

Package ‘GsymPoint’

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Type Package

Title Estimation of the Generalized Symmetry Point, an Optimal
Cutpoint in Continuous Diagnostic Tests

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Description Estimation of the cutpoint defined by the Generalized Symmetry point in a binary classification setting based on a continuous diagnostic test or marker. Two methods have been implemented to construct confidence intervals for this optimal cutpoint, one based on the Generalized Pivotal Quantity and the other based on Empirical Likelihood. Numerical and graphical outputs for these two methods are easily obtained.

License GPL

LazyData TRUE

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GsymPoint-package	<i>Estimation of the Generalized Symmetry Point, an Optimal Cutpoint in Continuous Diagnostic Tests</i>
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Description

Continuous biomarkers or diagnostic tests are often used to discriminate between healthy and diseased populations. In clinical practice, it is useful to select an appropriate cutpoint or discrimination value c which defines the positive and negative test results. Several methods for selecting optimal cutpoints in diagnostic tests in the sense of a specific optimality criterion have been proposed in the literature depending on the underlying reason for this choice (see for example, Youden, 1950; Pepe, 2003; Liu, 2012; Rota and Antolini, 2014). One of the best-known methods is based on the Symmetry point, also known in the literature as the point of equivalence (Greiner et al., 1995; Defreitas et al., 2004; Adlhoch et al., 2011), defined as the point where the sensitivity and specificity measures are equal. Taking into account the costs associated to the false positives and false negatives misclassifications, the Generalized Symmetry point can be defined. This package allows the user to compute the Generalized Symmetry point as the optimal cutpoint for a diagnostic test or continuous marker. The two methods introduced in López-Ratón et al. (2016) for estimating the Generalized Symmetry point and its sensitivity and specificity accuracy measures have been implemented in this package. One of them is based on the Generalized Pivotal Quantity (Weerahandi, 1993; 1995) and the other based on Empirical Likelihood (Thomas and Grunkemeier, 1975). Numerical and graphical outputs for these two methods are easily obtained.

Details

Package: GsymPoint
Type: Package
Version: 1.1.2
Date: 2023-10-31
License: GPL

The GsymPoint package only requires a data-entry file, which must, at minimum, contain the following variables: diagnostic marker; disease status (diseased/healthy); and whether adjustment is to be made for any categorical covariate of interest, a variable that indicates the levels of this covariate. A standard-type data input structure is used, with each row of the database indicating a patient/case and each column referring to a variable.

The most important functions are `gsym.point()`, `control.gsym.point()`, `summary.gsym.point()` and `plot.gsym.point()` functions. The `gsym.point()` function computes the Generalized Symmetry point and its corresponding sensitivity and specificity indexes, according to the method selected. The two methods can be chosen simultaneously for estimating the optimal cutpoint. The

control.gsym.point() function is used to set several parameters that are specific of each method, such as the number of simulations or the constants needed for the Empirical Likelihood method. The summary.gsym.point() and plot.gsym.point() functions produce numerical and graphical outputs, respectively.

Author(s)

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control.gsym.point	<i>Control of the Generalized Symmetry point computing process</i>
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Description

control.gsym.point is used to set various parameters that control the Generalized Symmetry point computing process.

Usage

```
control.gsym.point(B = 499, c_sampling = 0.25, c_F = 0.25, c_ELq = 0.25,
c_R = 0.25, I = 2500)
```

Arguments

B	a numerical value meaningful only in the "EL" method. It specifies the number of simulations in the Empirical Likelihood method. The default value is 499.
c_sampling	a numerical value meaningful only in the "EL" method. It specifies the constant needed for resampling in the Empirical Likelihood method. The default value is 0.25.
c_F	a numerical value meaningful only in the "EL" method. It specifies the constant needed for estimating the distribution in the Empirical Likelihood method. The default value is 0.25.
c_ELq	a numerical value meaningful only in the "EL" method. It specifies the constant needed for estimating the empirical likelihood function in the Empirical Likelihood method. The default value is 0.25.
c_R	a numerical value meaningful only in the "EL" method. It specifies the constant needed for estimating the ROC Curve in the Empirical Likelihood method. The default value is 0.25.
I	a numerical value meaningful only in the "GPQ" method. It specifies the number of replicates in the Generalized Pivotal Quantity method. The default value is 2500.

Details

The value yielded by this function is used as the control argument of the `gsym.point()` function.

Author(s)

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See Also

[gsym.point](#)

Examples

```
library(GsymPoint)

data(melanoma)

#####
# Generalized Pivotal Quantity Method ("GPQ"):
#####

# How to set the number of replicates I equal to 2000:

gsym.point.GPQ.melanoma<-gsym.point(methods = "GPQ", data = melanoma,
marker = "X", status = "group", tag.healthy = 0, categorical.cov = NULL,
CFN = 1, CFP = 1, control = control.gsym.point(I = 2000),
confidence.level = 0.95, trace = FALSE, seed = FALSE, value.seed = 3, verbose = FALSE)

summary(gsym.point.GPQ.melanoma)
```

```

data(prostate)

#####
# Empirical Likelihood Method ("EL")
#####

# How to set the number of resamples B equal to 99:

gsym.point.GPQ.prostate <- gsym.point (methods = "GPQ", data = prostate,
marker = "marker", status = "status", tag.healthy = 0, categorical.cov = NULL,
CFN = 1, CFP = 1, control = control.gsym.point(B=99), confidence.level = 0.95,
trace = FALSE, seed = FALSE, value.seed = 3, verbose = FALSE)

summary(gsym.point.GPQ.prostate)

```

elastase

Leukocyte Elastase dataset

Description

The elastase dataset was obtained from a study carried out in the Cardiology Department at the Galicia General Hospital (Santiago de Compostela, Spain). This study (Amaro et al., 1995) was conducted to assess the clinical usefulness of leukocyte elastase determination in the diagnosis of coronary artery disease (CAD).

Usage

```
data(elastase)
```

Format

A data frame with 141 observations on the following 3 variables.

elas leukocyte elastase. Numerical vector

status true disease status (absence/presence of coronary artery disease). Numerical vector (0=absence, 1=presence)

gender patient's gender. Factor with Male and Female levels

Source

Amaro, A., Gude, F., González-Juanatey, R., Iglesias, C., Fernández-Vázquez, F., García-Acuña, J. and Gil, M. (1995). Plasma leukocyte elastase concentration in angiographically diagnosed coronary artery disease. *European Heart Journal* **16**, 615–622.

References

Amaro, A., Gude, F., González-Juanatey, R., Iglesias, C., Fernández-Vázquez, F., García-Acuña, J. and Gil, M. (1995). Plasma leukocyte elastase concentration in angiographically diagnosed coronary artery disease. *European Heart Journal* **16**, 615–622.

Examples

```
data(elastase)
summary(elastase)
```

gsym.point	<i>Construction of confidence intervals for the Generalized Symmetry point and its accuracy measures through two methods</i>
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Description

gsym.point is used to construct confidence intervals for the Generalized Symmetry point and its accuracy measures (sensitivity and specificity) for a continuous diagnostic test using two methods: the Generalized Pivotal Quantity (GPQ) method and the Empirical Likelihood (EL) method.

Usage

```
gsym.point (methods, data, marker, status, tag.healthy, categorical.cov = NULL,
CFN = 1, CFP = 1, control = control.gsym.point(), confidence.level = 0.95,
trace = FALSE, seed = FALSE, value.seed = 3, verbose = FALSE)
```

Arguments

methods	a character vector selecting the method(s) to be used for estimating the Generalized Symmetry point and its accuracy measures. The possible options are: "GPQ", "EL", "auto", c("GPQ", "EL") or c("EL", "GPQ").
data	a data frame containing all needed variables: the diagnostic marker, the true disease status and, when it is necessary, the categorical covariate.
marker	a character string with the name of the diagnostic test variable.
status	a character string with the name of the variable that distinguishes healthy from diseased individuals.
tag.healthy	the value codifying healthy individuals in the status variable.
categorical.cov	a character string with the name of the categorical covariate according to which the Generalized Symmetry point is to be calculated. The default is NULL (no categorical covariate is considered in the analysis).
CFN	a numerical value that specifies the cost of a false negative decision. The default value is 1.
CFP	a numerical value that specifies the cost of a false positive decision. The default value is 1.

control	output of the <code>control.gsym.point</code> function that controls the whole calculation process of the Generalized Symmetry point.
confidence.level	a numerical value with the confidence level for the construction of the confidence intervals. The default value is 0.95.
trace	a logical value to show information on progress when it is TRUE. The default value is FALSE.
seed	a logical value to choose if a seed is fixed for generating the trials in the computation of the confidence intervals in order to reproduce the same simulation process. The default value is FALSE.
value.seed	the numerical value for the fixed seed when seed is TRUE. The default value is 3.
verbose	a logical value that allows to show extra information on the normality assumption and the Shapiro-Wilk normality p-values. The default value is FALSE.

Details

The Symmetry point c_S satisfies the equality $p(c_S) = q(c_S)$, where p and q denote, respectively, the specificity (or true negative fraction) and sensitivity (or true positive fraction). Geometrically, it is the point where the ROC curve and the line $y = 1 - x$ (the perpendicular to the positive diagonal line) intersect, and it can also be seen as the point that maximizes simultaneously both types of correct classifications (Riddle and Stratford, 1999; Gallop et al., 2003) corresponding, therefore, to the probability of correctly classifying any subject, whether it is healthy or diseased (Jiménez-Valverde et al., 2012; 2014).

Taking into account the costs associated to the false positives and false negatives misclassifications, C_{FP} and C_{FN} , an extension of the Symmetry point called the Generalized Symmetry point, c_{GS} , can be defined as follows (López-Ratón et al., 2015):

$$\rho(1 - p(c_{GS})) = 1 - q(c_{GS})$$

where $\rho = \frac{C_{FP}}{C_{FN}}$ is the relative loss (cost) of a false positive classification as compared with a false negative classification. Analogously to the Symmetry point, c_{GS} is obtained graphically by the intersection point between the ROC curve and the line $y = 1 - \rho x$.

In this package, the two methods proposed in López-Ratón et al. (2016) for estimating the Generalized Symmetry point and its sensitivity and specificity indexes are available:

"GPQ": Method based on the Generalized Pivotal Quantity (Weerahandi, 1993; 1995; Lai et al., 2012). It assumes that the diagnostic test on both groups or a monotone Box-Cox transformation is Normal distributed. So, the Generalized Symmetry point c_{GS} can be estimated from the following equation:

$$\Phi(a + b\Phi^{-1}(t)) = 1 - \rho t \Leftrightarrow \Phi\left(\frac{\Phi^{-1}(1 - \rho t) - a}{b}\right) - t = 0$$

where $a = \frac{\mu_1 - \mu_0}{\sigma_1}$, $b = \frac{\sigma_0}{\sigma_1}$, $t = 1 - p(c_{GS})$ and Φ denotes the standard Normal cumulative distribution function (cdf), with μ_i and σ_i , $i = 0, 1$, the mean and standard deviation of healthy ($i=0$) and diseased ($i=1$) populations, respectively. To check the assumption of normality, the Shapiro-Wilk test is used with a significance level of 5%.

"EL": Method based on the Empirical Likelihood (Thomas and Grunkemeier, 1975). It takes into account that c_{GS} can be seen as two specific quantiles, the $p(c_{GS})$ -th quantile of the healthy population and the $\rho(1 - q(c_{GS}))$ -th quantile of the diseased population. Following the same reasoning as in Molanes-López and Letón (2011), and considering that the value of $p(c_{GS})$ is known in advance and the Generalized Symmetry point defines an operating point on the ROC curve fulfilling $1 - x = p(c_{GS})$, the following adjusted empirical log-likelihood ratio function is derived to make inference on c_{GS} :

$$\begin{aligned} \ell(c) = & 2n_0 \hat{F}_{0,g_0}(c) \log \left(\frac{\hat{F}_{0,g_0}(c)}{p(c)} \right) + 2n_0(1 - \hat{F}_{0,g_0}(c)) \log \left(\frac{1 - \hat{F}_{0,g_0}(c)}{1 - p(c)} \right) \\ & + 2n_1 \hat{F}_{1,g_1}(c) \log \left(\frac{\hat{F}_{1,g_1}(c)}{\rho(1 - p(c))} \right) + 2n_1(1 - \hat{F}_{1,g_1}(c)) \log \left(\frac{1 - \hat{F}_{1,g_1}(c)}{1 - \rho(1 - p(c))} \right), \end{aligned}$$

where $\hat{F}_{i,g_i}(y) = \frac{1}{n_i} \sum_{k_i=1}^{n_i} K \left(\frac{y - Y_{ik_i}}{g_i} \right)$ are kernel-type estimates of the cdfs F_i , of the two populations, $i = 0, 1$, with $K(y) = \int_{-\infty}^y K(z)dz$ a kernel function and g_i the smoothing parameter, for $i = 0, 1$.

"auto": the program selects automatically the most appropriate method of the two available, based on the normality assumption. The GPQ is selected under the normality assumption and the EL otherwise.

Value

Returns an object of class "gsym.point" with the following components:

methods	a character vector with the value of the methods argument used in the call.
levels.cat	a character vector indicating the levels of the categorical covariate if the categorical.cov argument in the gsym.point function is not NULL.
call	the matched call.
data	the data frame with the variables used in the call.

For each of the methods used in the call, a list with the following components is obtained:

"optimal.result"	a list with the Generalized Symmetry point and its associated sensitivity and specificity accuracy measures with the corresponding confidence intervals.
"AUC"	the numerical value of the Area Under the ROC Curve.
"rho"	the numerical value of the cost ratio $\rho = \frac{C_{FP}}{C_{FN}}$.
"pvalue.healthy"	the numerical value of the p-value obtained by the Shapiro-Wilk normality test for checking the normality assumption of the marker in the healthy population.
"pvalue.diseased"	the numerical value of the p-value obtained by the Shapiro-Wilk normality test for checking the normality assumption of the marker in the diseased population.

In addition, if the original data are not normally distributed the following components also appears:

"lambda"	the estimated numerical value of the power used in the Box-Cox transformation.
"normality.transformed"	a character string indicating if the transformed marker values by the Box-Cox transformation are normally distributed ("yes") or not ("no").
"pvalue.healthy.transformed"	the numerical value of the p-value obtained by the Shapiro-Wilk normality test for checking the normality assumption of the Box-Cox transformed marker in the healthy population.
"pvalue.diseased.transformed"	the numerical value of the p-value obtained by the Shapiro-Wilk normality test for checking the normality assumption of the Box-Cox transformed marker in the diseased population.

Author(s)

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See Also

[control.gsym.point](#), [summary.gsym.point](#)

Examples

```
library(GsymPoint)

data(melanoma)

#####
# marker: X
# status: group
#####

#####
# Generalized Pivotal Quantity Method ("GPQ"):
# Original data normally distributed
#####

gsym.point.GPQ.melanoma<-gsym.point(methods = "GPQ", data = melanoma,
marker = "X", status = "group", tag.healthy = 0, categorical.cov = NULL,
CFN = 1, CFP = 1, control = control.gsym.point(),confidence.level = 0.95,
trace = FALSE, seed = FALSE, value.seed = 3, verbose = FALSE)

summary(gsym.point.GPQ.melanoma)

plot(gsym.point.GPQ.melanoma)

data(prostate)

#####
# marker: marker
# status: status
#####
```

```
#####
# Generalized Pivotal Quantity Method ("GPQ"):
# Box-Cox transformed data normally distributed
#####

gsym.point.GPQ.prostate <- gsym.point (methods = "GPQ", data = prostate,
marker = "marker", status = "status", tag.healthy = 0, categorical.cov = NULL,
CFN = 1, CFP = 1, control = control.gsym.point(), confidence.level = 0.95,
trace = FALSE, seed = FALSE, value.seed = 3, verbose = FALSE)

summary(gsym.point.GPQ.prostate)

plot(gsym.point.GPQ.prostate)

data(elastase)

#####
# marker: elas
# status: status
#####

#####
# Generalized Pivotal Quantity Method ("GPQ"):
# Original data not normally distributed
# Box-Cox transformed data not normally distributed
#####

gsym.point.GPQ.elastase <- gsym.point(methods = "GPQ", data = elastase,
marker = "elas", status = "status", tag.healthy = 0, categorical.cov = NULL,
CFN = 1, CFP = 1, control = control.gsym.point(), confidence.level = 0.95,
trace = FALSE, seed = FALSE, value.seed = 3, verbose = FALSE)

summary(gsym.point.GPQ.elastase)

plot(gsym.point.GPQ.elastase)
```

melanoma

Melanoma dataset

Description

The melanoma dataset was obtained from Venkatram and Begg (1996). This study was conducted to assess the clinical usefulness of a clinical scoring scheme without dermoscope (CSS) used by dermatologists in order to determine if a suspicious pigmented lesion on the skin is a melanoma.

Usage

```
data(melanoma)
```

Format

A data frame with 72 observations on the following 2 variables.

X clinical scoring scheme without dermoscope. Numerical vector.

group true disease status (absence/presence of melanoma). Numerical vector (0=absence, 1=presence)

Source

Venkatraman, ES., Begg, CB. (1996). A distribution-free procedure for comparing receiver operating characteristic curves from a paired experiment. *Biometrika* **83**, 835–848.

References

Venkatraman, ES., Begg, CB. (1996). A distribution-free procedure for comparing receiver operating characteristic curves from a paired experiment. *Biometrika* **83**, 835–848.

Examples

```
data(melanoma)
summary(melanoma)
```

plot.gsym.point

Default plotting of a gsym.point object

Description

On the basis of a [gsym.point](#) object, it is used to plot the Receiver Operating Characteristic (ROC) curve, the line $y = 1 - \rho x$ and the optimal ROC coordinates associated to the Generalized Symmetry point.

Usage

```
## S3 method for class 'optimal.cutpoints'
## S3 method for class 'gsym.point'
plot(x, xlab, ylab, main, ...)
```

Arguments

x	an object of class gsym.point as produced by the gsym.point() function
xlab	the x axis label of the plot. By default this label is set to "False Positive Rate"
ylab	the y axis label of the plot. By default this label is set to "True Positive Rate"
main	the title of the plot. By default this title is set to "Empirical ROC Curve and line $y = 1 - \rho x$ "
...	further arguments passed to or from other methods

Author(s)

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See Also

[gsym.point](#), [control.gsym.point](#)

Examples

```
library(GsymPoint)

data(melanoma)

#####
# Generalized Pivotal Quantity Method ("GPQ"):
#####

gsym.point.GPQ.melanoma<-gsym.point(methods = "GPQ", data = melanoma,
marker = "X", status = "group", tag.healthy = 0, categorical.cov = NULL,
CFN = 1, CFP = 1, control = control.gsym.point(),confidence.level = 0.95,
trace = FALSE, seed = FALSE, value.seed = 3, verbose = FALSE)

plot(gsym.point.GPQ.melanoma)

data(prostate)

#####
# Generalized Pivotal Quantity Method ("GPQ"):
#####

gsym.point.GPQ.prostate <- gsym.point (methods = "GPQ", data = prostate,
marker = "marker", status = "status", tag.healthy = 0, categorical.cov = NULL,
CFN = 1, CFP = 1, control = control.gsym.point(), confidence.level = 0.95,
trace = FALSE, seed = FALSE, value.seed = 3, verbose = FALSE)

plot(gsym.point.GPQ.prostate)

data(elastase)

#####
# Generalized Pivotal Quantity Method ("GPQ"):
#####

gsym.point.GPQ.elastase <- gsym.point(methods = "GPQ", data = elastase,
marker = "elas", status = "status", tag.healthy = 0, categorical.cov = NULL,
CFN = 1, CFP = 1, control = control.gsym.point(), confidence.level = 0.95,
trace = FALSE, seed = FALSE, value.seed = 3, verbose = FALSE)

plot(gsym.point.GPQ.elastase)
```

print.gsym.point	<i>Print method for gsym.point objects</i>
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Description

Default print method for objects fitted with `gsym.point()` function. A short summary is printed with: the call to the `gsym.point()` function for each categorical covariate level (if the `categorical.cov` argument of the `gsym.point()` function is not NULL).

Usage

```
## S3 method for class 'gsym.point'
print(x, digits = max(3L, getOption("digits") - 3L), ...)
```

Arguments

<code>x</code>	an object of class <code>gsym.point</code> as produced by <code>gsym.point()</code> function.
<code>digits</code>	controls number of digits printed in the output.
<code>...</code>	further arguments passed to or from other methods.

Author(s)

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See Also

[gsym.point](#), [summary.gsym.point](#)

Examples

```
library(GsymPoint)
data(elastase)

#####
# Empirical Likelihood Method ("GPQ"):
#####

gsym.point.GPQ.elastase<-gsym.point(methods = "GPQ", data = elastase, marker = "elas",
status = "status", tag.healthy = 0, categorical.cov = NULL, CFN = 1, CFP = 1,
control = control.gsym.point(), confidence.level = 0.95, trace = FALSE,
seed = FALSE, value.seed = 3, verbose = FALSE)

gsym.point.GPQ.elastase

print(gsym.point.GPQ.elastase)
```

prostate	<i>Prostate cancer dataset</i>
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Description

The prostate dataset was obtained from a study carried in Le (2006). This study was conducted to evaluate the clinical usefulness of the level of acid phosphatase in blood serum (APBS) x 100 to predict whether nodal involvement is present.

Usage

```
data(prostate)
```

Format

A data frame with 53 observations on the following 2 variables.

marker level of acid phosphatase in blood serum. Numeric vector

status true disease status (absence/presence of nodal involvement). Numerical vector (0=absence, 1=presence)

Source

Le, C.T. (2006). A solution for the most basic optimization problem associated with an ROC curve. *Statistical Methods in Medical Research* **15**, 571–584.

References

Le, C.T. (2006). A solution for the most basic optimization problem associated with an ROC curve. *Statistical Methods in Medical Research* **15**, 571–584.

Examples

```
data(prostate)
summary(prostate)
```

summary.gsym.point	<i>Summary method for gsym.point objects</i>
--------------------	--

Description

Produces a summary of a gsym.point object. The following is printed: the matched call to the gsym.point() main function; the area under the ROC curve (AUC) estimate; the Generalized Symmetry point obtained with the method(s) selected and the point estimates of the associated sensitivity and specificity indexes with their corresponding confidence intervals. All this information will be shown for each categorical covariate level (if the categorical.cov argument in the gsym.point() function is not NULL).

Usage

```
## S3 method for class 'gsym.point'
summary(object, ...)
```

Arguments

object	an object of class gsym.point as produced by gsym.point() function.
...	further arguments passed to or from other methods. None are used in this method.

Details

The summary.gsym.point function produces a list of summary information for a fitted gsym.point object. The result depends on the two arguments, namely, methods, and categorical.cov of the gsym.point() function used in the Generalized Symmetry point computing process.

Value

Returns an object of class "summary.gsym.point" with the same components as the gsym.point function (see [gsym.point](#))

Author(s)

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See Also

[gsym.point](#)

Examples

```
library(GsymPoint)

data(melanoma)

#####
# Generalized Pivotal Quantity Method ("GPQ"):
#####

gsym.point.GPQ.melanoma<-gsym.point(methods = "GPQ", data = melanoma,
marker = "X", status = "group", tag.healthy = 0, categorical.cov = NULL,
CFN = 1, CFP = 1, control = control.gsym.point(),confidence.level = 0.95,
trace = FALSE, seed = FALSE, value.seed = 3, verbose = FALSE)

summary(gsym.point.GPQ.melanoma)

data(prostate)
```



```
#####  
# Generalized Pivotal Quantity Method ("GPQ"):  
#####  
  
gsym.point.GPQ.prostate <- gsym.point (methods = "GPQ", data = prostate,  
marker = "marker", status = "status", tag.healthy = 0, categorical.cov = NULL,  
CFN = 1, CFP = 1, control = control.gsym.point(), confidence.level = 0.95,  
trace = FALSE, seed = FALSE, value.seed = 3, verbose = FALSE)  
  
summary(gsym.point.GPQ.prostate)  
  
data(elastase)  
  
#####  
# Generalized Pivotal Quantity Method ("GPQ"):  
#####  
  
gsym.point.GPQ.elastase <- gsym.point(methods = "GPQ", data = elastase,  
marker = "elas", status = "status", tag.healthy = 0, categorical.cov = NULL,  
CFN = 1, CFP = 1, control = control.gsym.point(), confidence.level = 0.95,  
trace = FALSE, seed = FALSE, value.seed = 3, verbose = FALSE)  
  
summary(gsym.point.GPQ.elastase)
```

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