## CBL_0.1            Genes  0.495353 -0.019175 0.10735  4.61426  1 3.94e-06 ***
## DNMT3A_0.1         Genes  0.328415 -0.186113 0.13178  2.49210  1 1.27e-02   *
## JAK2_0.1           Genes  0.493355 -0.021173 0.11739  4.20278  1 2.64e-05 ***
## KMT2C_0.1          Genes  0.519077  0.004549 0.10042  5.16888  1 2.36e-07 ***
## KMT2D_0.1          Genes  0.341708 -0.172820 0.16670  2.04989  1 4.04e-02   *
## KRAS_0.1           Genes  0.517799  0.003272 0.09650  5.36592  1 8.05e-08 ***
## NF1_0.1            Genes  0.501902 -0.012625 0.09919  5.06022  1 4.19e-07 ***
## NRAS_0.1           Genes  0.534425  0.019897 0.09703  5.50790  1 3.63e-08 ***
## RAD21_0.1          Genes  0.503868 -0.010660 0.09793  5.14544  1 2.67e-07 ***
## SF3B1_0.1          Genes  0.507855 -0.006673 0.09801  5.18184  1 2.20e-07 ***
## SRSF2_0.1          Genes  0.529928  0.015400 0.14168  3.74021  1 1.84e-04 ***
## TET2_0.1           Genes  0.593720  0.079192 0.12273  4.83743  1 1.32e-06 ***
## TP53_0.1           Genes  0.584538  0.070010 0.09773  5.98121  1 2.21e-09 ***
## U2AF1_0.1          Genes  0.592496  0.077968 0.09770  6.06442  1 1.32e-09 ***
## age_10       Demographics  0.084731  0.084731 0.12166  0.69645  1 4.86e-01
## gender       Demographics -0.007960 -0.007960 0.10340 -0.07698  1 9.39e-01
## systol_100          Blood  0.033564  0.033564 0.03644  0.92111  1 3.57e-01
## diastol_100         Blood  0.032432  0.032432 0.02299  1.41095  1 1.58e-01
## bmi_10              Blood  0.081752  0.081752 0.06892  1.18610  1 2.36e-01
## cholestl_10         Blood  0.014082  0.014082 0.01344  1.04742  1 2.95e-01
## triglyc             Blood -0.000827 -0.000827 0.10813 -0.00765  1 9.94e-01
## hdl                 Blood -0.007587 -0.007587 0.06927 -0.10952  1 9.13e-01
## ldl                 Blood  0.134372  0.134372 0.11043  1.21684  1 2.24e-01
## lym                 Blood  0.076500  0.076500 0.08867  0.86278  1 3.88e-01
## mcv_100             Blood -0.012801 -0.012801 0.00713 -1.79436  1 7.28e-02   .
## rdw_10              Blood  0.058557  0.058557 0.01828  3.20254  1 1.36e-03  **
## wbc_10              Blood  0.016691  0.016691 0.03908  0.42707  1 6.69e-01
## plt_100             Blood  0.095820  0.095820 0.09229  1.03821  1 2.99e-01
## hgb_10              Blood  0.006904  0.006904 0.01981  0.34856  1 7.27e-01
```

```
survConcordance(sangerSurv ~ fitSanger$linear.predictors)
```

```
## Call:
## survConcordance(formula = sangerSurv ~ fitSanger$linear.predictors)
##
##   n= 149
## Concordance= 0.7918502 se= 0.06247796
## concordant discordant  tied.risk  tied.time   std(c-d)
##    1438.00     378.00       0.00       0.00     226.92
```

### 12.5.2.2 Adjusted

```
fitWeightedSanger <- CoxRFX(sangerX, sangerSurv, sangerGroups, which.mu=which.mu,
sigma0=sigma0, nu=nu, weights=weights[cohort=="Sanger"])
waldWeightedSanger <- WaldTest(fitWeightedSanger)
```

```
##                    group    coef coef-mu     sd       z df  p.value sig
```

```
## ASXL1_0.1          Genes  3.2736  1.1639 0.5035  6.5016  1 7.95e-11 ***
## CBL_0.1            Genes  0.4415 -1.6682 1.4885  0.2966  1 7.67e-01
## DNMT3A_0.1         Genes  0.5963 -1.5134 0.2434  2.4497  1 1.43e-02   *
## JAK2_0.1           Genes -0.0225 -2.1322 1.0506 -0.0214  1 9.83e-01
## KMT2C_0.1          Genes  0.8233 -1.2864 1.4975  0.5498  1 5.82e-01
## KMT2D_0.1          Genes -0.1936 -2.3033 0.9186 -0.2108  1 8.33e-01
## KRAS_0.1           Genes  2.6546  0.5449 0.6402  4.1468  1 3.37e-05 ***
## NF1_0.1            Genes  0.8839 -1.2258 1.4275  0.6192  1 5.36e-01
## NRAS_0.1           Genes  4.8796  2.7699 0.6294  7.7532  1 8.96e-15 ***
## RAD21_0.1          Genes  0.8665 -1.2432 1.4103  0.6144  1 5.39e-01
## SF3B1_0.1          Genes  1.2701 -0.8396 1.4768  0.8601  1 3.90e-01
## SRSF2_0.1          Genes  1.6909 -0.4188 0.2626  6.4399  1 1.20e-10 ***
## TET2_0.1           Genes  1.3640 -0.7457 0.1595  8.5534  1 1.19e-17 ***
## TP53_0.1           Genes  5.1102  3.0005 1.0728  4.7634  1 1.90e-06 ***
## U2AF1_0.1          Genes  8.0069  5.8972 0.9739  8.2214  1 2.01e-16 ***
## age_10       Demographics -0.0522 -0.0522 0.1212 -0.4306  1 6.67e-01
## gender       Demographics -0.0216 -0.0216 0.0988 -0.2185  1 8.27e-01
## systol_100          Blood  0.0064  0.0064 0.0409  0.1566  1 8.76e-01
## diastol_100         Blood  0.0251  0.0251 0.0269  0.9320  1 3.51e-01
## bmi_10              Blood  0.0956  0.0956 0.0826  1.1574  1 2.47e-01
## cholestl_10         Blood  0.0143  0.0143 0.0155  0.9246  1 3.55e-01
## triglyc             Blood -0.0533 -0.0533 0.1279 -0.4169  1 6.77e-01
## hdl                 Blood -0.0505 -0.0505 0.0839 -0.6015  1 5.48e-01
## ldl                 Blood  0.2011  0.2011 0.1239  1.6229  1 1.05e-01
## lym                 Blood  0.0499  0.0499 0.0996  0.5009  1 6.16e-01
## mcv_100             Blood -0.0238 -0.0238 0.0075 -3.1777  1 1.48e-03  **
## rdw_10              Blood  0.0832  0.0832 0.0142  5.8698  1 4.36e-09 ***
## wbc_10              Blood  0.0108  0.0108 0.0544  0.1988  1 8.42e-01
## plt_100             Blood  0.1509  0.1509 0.1056  1.4297  1 1.53e-01
## hgb_10              Blood -0.0224 -0.0224 0.0217 -1.0308  1 3.03e-01
```

```
survConcordance(sangerSurv ~ fitWeightedSanger$linear.predictors, weights=weights[
cohort=="Sanger"])
```

```
## Call:
## survConcordance(formula = sangerSurv ~ fitWeightedSanger$linear.predictors,
##     weights = weights[cohort == "Sanger"])
##
##   n= 149
## Concordance= 0.8671072 se= 0.06105924
## concordant discordant  tied.risk  tied.time   std(c-d)
##  135478.93   20763.49       0.00       0.00   19080.09
```

Uno's estimator of cumulative/dynamic AUC

```
w <- c(which(sangerSurv[,1]==0)[-1]-1, nrow(sangerSurv))
s <- Surv(sangerSurv[w,2], sangerSurv[w,3])
a <- AUC.uno(s, s, fitWeightedSanger$linear.predictors[w], times= c(0, 22, 0.1))
round(a$iauc, digits = 3)
```

```
## [1] 0.587
```

# 13 Session

```
devtools::session_info()
```

```
## Session info -------------------------------------------------------------
-----------------------------------------
```

```
##  setting  value
##  version  R version 3.5.1 (2018-07-02)
##  system   x86_64, darwin17.6.0
##  ui       X11
##  language (EN)
##  collate  C
##  tz       Europe/London
##  date     2018-07-24
```

```
## Packages -----------------------------------------------------------------
-----------------------------------------
```

```
##  package      * version  date       source
##  abind          1.4-5    2016-07-21 CRAN (R 3.5.1)
##  assertthat     0.2.0    2017-04-11 CRAN (R 3.5.1)
```

```
##  backports      1.1.2    2017-12-13 cran (@1.1.2)
##  base         * 3.5.1    2018-07-09 local
##  bindr          0.1.1    2018-03-13 CRAN (R 3.5.1)
##  bindrcpp       0.2.2    2018-03-29 CRAN (R 3.5.1)
##  bitops         1.0-6    2013-08-17 CRAN (R 3.5.1)
##  broom          0.5.0    2018-07-17 cran (@0.5.0)
##  car            3.0-0    2018-04-02 CRAN (R 3.5.1)
##  carData        3.0-1    2018-03-28 CRAN (R 3.5.1)
##  caTools        1.17.1.1 2018-07-20 CRAN (R 3.5.1)
##  cellranger     1.1.0    2016-07-27 CRAN (R 3.5.1)
##  codetools      0.2-15   2016-10-05 CRAN (R 3.5.1)
##  compiler       3.5.1    2018-07-09 local
##  CoxHD        * 0.0.73   2018-07-23 Github (gerstung-lab/CoxHD@bc60c16)
##  crayon         1.3.4    2017-09-16 CRAN (R 3.5.1)
##  curl           3.2      2018-03-28 CRAN (R 3.5.1)
##  data.table     1.11.4   2018-05-27 CRAN (R 3.5.1)
##  datasets     * 3.5.1    2018-07-09 local
##  devtools       1.13.6   2018-06-27 CRAN (R 3.5.1)
##  digest         0.6.15   2018-01-28 CRAN (R 3.5.1)
##  dplyr        * 0.7.6    2018-06-29 CRAN (R 3.5.1)
##  evaluate       0.11     2018-07-17 CRAN (R 3.5.1)
##  forcats        0.3.0    2018-02-19 cran (@0.3.0)
##  foreach      * 1.4.4    2017-12-12 CRAN (R 3.5.1)
##  foreign        0.8-71   2018-07-20 CRAN (R 3.5.1)
##  gdata          2.18.0   2017-06-06 CRAN (R 3.5.1)
##  glmnet       * 2.0-16   2018-04-02 CRAN (R 3.5.1)
##  glue           1.3.0    2018-07-17 CRAN (R 3.5.1)
##  gplots       * 3.0.1    2016-03-30 CRAN (R 3.5.1)
##  graphics     * 3.5.1    2018-07-09 local
##  grDevices    * 3.5.1    2018-07-09 local
##  grid           3.5.1    2018-07-09 local
##  gtools         3.8.1    2018-06-26 CRAN (R 3.5.1)
##  haven          1.1.2    2018-06-27 cran (@1.1.2)
##  hms            0.4.2    2018-03-10 CRAN (R 3.5.1)
##  htmltools      0.3.6    2017-04-28 CRAN (R 3.5.1)
##  iterators      1.0.10   2018-07-13 CRAN (R 3.5.1)
##  jomo           2.6-2    2018-04-26 cran (@2.6-2)
##  jsonlite       1.5      2017-06-01 CRAN (R 3.5.1)
##  KernSmooth     2.23-15  2015-06-29 CRAN (R 3.5.1)
##  knitr        * 1.20     2018-02-20 CRAN (R 3.5.1)
##  lattice        0.20-35  2017-03-25 CRAN (R 3.5.1)
##  lme4           1.1-17   2018-04-03 cran (@1.1-17)
##  magrittr       1.5      2014-11-22 CRAN (R 3.5.1)
##  MASS           7.3-50   2018-04-30 cran (@7.3-50)
##  Matrix       * 1.2-14   2018-04-09 CRAN (R 3.5.1)
##  memoise        1.1.0    2017-04-21 CRAN (R 3.5.1)
##  methods      * 3.5.1    2018-07-09 local
##  mg14           0.0.5    2018-07-23 Github (mg14/mg14@6a63283)
##  mice           3.1.0    2018-06-20 cran (@3.1.0)
##  minqa          1.2.4    2014-10-09 cran (@1.2.4)
##  mitml          0.3-6    2018-07-10 cran (@0.3-6)
##  mvtnorm        1.0-8    2018-05-31 cran (@1.0-8)
##  nlme           3.1-137  2018-04-07 cran (@3.1-137)
##  nloptr         1.0.4    2017-08-22 cran (@1.0.4)
##  nnet           7.3-12   2016-02-02 cran (@7.3-12)
##  openxlsx       4.1.0    2018-05-26 CRAN (R 3.5.1)
##  pan            1.6      2018-06-29 cran (@1.6)
##  parallel     * 3.5.1    2018-07-09 local
##  pillar         1.3.0    2018-07-14 CRAN (R 3.5.1)
##  pkgconfig      2.0.1    2017-03-21 CRAN (R 3.5.1)
##  purrr          0.2.5    2018-05-29 CRAN (R 3.5.1)
##  R6             2.2.2    2017-06-17 CRAN (R 3.5.1)
##  RColorBrewer * 1.1-2    2014-12-07 CRAN (R 3.5.1)
##  Rcpp           0.12.18  2018-07-23 CRAN (R 3.5.1)
##  readr        * 1.1.1    2017-05-16 CRAN (R 3.5.1)
##  readxl         1.1.0    2018-04-20 CRAN (R 3.5.1)
##  rio            0.5.10   2018-03-29 CRAN (R 3.5.1)
##  rj           * 2.0.5-2  2018-07-23 local
##  rj.gd          2.0.0-1  2018-07-23 local
##  rlang          0.2.1    2018-05-30 CRAN (R 3.5.1)
##  rmarkdown      1.10     2018-06-11 CRAN (R 3.5.1)
##  ROCR         * 1.0-7    2015-03-26 CRAN (R 3.5.1)
##  rpart          4.1-13   2018-02-23 cran (@4.1-13)
##  rprojroot      1.3-2    2018-01-03 CRAN (R 3.5.1)
##  splines        3.5.1    2018-07-09 local
##  stats        * 3.5.1    2018-07-09 local
##  stringi        1.2.4    2018-07-20 CRAN (R 3.5.1)
##  stringr      * 1.3.1    2018-05-10 CRAN (R 3.5.1)
##  survAUC      * 1.0-5    2012-09-04 CRAN (R 3.5.1)
##  survival     * 2.42-6   2018-07-13 CRAN (R 3.5.1)
##  survivalROC  * 1.0.3    2013-01-13 CRAN (R 3.5.1)
##  tibble         1.4.2    2018-01-22 CRAN (R 3.5.1)
##  tidyr          0.8.1    2018-05-18 cran (@0.8.1)
```

```
##  tidyselect     0.2.4    2018-02-26 CRAN (R 3.5.1)
##  tools          3.5.1    2018-07-09 local
##  utils        * 3.5.1    2018-07-09 local
##  withr          2.1.2    2018-03-15 CRAN (R 3.5.1)
##  yaml           2.1.19   2018-05-01 CRAN (R 3.5.1)
##  zip            1.0.0    2017-04-25 CRAN (R 3.5.1)
```

This code and all data necessary to execute it is available from http://www.github.com/gerstung-lab/ (http://www.github.com/gerstung-lab/)