Package 'diagmeta'

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Title Meta-Analysis of Diagnostic Accuracy Studies with Several Cutpoints

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URL https://github.com/guido-s/diagmeta

Description Provides methods by Steinhauser et al. (2016) <<u>DOI:10.1186/s12874-016-0196-</u> 1> for meta-analysis of diagnostic accuracy studies with several cutpoints.

License GPL (≥ 2)

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diagmeta-package diagmeta: Brief overview of methods and general hints

Description

R package **diagmeta** implements the method by Steinhauser et al. (2016) for the meta-analysis of diagnostic test accuracy studies with multiple cutoffs.

Details

Main function of R package **diagmeta** is the eponymous diagmeta. Corresponding functions for printing and plotting are available: print.diagmeta, plot.diagmeta

Furthermore, a summary function and corresponding print function are available to provide a briefer output: summary.diagmeta, print.summary.diagmeta

Additional functions provided in **diagmeta** are diagstats to calculate additional statistical measures for the diagnostic test accuracy meta-analysis and ipd2diag to transform individual participant data to the data format required by diagmeta.

Type help(package = "diagmeta") for a listing of R functions and datasets available in diagmeta.

Type citation("diagmeta") for the preferred citation of R package diagmeta.

To report problems and bugs

- type bug.report(package = "diagmeta") if you do not use RStudio,
- send an email to Guido Schwarzer <guido.schwarzer@uniklinik-freiburg.de>if you use RStudio.

The development version of diagmeta is available on GitHub https://github.com/guido-s/diagmeta.

Author(s)

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References

Steinhauser S, Schumacher M, Rücker G (2016): Modelling multiple thresholds in meta-analysis of diagnostic test accuracy studies. *BMC Medical Research Methodology*, **16**, 97

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as.data.frame.diagmeta

Extract data frame from diagmeta objects

Description

Extract data frame from objects of class diagmeta.

Usage

```
## S3 method for class 'diagmeta'
as.data.frame(x, row.names = NULL, optional = FALSE, ...)
```

Arguments

х	An object of class diagmeta.
row.names	Argument of R function as.data.frame (ignored).
optional	Argument of R function as.data.frame (ignored).
	Other arguments.

Value

A data frame is returned by the function as.data.frame.

Author(s)

Guido Schwarzer <guido.schwarzer@uniklinik-freiburg.de>

See Also

diagmeta summary.diagmeta

Examples

as.data.frame(diag1)

diagmeta

Meta-analysis of diagnostic test accuracy studies with the multiple cutoffs model

Description

Diagnostic tests may be based on an ordinal or continuous biomarker or an ordinal score together with a cutoff. The decision whether the target condition is present or not (positive or negative test result) depends on whether the observed value is above or below the cutoff. Here we assume that higher values of the biomarker indicate a greater probability for the target condition (e.g., a disease); otherwise, the poling must be changed by multiplying all values of the biomarker by -1. Sensitivity and specificity of the test depend on the chosen cutoff and vary with the cutoff. In meta-analysis of diagnostic accuracy studies, results are often reported for multiple cutoffs within a study, and the cutoffs may differ between studies. The multiple cutoffs model creates a link between the range of cutoffs and the respective pairs of sensitivity and specificity and thus allows identifying cutoffs at which the test is likely to perform best (Steinhauser et al., 2016).

Usage

```
diagmeta(
  TΡ,
 FΡ,
  TN.
  FN.
  cutoff,
  studlab,
  data = NULL,
  distr = "logistic",
 model = "CICS",
  equalvar = FALSE,
  lambda = 0.5,
  log.cutoff = FALSE,
 method.weights = "invvar",
 level = 0.95,
  incr = 0.5,
  n.iter.max = 1000,
  tol = 1e-08,
  silent = TRUE,
)
```

Arguments

TP, FP, TN, FN	Numeric vectors giving the number of true positives, false positives, true nega- tives and false negatives
cutoff	A number vector indicating the cutoff values

diagmeta

studlab	A numeric or a character vector with study labels
data	An optional data frame containing the study information
distr	A character indicating the distribution (see Details)
model	A character indicating the model (see Details)
equalvar	A logical indicating whether the variances of the biomarker in both groups are thought equal (see Details)
lambda	A numeric between 0 and 1 indicating the weight of the sensitivity (such that specificity receives weight 1 - lambda)
log.cutoff	A logical indicating whether the cutoffs should be log-transformed
method.weights	A character indicating the method for weighting the studies: invvar (default) means inverse variance weighting, size means weighting by group sample size, equal means that all studies are equally weighted
level	A numeric indicating the significance level (1 - alpha) for tests (default is 0.95)
incr	A numeric between 0 and 1 that is added as a continuity correction
n.iter.max	A numeric indicating the maximal number of common point iterations for find- ing the optimal cutoff
tol	A numeric indicating the tolerance for convergence of the common point itera- tion
silent	A logical indicating whether iterations should be suppressed
	additional arguments

Details

Each row of the data set provides at least a study label, a cutoff and the numbers of true positives, false positives, true negatives and false negatives. Different studies may contribute a varying number of cutoffs, as well as different sets of cutoffs.

The multiple cutoffs model is a multi-level random effects model. At the study level, for the group of patients without the target condition (in short disease-free), the specificities at all available cutoffs together provide an estimate of the cumulative distribution function (cdf) of the test results within the disease-free individuals. Likewise, for patients with the target condition (in short diseased), via the observed sensitivities at all observed cutoffs we obtain an estimate of the cdf of the test results within the diseased patients. At the meta-analytic level, the model fits the data for both groups and all available cutoffs over all studies. Based on a parametric model, it provides estimates of the two cdfs for the two groups across all studies, accounting for the between-study heterogeneity and correlation between groups.

Users have the choice between the normal (argument distr="normal") and the logistic distribution (argument distr="logistic" which is the default). In addition, it is possible to log-transform the cutoffs (argument log.cutoff, default is FALSE).

The cdf, transformed using the quantile function of the chosen distribution, is modelled by one of eight mixed linear models ("DIDS", "CIDS", "DICS", "CICS", "DS", "CS", "DI", "CI") as described in Steinhauser et al. (2016). The argument equalvar indicates if the variances of the biomarker in both groups are assumed to be equal (equalvar = TRUE) or unequal (equalvar = FALSE).

The pooled sensitivity and specificity values can be obtained at every cutoff; a multiple cutoffs summary ROC (sROC) naturally follows while preserving cutoff information. The optimal cutoff is defined as the cutoff where the maximum of a weighted sum of sensitivity and specificity is obtained: lambda * sensitivity + (1 - lambda) * specificity. The 95% confidence intervals of sensitivities, specificities and the optimal cutoff are estimated using the delta method (Steinhauser et al., 2016).

Value

An object of class "diagmeta" with corresponding print, summary, and plot function. The object is a list containing the following components

TP, FP, TN, FN	As defined above
cutoff, studlab	
,	As defined above.
Sens	Sensitivity (original data).
Spec	Specificity (original data).
distr, model, eq	ualvar, lambda
	As defined above.
<pre>log.cutoff, meth</pre>	nod.weights
	As defined above.
level, incr	As defined above.
k	The number of studies in the meta-analysis.
optcut	The optimal cutoff.
lower.optcut, up	oper.optcut
	Corresponding lower and upper confidence limits (for normal distribution).
Sens.optcut	The sensitivity at the optimal cutoff.
lower.Sens.optc	ut, upper.Sens.optcut
	Corresponding lower and upper confidence limits.
Spec.optcut	The specificity at the optimal cutoff.
<pre>lower.Spec.optc</pre>	ut, upper.Spec.optcut
	Corresponding lower and upper confidence limits.
AUCSens, AUCSpec	
	Area under the curve (AUC)
AUCSens.lower, A	
	Corresponding lower and upper confidence limits (based on the confidence re- gion for the sensitivity, given the specificity)
AUCSpec.lower, A	NUCSpec.upper
	Corresponding lower and upper confidence limits (based on the confidence re- gion for the specificity, given the sensitivity)
var.diseased, va	ar.nondiseased
	The within-study variance for the diseased and non-diseased group, respectively.
AIC	The value of the Akaike information criterion of the lmer object.
BIC	The value of the Bayesian information criterion of the lmer object.

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diagmeta

data.lmer	A list with elements Study (study labels), Group (group labels (0 or 1)), Cutoff, N (group sizes), Negative (number of negative test results), NN (frequencies of negative test results).
result.lmer	An object of class lmer.
weights	Normalized weights per study, group, and cutoff such that the sum of weights is twice the number of cutoffs over all studies.
regr	A list with point estimates, variances, and covariances from regression parameters of lmer object.
dist	A list containing estimated means, standard deviations, and variances of distributions from diseased (ending with 1) and non-diseased (ending with 0).
Cov.common	Covariance matrix from common effects model.
call	Function call.
version	Version of R package diagmeta used to create object.

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References

Steinhauser S, Schumacher M, Rücker G (2016): Modelling multiple thresholds in meta-analysis of diagnostic test accuracy studies. *BMC Medical Research Methodology*, **16**, 97

See Also

plot.diagmeta, summary.diagmeta

diagstats

Description

The user can provide cutoffs, sensitivities, and / or specificities to calculate the respective quantities (with confidence intervals). Furthermore, positive predictive values (PPV), negative predictive values (NPV), and probabilities of disease (PD) are calculated if the prevalence is provided.

Usage

```
diagstats(x, cutoff = x$optcut, sens, spec, prevalence, level = 0.95)
```

Arguments

х	An object of class diagmeta
cutoff	A numeric or vector with cutoff value(s)
sens	A numeric or vector with sensitivity value(s)
spec	A numeric or vector with specificity value(s)
prevalence	A numeric or vector with the prevalence(s)
level	The level used to calculate confidence intervals

Value

A data frame of class "diagstats" with the following variables:

cutoff	Cutoffs provided in argument "cutoff" and / or model-based cutoff values for given sensitivities / specificities.
Sens	Sensitivities provided in argument "sens" and / or model-based estimates of the sensitivity for given cutoffs / specificities
seSens	Standard error of sensitivity
lower.Sens, upp	er.Sens
	Lower and upper confidence limits of the sensitivity
Spec	Specificities provided in argument "spec" and / or model-based estimates of the specificity for given cutoffs / sensitivities
seSpec	Standard error of specificity
lower.Spec, upp	er.Spec
	Lower and upper confidence limits of the specificity
prevalence	As defined above.
PPV	Positive predictive value (based on the cutoff)
NPV	Negative predictive value (based on the cutoff)

ipd2diag

PD	Probability of disease if the given cutoff value was observed as the measurement
	for an individual
dens.nondisease	ed
	Value of the model-based density function at the cutoff(s) for non-diseased in- dividuals
dens.diseased	Value of the model-based density function at the cutoff(s) for diseased individ- uals

Author(s)

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See Also

diagmeta print.diagstats

Examples

```
# FENO dataset
#
data(Schneider2017)
diag1 <- diagmeta(tpos, fpos, tneg, fneg, cutpoint,</pre>
                  studlab = paste(author, year, group),
                  data = Schneider2017,
                  log.cutoff = TRUE)
# Results at the optimal cutoff
#
diagstats(diag1)
# Results for cutoffs 25 and 50 (and a prevalence of 10%)
#
diagstats(diag1, c(25, 50), prevalence = 0.10)
# Results for sensitivity and specificity of 0.95
#
diagstats(diag1, sens = 0.95, spec = 0.95)
```

ipd2diag

Individual participant data to enter them into diagmeta

Description

Function to transform individual patient data (IPD) to enter them into diagmeta

Usage

ipd2diag(studlab, value, status)

Arguments

studlab	A vector with study labels
value	A vector with individual patients' measurements of a discrete or continuous variable
status	A vector with information of the individual's status ($0 = \text{non-diseased}$, $1 = \text{diseased}$)

Value

A data frame with values that can be entered into diagmeta.

Author(s)

Gerta Rücker <gerta.ruecker@uniklinik-freiburg.de>, Srinath Kolampally <kolampal@imbi.uni-freiburg.de>

See Also

diagmeta, plot.diagmeta, print.diagmeta, summary.diagmeta

```
# Simulate IPD data for three studies, each with 30 patients based
# on normally distributed marker values
#
set.seed(20)
k <- 3
n <- 60
m <- c(20, 23, 26)
d <- 10
s <- 5
studlab <- c(rep(1, n), rep(2, n), rep(3, n))</pre>
status <- rep(c(rep(0, n / 2), rep(1, n / 2)), k)</pre>
measurement <- c(rnorm(n / 2, m[1], s), rnorm(n/2, m[1] + d, s),</pre>
                  rnorm(n / 2, m[2], s), rnorm(n/2, m[2] + d, s),
                  rnorm(n / 2, m[3], s), rnorm(n/2, m[3] + d, s))
#
IPDdata <- data.frame(studlab, measurement, status)</pre>
str(IPDdata)
# Transform these data using ipd2diag()
#
diagdata <- ipd2diag(studlab, value = measurement, status = status)</pre>
str(diagdata)
# Run diagmeta()
#
diag1 <- diagmeta(TP, FP, TN, FN, cutoff, studlab,</pre>
```

plot.diagmeta

```
plot.diagmeta
```

Plot for meta-analysis of diagnostic test accuracy studies with the multiple cutoffs model

Description

Provides several plots for meta-analysis of diagnostic test accuracy studies with the multiple cutoffs model

Usage

```
## S3 method for class 'diagmeta'
plot(
  х,
 which = c("survival", "youden", "roc", "sroc"),
  xlab = "Threshold",
 main,
  ci = FALSE,
  ciSens = FALSE,
  ciSpec = FALSE,
 mark.optcut = FALSE,
 mark.cutpoints = FALSE,
  points = TRUE,
  lines = FALSE,
  rlines = TRUE,
  line.optcut = TRUE,
  col.points = "rainbow",
  cex = 1,
  pch.points = 16,
  col = "black",
  col.ci = "gray",
  col.optcut = "black",
  cex.marks = 0.7 * cex,
  1wd = 1,
  lwd.ci = lwd,
  lwd.optcut = 2 * lwd,
  lwd.study = lwd,
  shading = "none",
```

```
col.hatching = col.ci,
lwd.hatching = lwd.ci,
ellipse = FALSE,
xlim = NULL,
...
```

Arguments

Х	An object of class diagmeta
which	A character vector indicating the type of plot, either "regression" or "cdf" or "survival" or "Youden" or "ROC" or "SROC" or "density" or "sensspec", can be abbreviated
xlab	An x axis label
main	A logical indicating title to the plot
ci	A logical indicating whether confidence intervals should be plotted for "regression", "cdf", "survival", "Youden", and "sensspec"
ciSens	A logical indicating whether confidence intervals should be plotted for sensitiv- ity, given the specificity in "SROC" plot
ciSpec	A logical indicating whether confidence intervals should be plotted for speci- ficity, given the sensitivity in "SROC" plot
mark.optcut	A logical indicating whether the optimal cutoff should be marked on "SROC" plot
mark.cutpoints	A logical indicating whether the given cutoffs should be marked on "SROC" plot
points	A logical indicating whether points should be plotted in plots "regression", "cdf", "survival", "Youden", "ROC", and "sensspec"
lines	A logical indicating whether polygonal lines connecting points belonging to the same study should be printed in plots "regression", "cdf", "survival", "Youden", and "sensspec"
rlines	A logical indicating whether regression lines or curves should be plotted for plots "regression", "cdf", "survival", "Youden", and "sensspec"
line.optcut	A logical indicating whether a vertical line should be plotted at the optimal cut- off line for plots "cdf", "survival", "Youden", and "density"
col.points	A character string indicating color of points, either "rainbow", "topo", "heat", "terrain", "cm", "grayscale", or any color defined in colours
cex	A numeric indicating magnification to be used for plotting text and symbols
pch.points	A numeric indicating plot symbol(s) for points
col	A character string indicating color of lines
col.ci	A character string indicating color of confidence lines
col.optcut	A character string indicating color of optimal cutoff line
cex.marks	A numeric indicating magnification(s) to be used for marking cutoffs
lwd	A numeric indicating line width

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plot.diagmeta

lwd.ci	A numeric indicating line width of confidence lines
lwd.optcut	A numeric indicating line width of optimal cutoff
lwd.study	A numeric indicating line width of individual studies
shading	A character indicating shading and hatching confidence region in "SROC" plot, either "none" or "shade" or "hatch"
col.hatching	A character string indicating color used in hatching of the confidence region
lwd.hatching	A numeric indicating line width used in hatching of the confidence region
ellipse	A logical indicating whether a confidence ellipse should be drawn around the optimal cutoff
xlim	A character or numerical vector indicating the minimum and maximum value for the horizontal axes
	Additional graphical arguments

Details

The first argument of the plot function is an object of class "diagmeta".

The second argument which indicates which sort of plot(s) should be shown. For which="regression", a scatter plot of the quantile-transformed proportions of negative test results with two regression lines is shown. Points belonging to the same study are marked with the same colour. For which="cdf", the two cumulative distribution functions are shown, corresponding to the proportions of negative test results. For which="survival", the survival functions are shown, corresponding to the proportions of positive test results. For which="Youden", the (potentially weighted) sum of sensitivity and specificity minus 1 is shown; in case of lambda=0.5 (the default) this is the Youden index. For which="ROC", study-specific ROC curves are shown. For which="SROC", the model-based summary ROC curve is shown. For which="density", the model-based densities of both groups are shown. For which="sensspec", the sensitivity (decreasing with increasing cutoff) and the specificity (increasing with increasing cutoff) are shown. Instead of character strings, a numeric value or vector can be used to specify plots with numbers corresponding to the following order of plots: "regression", "cdf", "survival", "youden", "roc", "sroc", "density", and "sensspec".

Other arguments refer to further plot parameters, such as lines (whether points belonging to the same study should be joined), rlines (whether regression curves should be drawn), ci / ciSens / ciSpec / ellipse (whether confidence regions should be shown), line.optcut / mark.optcut (whether the optimal cutoff should be indicated), and additional plot parameters (see Arguments).

If no further arguments are provided, four standard plots ("survival", "Youden", "ROC", and "SROC") are produced in a 2 x 2 format.

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References

Schneider A, Linde K, Reitsma JB, Steinhauser S, Rücker G (2017): A novel statistical model for analyzing data of a systematic review generates optimal cutoff values for fractional exhaled nitric oxide for asthma diagnosis. *Journal of Clinical Epidemiology*, **92**, 69–78

Steinhauser S, Schumacher M, Rücker G (2016): Modelling multiple thresholds in meta-analysis of diagnostic test accuracy studies. *BMC Medical Research Methodology*, **16**, 97

See Also

diagmeta

```
# FENO dataset
#
data(Schneider2017)
diag1 <- diagmeta(tpos, fpos, tneg, fneg, cutpoint,</pre>
                  studlab = paste(author, year, group),
                  data = Schneider2017,
                  log.cutoff = TRUE)
# Regression plot with confidence intervals
#
plot(diag1, which = "regr", lines = FALSE, ci = TRUE)
# Cumulative distribution plot with optimal cutoff line and
# confidence intervals
#
plot(diag1, which = "cdf", line.optcut = TRUE, ci = TRUE)
# Survival plot with optimal cutoff line and confidence intervals
#
plot(diag1, which = "survival", line.optcut = TRUE, ci = TRUE)
# Youden plot of optimal cutoff line and confidence intervals
#
plot(diag1, which = "youden",
     lines = TRUE, line.optcut = TRUE, ci = TRUE)
# ROC plot of lines connecting points belonging to the same study
#
plot(diag1, which = "ROC", lines = TRUE)
# SROC plot of confidence regions for sensitivity and specificity
# with optimal cutoff mark
#
plot(diag1, which = "SROC",
     ciSens = TRUE, ciSpec = TRUE, mark.optcut = TRUE,
     shading = "hatch")
# Density plot of densities for both groups with optimal cutoff
# line
#
plot(diag1, which = "density", line.optcut = TRUE)
```

print.diagmeta

Description

Print method for objects of class diagmeta.

Usage

```
## S3 method for class 'diagmeta'
print(x, digits = 3, digits.prop = gs("digits.prop"), ...)
```

Arguments

х	An object of class diagmeta.
digits	Number of significant digits for printing of optimal cutoff.
digits.prop	Number of significant digits for proportions, e.g., sensitivities and specificities.
	Additional arguments.

Author(s)

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See Also

diagmeta summary.diagmeta

Examples

diag1

print.diagstats

Description

Print method for objects of class diagstats.

Usage

```
## S3 method for class 'diagstats'
print(
    x,
    sensspec = TRUE,
    predicted = TRUE,
    density = FALSE,
    digits = 3,
    digits.prop = gs("digits.prop"),
    ...
)
```

Arguments

х	An object of class diagmeta.
sensspec	A logical indicating whether sensitivities and specificies should be printed.
predicted	A logical indicating whether predicted values should be printed.
density	A logical indicating whether values of the model-based density functions should be printed.
digits	Number of significant digits for printing of cutoffs.
digits.prop	Number of significant digits for proportions, e.g., sensitivities and specificities.
	Additional arguments.

Author(s)

Guido Schwarzer <guido.schwarzer@uniklinik-freiburg.de>

See Also

diagstats diagmeta

```
# FEN0 dataset
#
data(Schneider2017)
diag1 <- diagmeta(tpos, fpos, tneg, fneg, cutpoint,</pre>
```

print.summary.diagmeta

print.summary.diagmeta

Print detailed results for diagmeta objects

Description

Print detailed results for objects of class summary.diagmeta.

Usage

S3 method for class 'summary.diagmeta'
print(x, digits = 3, ...)

Arguments

Х	An object of class summary.diagmeta.
digits	Number of significant digits for printing.
	Additional arguments.

Author(s)

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See Also

diagmeta summary.diagmeta

```
summary(diag1)
print(summary(diag1), digits.prop = 2)
```

Schneider2017

Meta-analysis of studies of the diagnostic test accuracy of FENO for diagnosis of asthma

Description

Meta-analysis of studies of the diagnostic test accuracy of fractional exhaled nitric oxide (FENO) for diagnosis of asthma.

The data were collected for a systematic review by Karrasch et al. (2017) and are published as a supplement (Appendix 1) to Schneider et al. (2017). They have been preprocessed for use in R package **diagmeta**.

Format

A data frame with the following columns:

study_id	numeric study ID
author	first author
year	year of publication
group	information on subgroup
cutpoint	cutpoint (FeNO [ppb])
tpos	number of true positives
fneg	number of false negatives
fpos	number of false positives
tneg	number of true negatives

Source

Karrasch S, Linde K, Rücker G, Sommer H, Karsch-Volk M, Kleijnen J, Jörres RA, Schneider A (2017): Accuracy of FENO for diagnosing asthma: a systematic review. *Thorax*, **72**, 109e16

Schneider A, Linde K, Reitsma JB, Steinhauser S, Rücker G (2017): A novel statistical model for analyzing data of a systematic review generates optimal cutoff values for fractional exhaled nitric oxide for asthma diagnosis. *Journal of Clinical Epidemiology*, **92**, 69–78

```
# FEN0 dataset
#
data(Schneider2017)
diag1 <- diagmeta(tpos, fpos, tneg, fneg, cutpoint,</pre>
```

```
studlab = paste(author, year, group),
data = Schneider2017,
log.cutoff = TRUE)
```

plot(diag1)

summary.diagmeta Summary method for diagmeta

Description

Summary method for objects of class diagmeta.

Usage

S3 method for class 'diagmeta'
summary(object, ...)

Arguments

object	An object of class diagmeta.
	Additional arguments.

Value

A list with classes 'summary.diagmeta' and 'diagmeta' is returned. The list elements are identical to a diagmeta object.

Author(s)

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See Also

diagmeta

Examples

summary(diag1)

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