Introduction to dtametaTMB

This vignette introduces the main functionality of the `dtametaTMB` package for meta-analysis of diagnostic test accuracy (DTA) studies. We demonstrate how to fit three commonly used models:

- the Reitsma bivariate model
- the Rutter and Gatsonis (HSROC) model
- the Hoyer model for multiple thresholds

using real datasets included in the package.

Subgroup analyses, meta-regression, and latent class analysis allowing for an imperfect reference standard are covered in separate vignettes.

Note: Rendering forest plots via `forest` may take longer in an interactive R session due to the underlying grid graphics. Performance is typically faster when knitting the vignette (e.g. via RMarkdown or Quarto).

How do I load the package?

```
#install.packages("dtametaTMB")
library(dtametaTMB)
```

Which model should I use?

- **Reitsma model:** single threshold per study: use when studies apply similar thresholds.
- **Rutter and Gatsonis model:** single threshold per study: use when thresholds vary between studies
- **Hoyer model:** multiple thresholds per study

The Reitsma and Rutter-Gatsonis model classes support parameter constraints for simplified analyses and sparse datasets.

Validation

The implementations reproduce benchmark results from the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (including parameter estimates, standard errors, and graphical outputs) for standard datasets such as the Anti-CCP and RF examples.

How do I use the Reitsma model?

Unlike the `mada` package, `dtametaTMB` uses the binomial likelihood to model the within study distribution as recommended by The Cochrane Handbook.

For sensitivity in study i, we have the number of diseased individuals testing positive: $y_{Ai} \sim \mathcal{B}(n_{Ai}, \pi_{Ai})$.

Similarly for specificity, we have the number of non-diseased individuals testing negative: $y_{Bi} \sim \mathcal{B}(n_{Bi}, \pi_{Bi})$.

At the study level, we have

$$\begin{pmatrix} \text{logit}(\pi_{Ai}) \\ \text{logit}(\pi_{Bi}) \end{pmatrix} = \begin{pmatrix} \mu_{Ai} \\ \mu_{Bi} \end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} \mu_A \\ \mu_B \end{pmatrix}, \Sigma \right), \quad \text{with} \quad \Sigma = \begin{pmatrix} \sigma_A^2 & \sigma_{AB} \\ \sigma_{AB} & \sigma_B^2 \end{pmatrix}.$$

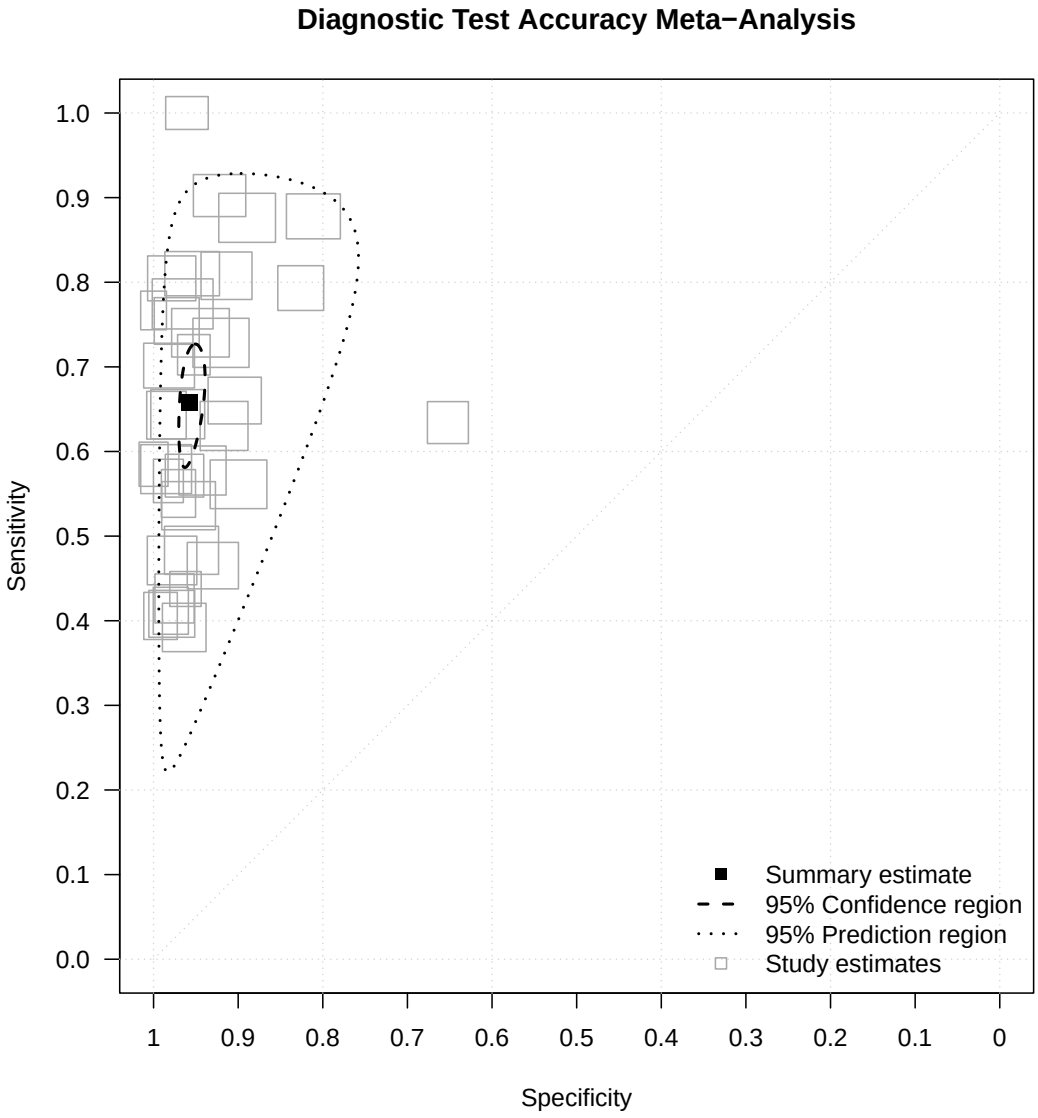
```
data("anticcp")
reitsma <- fitReitsma(data=anticcp,
                      TP=TP,
                      FP=FP,
                      FN=FN,
                      TN=TN,
                      study=study)
reitsma
#>
#> Reitsma Model
#> -------------
#>
#> Number of studies : 37
#> Optimizer         : Converged
#> Hessian           : Positive definite
#> Max |grad|        : 0.000297943
#> -2 log likelihood : 545.56 ( df = 5 )
#> AIC               : 555.56
#> BIC               : 563.614
#>
#> mu_A (logitsens)  : 0.653
```

```
#> mu_B (logitspec)  : 3.109
#>
#> Use summary() for parameter estimates.
summary(reitsma)
#>
#> Summary: Reitsma Model
#> ----------------------
#>
#> Parameter estimates
#> -------------------
#>                  Estimate  Std_Error
#> mu_A.sens      0.65340680 0.12748621
#> mu_B.spec      3.10898200 0.14588336
#> sigma2_A.sens  0.54263596 0.14634633
#> sigma2_B.spec  0.57169194 0.18731743
#> sigma_AB      -0.27040551 0.11984924
#>
#> Sensitivity / specificity
#> -------------------------
#>        Estimate conflevel   CI_Lower   CI_Upper
#> sens 0.65777777      0.95 0.59953751 0.71162209
#> spec 0.95726173      0.95 0.94390908 0.96754502
#>
#> Recovered HSROC parameters (Rutter-Gatsonis)
#> -------------------------------------------
#>                          Lambda      Theta        beta sigma2_alpha sigma2_theta
#> Estimate (recovered) 3.7306861 -1.2033598 0.026080802   0.57313799   0.41369001
```

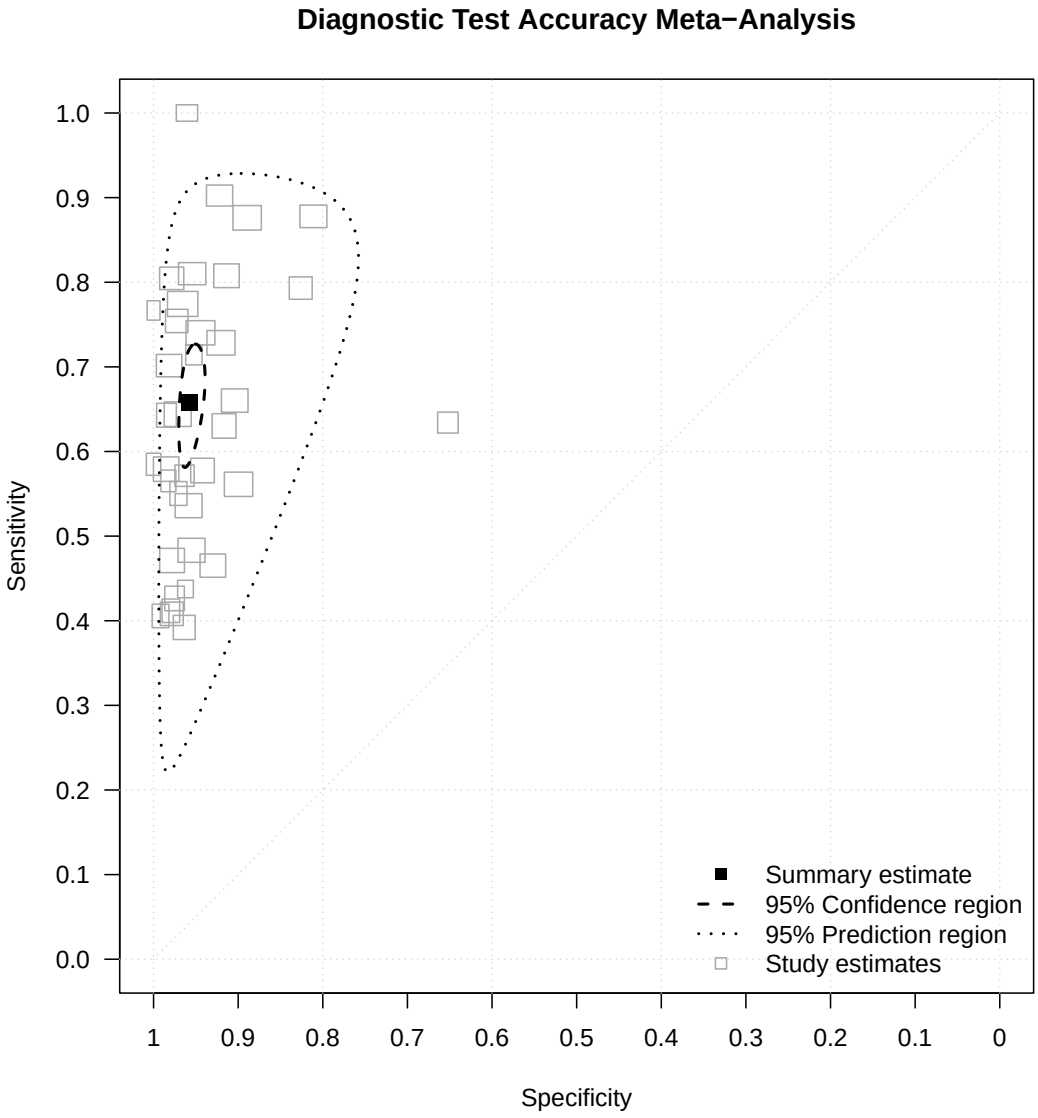
How do I get a summary plot of the Reitsma model?

The confidence region reflects uncertainty in the estimated summary point, whereas the prediction region reflects the likely location of a future study.

```
plot(reitsma)
```



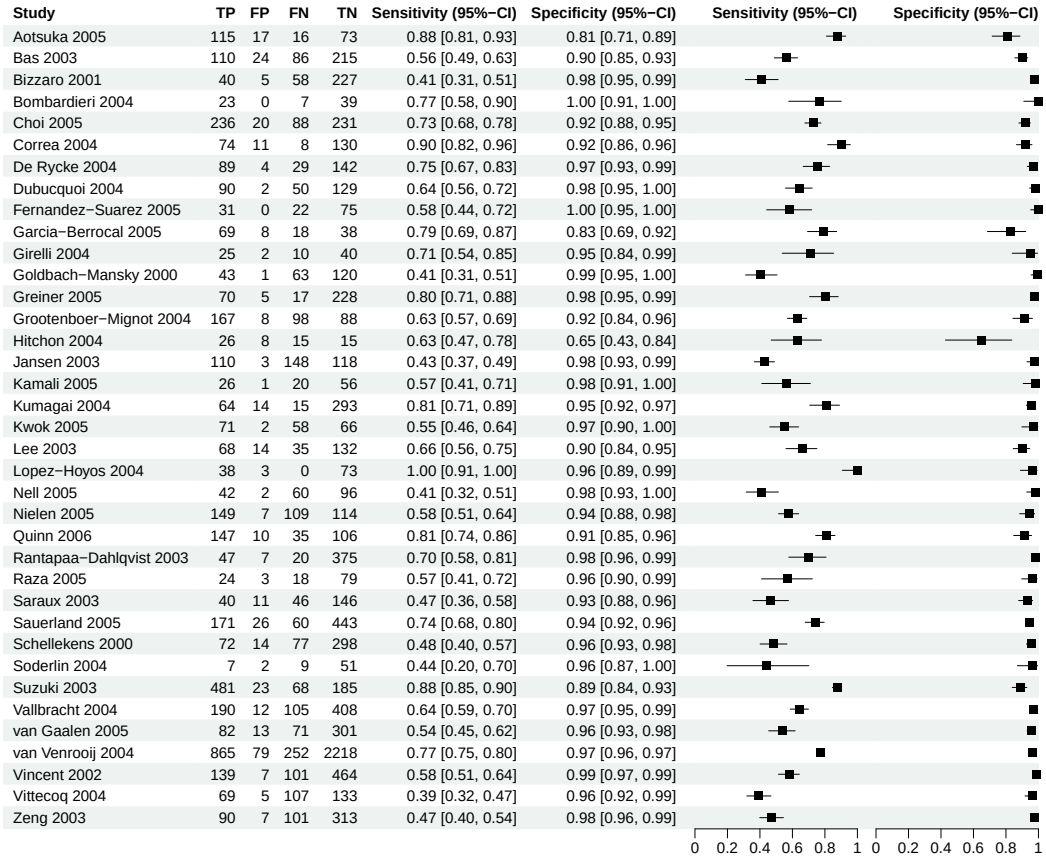
```r
plot(reitsma,scale=0.01)
```



How do I get a coupled forest plot?

Note: Rendering forest plots may take longer in an interactive R session due to the underlying grid graphics. Performance is typically faster when knitting the vignette (e.g. via RMarkdown or Quarto).

```
forest(reitsma)
```



How do I export results to RevMan?

```
as_revman(reitsma)
#>     Externally_Calculated_Parameters      Parameter     Estimate
#> 1             HSROC model parameters         Lambda  3.730686100
#> 2             HSROC model parameters          Theta -1.203359765
#> 3             HSROC model parameters           beta  0.026080802
#> 4             HSROC model parameters  Var(accuracy)  0.573137991
#> 5             HSROC model parameters Var(threshold)  0.413690010
```

```
#> 6         Bivariate model parameters     E(logitSe)  0.653406799
#> 7         Bivariate model parameters     E(logitSp)  3.108981987
#> 8         Bivariate model parameters   Var(logitSe)  0.542635959
#> 9         Bivariate model parameters   Var(logitSp)  0.571691936
#> 10        Bivariate model parameters    Cov(logits) -0.270405512
#> 11        Bivariate model parameters   Corr(logits) -0.485489925
#> 12 Confidence and prediction regions SE(E(logitSe))  0.127486209
#> 13 Confidence and prediction regions SE(E(logitSp))  0.145883358
#> 14 Confidence and prediction regions        Cov(Es) -0.007412158
#> 15 Confidence and prediction regions        Studies 37.000000000
```

How do I fit the Reitsma model using the custom TMB backend?

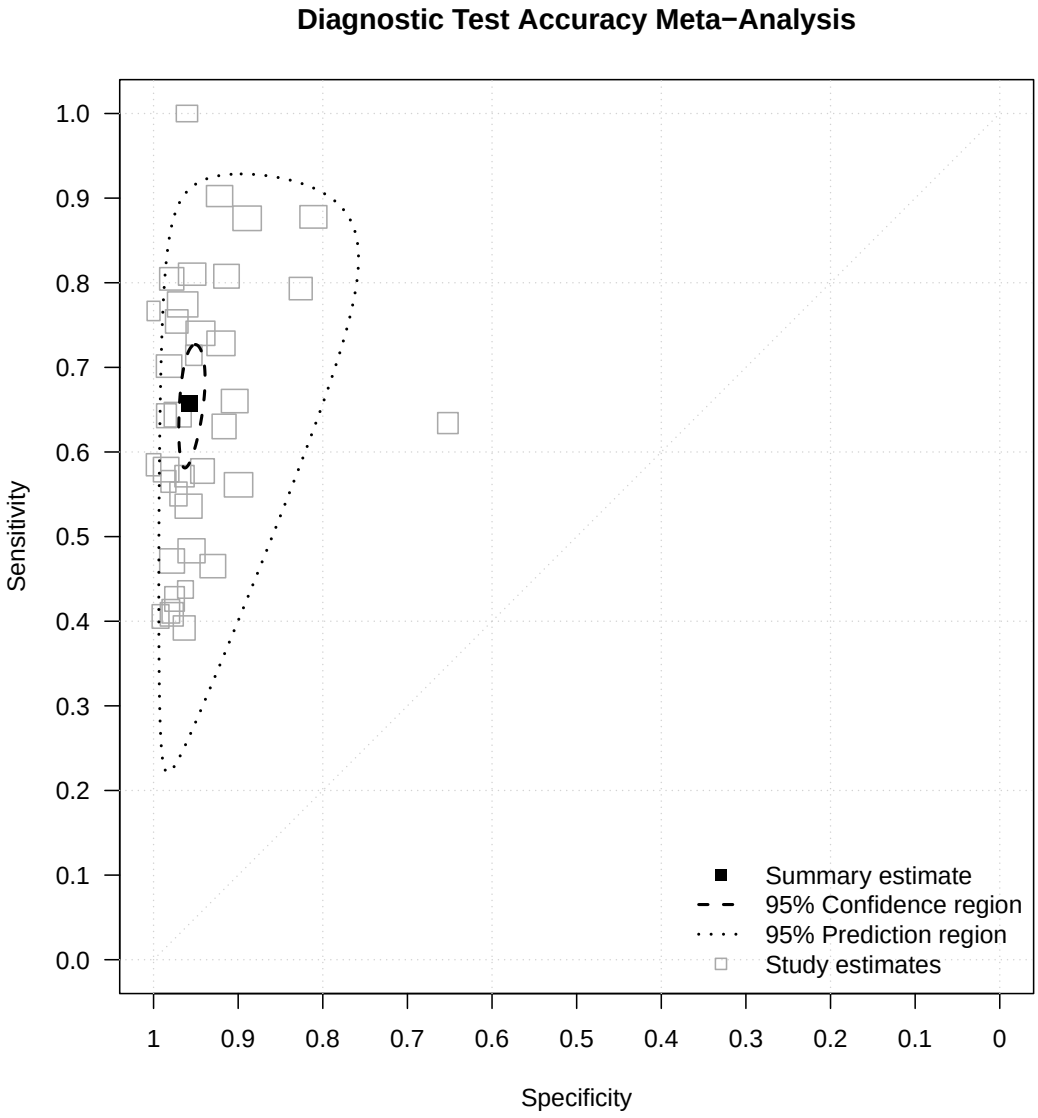
By default, `fitReitsma()` fits the Reitsma model using `glmmTMB`. The package also provides `fitReitsmaTMB()`, which fits the same binomial-normal model using a custom Template Model Builder (`TMB`) template.

The custom `TMB` backend may offer improved numerical robustness in difficult or near-boundary cases.

```
data("anticcp")
reitsmaTMB <- fitReitsmaTMB(data=anticcp,
                            TP=TP,
                            FP=FP,
                            FN=FN,
                            TN=TN,
                            study=study)
reitsmaTMB
#>
#> Reitsma TMB Model
#> -----------------
#>
#> Number of studies : 37
#> Optimizer         : Converged
#> Hessian           : Positive definite
#> Max |grad|        : 0.0004114546
#> -2 log likelihood : 545.56 ( df = 5 )
#> AIC               : 555.56
#> BIC               : 563.614
#>
#> mu_A (logitsens)  : 0.653
```

```
#> mu_B (logitspec)  : 3.109
#>
#> Use summary() for parameter estimates.
summary(reitsmaTMB)
#>
#> Summary: Reitsma TMB Model
#> --------------------------
#>
#> Parameter estimates
#> -------------------
#>                  Estimate Std. Error
#> mu_A.sens      0.65339642 0.12748598
#> mu_B.spec      3.10899660 0.14588404
#> sigma2_A.sens  0.54263463 0.14634598
#> sigma2_B.spec  0.57169319 0.18731826
#> sigma_AB      -0.27041467 0.11985014
#> rho_AB        -0.48550643 0.16226910
#>
#> Sensitivity / specificity
#> -------------------------
#>        Estimate conflevel   CI_Lower   CI_Upper
#> sens 0.65777543      0.95 0.59953512 0.71161987
#> spec 0.95726232      0.95 0.94390978 0.96754552
#>
#> Recovered HSROC parameters (Rutter-Gatsonis)
#> --------------------------------------------
#>                         Lambda    Theta        beta sigma2_alpha sigma2_theta
#> Estimate (recovered) 3.7306872 -1.20337 0.026083129   0.57311953   0.41369455
```

```
plot(reitsmaTMB,scale=0.01)
```



An example illustrating numerical behaviour near the boundary

The custom `TMB` implementation can be useful in cases where optimization with the `glmmTMB` backend encounters convergence difficulties. The following small example illustrates such a case. The estimated between-study correlation of the dataset is close to the boundary.

```
edge_data_set <- data.frame(study=1:7,
                            TP=c(18,27, 7, 5,28,14,48),
```

```
                            FP=c(32, 7,11,11,35,12,20),
                            FN=c( 3,12, 2, 2, 4, 8,23),
                            TN=c(51, 6,41,28,53,48,51))
glmmTMB <- fitReitsma(data=edge_data_set,
                      TP=TP,FP=FP,FN=FN,TN=TN,study=study)
#> Warning in finalizeTMB(TMBStruc, obj, fit, h, data.tmb.old): Model convergence
#> problem; singular convergence (7). See vignette('troubleshooting'),
#> help('diagnose')
#> Warning in fitReitsma(data = edge_data_set, TP = TP, FP = FP, FN = FN, TN = TN,
#> : TMB optimization did not converge. Estimates may be unreliable. Consider
#> checking starting values, model specification, or data quality.
glmmTMB
#>
#> Reitsma Model
#> -------------
#>
#> Number of studies : 7
#> Optimizer         : Not converged
#> Hessian           : Positive definite
#> Max |grad|        : 4.222584e-07
#> -2 log likelihood : 70.167 ( df = 5 )
#> AIC               : 80.167
#> BIC               : 79.896
#>
#> mu_A (logitsens)  : 1.026
#> mu_B (logitspec)  : 0.826
#>
#> Use summary() for parameter estimates.
summary(glmmTMB)
#>
#> Summary: Reitsma Model
#> ----------------------
#>
#> Parameter estimates
#> -------------------
#>                   Estimate   Std_Error
#> mu_A.sens      1.026397800 0.216870370
#> mu_B.spec      0.826120190 0.154243350
#> sigma2_A.sens  0.112008830 0.150316240
#> sigma2_B.spec  0.074965814 0.076649412
#> sigma_AB      -0.091634183 0.083421721
#>
```

```
#> Sensitivity / specificity
#> -------------------------
#>        Estimate conflevel   CI_Lower   CI_Upper
#> sens 0.73621694      0.95 0.64596275 0.81022240
#> spec 0.69553394      0.95 0.62803795 0.75554934
#>
#> Recovered HSROC parameters (Rutter-Gatsonis)
#> -------------------------------------------
#>                          Lambda        Theta        beta sigma2_alpha
#> Estimate (recovered) 1.8417212 0.0075037661 -0.20077275 1.047148e-07
#>                      sigma2_theta
#> Estimate (recovered)  0.091634209
TMB     <- fitReitsmaTMB(data=edge_data_set,
                         TP=TP,FP=FP,FN=FN,TN=TN,study=study)
TMB
#>
#> Reitsma TMB Model
#> -----------------
#>
#> Number of studies : 7
#> Optimizer         : Converged
#> Hessian           : Positive definite
#> Max |grad|        : 2.203348e-08
#> -2 log likelihood : 70.167 ( df = 5 )
#> AIC               : 80.167
#> BIC               : 79.897
#>
#> mu_A (logitsens)  : 1.026
#> mu_B (logitspec)  : 0.826
#>
#> Use summary() for parameter estimates.
summary(TMB)
#>
#> Summary: Reitsma TMB Model
#> --------------------------
#>
#> Parameter estimates
#> -------------------
#>                   Estimate    Std. Error
#> mu_A.sens      1.026403300 2.1686802e-01
#> mu_B.spec      0.826116370 1.5424263e-01
#> sigma2_A.sens  0.111999050 1.5030600e-01
```

```
#> sigma2_B.spec  0.074964307 7.6648618e-02
#> sigma_AB      -0.091620151 8.3407777e-02
#> rho_AB        -0.999900000 5.0547635e-05
#>
#> Sensitivity / specificity
#> -------------------------
#>        Estimate conflevel   CI_Lower   CI_Upper
#> sens 0.73621801      0.95 0.64596506 0.81022254
#> spec 0.69553313      0.95 0.62803739 0.75554837
#>
#> Recovered HSROC parameters (Rutter-Gatsonis)
#> -------------------------------------------
#>                          Lambda        Theta        beta  sigma2_alpha
#> Estimate (recovered) 1.8417222 0.0075238483 -0.20073915 1.8326471e-05
#>                      sigma2_theta
#> Estimate (recovered)  0.091624733
```

How do I use the Rutter and Gatsonis model?

The number of diseased individuals from study i who test positive is denoted by $y_{i1} \sim \mathcal{B}(n_{i1}, \pi_{i1})$.

Similarly, the number of non-diseased individuals who test positive is $y_{i2} \sim \mathcal{B}(n_{i2}, \pi_{i2})$.

At the study level, we have

$$\text{logit}(\pi_{ij}) = \left(\theta_i + \alpha_i x_{ij}\right) \exp(-\beta x_{ij}), \qquad \alpha_i \sim \mathcal{N}(\Lambda, \sigma_\alpha^2), \qquad \theta_i \sim \mathcal{N}(\Theta, \sigma_\theta^2),$$

where

$$x_{ij} = \begin{cases} -0.5 & \text{for non-diseased individuals,} \\ 0.5 & \text{for diseased individuals.} \end{cases}$$

In this parameterization Λ corresponds to accuracy, Θ to threshold, and β controls the shape of the HSROC curve.

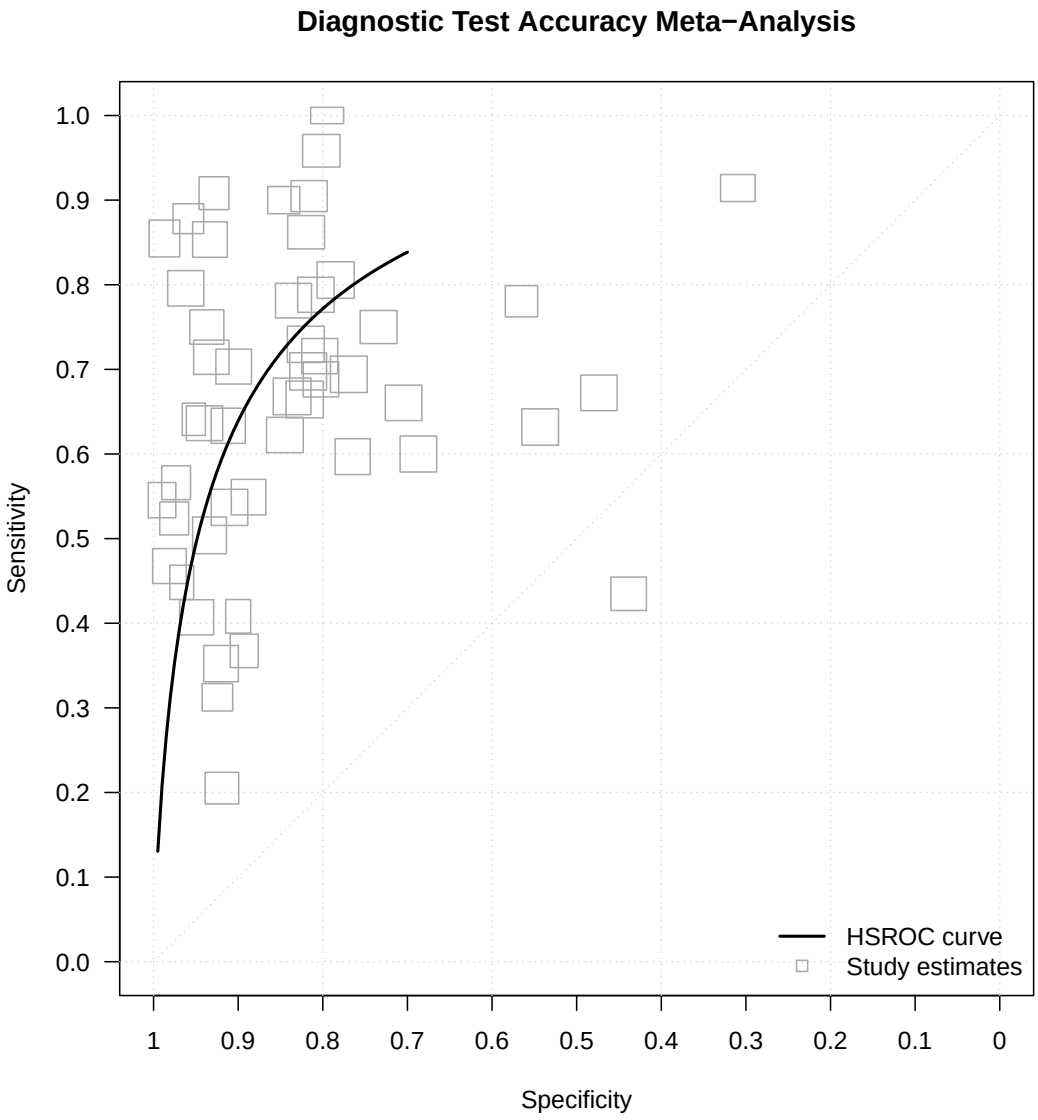
```
data("RF")
ruttergatsonis <- fitRutterGatsonis(data=RF,
                                    TP=TP,
                                    FP=FP,
                                    FN=FN,
                                    TN=TN,
                                    study=study)
```

```
ruttergatsonis
#>
#> Rutter & Gatsonis Model
#> -----------------------
#>
#> Number of studies : 50
#> Optimizer         : Converged
#> Hessian           : Positive definite
#> Max |grad|        : 0.0004308322
#> -2 log likelihood : 806.934 ( df = 5 )
#> AIC               : 816.934
#> BIC               : 826.494
#>
#> Lambda            : 2.602
#> Theta             : -0.437
#> beta              : 0.227
#>
#> Use summary() for parameter estimates.
summary(ruttergatsonis)
#>
#> Summary: Rutter & Gatsonis Model
#> --------------------------------
#>
#> Parameter estimates
#> -------------------
#>                 Estimate  Std. Error
#> Lambda        2.60159310 0.186165530
#> Theta        -0.43700385 0.146850950
#> beta          0.22670080 0.162369510
#> sigma2_alpha  1.30139230 0.304555310
#> sigma2_theta  0.54229002 0.123660680
#> logitsens     0.82868886 0.155392460
#> sens          0.69607762 0.032873828
#>
#> Sensitivity / specificity
#> -------------------------
#>         spec conflevel  logitsens  Std_Error   CI_Lower  CI_Upper       Sens
#> 1 0.86695447      0.95 0.82868886 0.15539246 0.52412524 1.1332525 0.69607762
#>   SensCI_Lower SensCI_Upper
#> 1   0.62811188   0.75643863
#>
#> Recovered bivariate parameters (Reitsma)
```

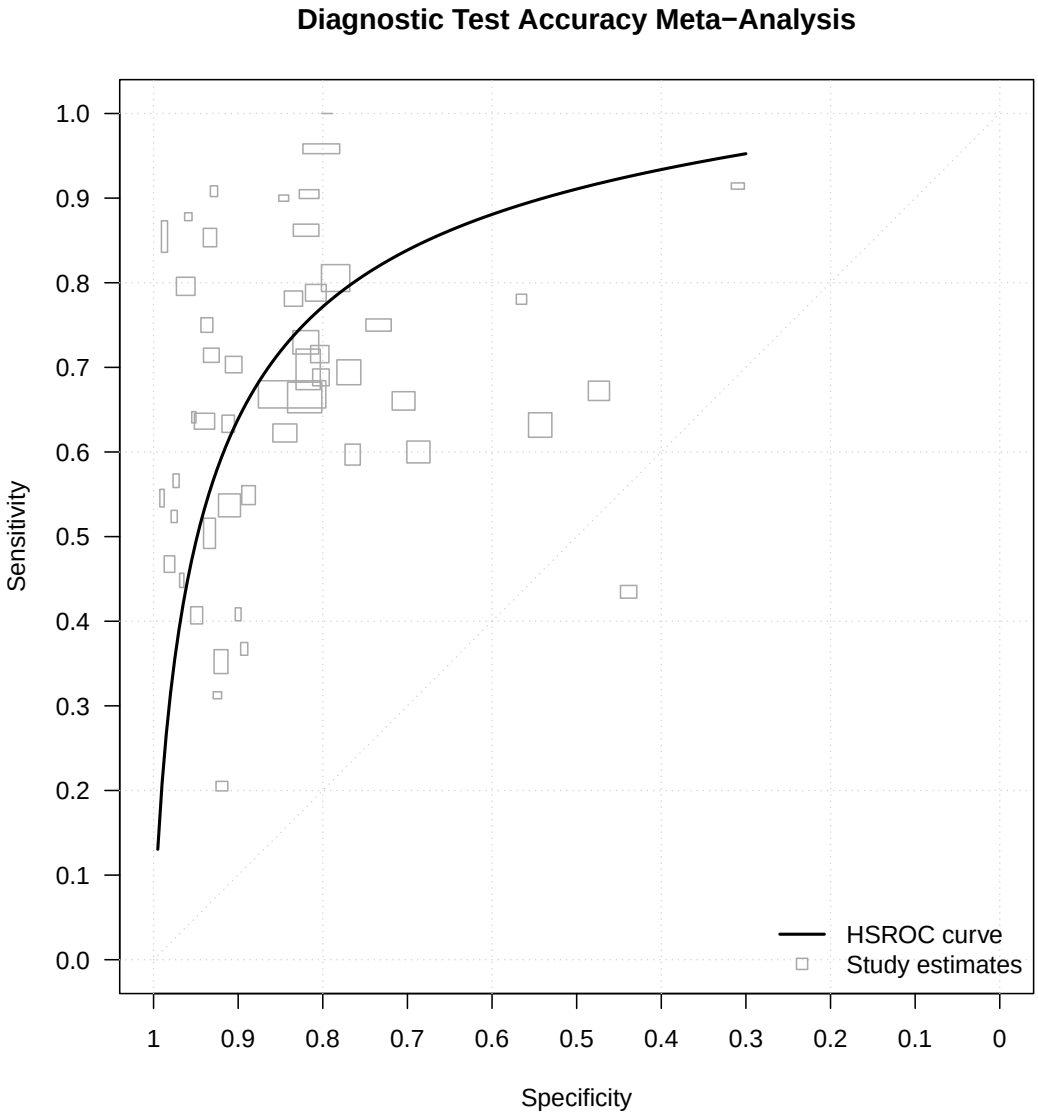
```
#> ----------------------------------------
#>                        mu_A.sens mu_B.spec sigma2_A.sens sigma2_B.spec
#> Estimate (recovered) 0.77122673 1.9463787    0.69164574     1.0884125
#>                           sigma_AB
#> Estimate (recovered) -0.21694195
```

How do I get a summary plot of the Rutter and Gatsonis model?

```
plot(ruttergatsonis)
```




```
plot(ruttergatsonis,size="se",specrange=c(0.3,0.995),scale=0.01)
```



How do I get a coupled forest plot?

Note: Rendering forest plots may take longer in an interactive R session due to the underlying grid graphics. Performance is typically faster when knitting the vignette (e.g. via RMarkdown or Quarto).

```
forest(ruttergatsonis)
```

How do I simplify the models via parameter constraints?

The package allows model parameters to be constrained to zero during estimation. This can be useful in meta-analysis of sparse data, when convergence is difficult, or when fitting simplified models as described in the Cochrane Handbook. For example,

```
reitsmacons <- fitReitsma(data = anticcp,
                          TP = TP,
                          FP = FP,
                          FN = FN,
                          TN = TN,
                          study = study,
                          constrain = "sigma_AB")
summary(reitsmacons)
#>
#> Summary: Reitsma Model
#> ----------------------
#>
#> Parameter estimates
#> -------------------
#>                  Estimate  Std_Error
#> mu_A.sens     0.65851688 0.12949981
#> mu_B.spec     3.10452120 0.14750139
#> sigma2_A.sens 0.56018968 0.15305472
#> sigma2_B.spec 0.58149319 0.19134635
#> sigma_AB      0.00000000 0.00000000
#>
#> Sensitivity / specificity
#> -------------------------
#>        Estimate conflevel   CI_Lower  CI_Upper
#> sens 0.65892715      0.95 0.59981682 0.7134771
#> spec 0.95707885      0.95 0.94350363 0.9675045
#>
#> Recovered HSROC parameters (Rutter-Gatsonis)
#> --------------------------------------------
#>                          Lambda      Theta        beta sigma2_alpha sigma2_theta
#> Estimate (recovered) 3.740378 -1.2054988 0.018661913    1.1414841   0.28537102
```

fixed the between-study random-effects covariance at zero. Other options include `constrain="sigma2_A"`, `"constrain=sigma2_B"`, or `"constrain=all"`.

The Rutter and Gatsonis model allows for the constraint $\sigma_\alpha^2 = 0$, $\sigma_\theta^2 = 0$ and/or $\beta = 0$ (shape parameter). For example

```r
ruttergatsoniscons <- fitRutterGatsonis(data = RF,
                                        TP = TP,
                                        FP = FP,
                                        FN = FN,
                                        TN = TN,
                                        study = study,
                                        constrain = c("sigma2_theta","shape"))
summary(ruttergatsoniscons)
#>
#> Summary: Rutter & Gatsonis Model
#> --------------------------------
#>
#> Parameter estimates
#> -------------------
#>                    Estimate  Std. Error
#> Lambda        2.4745580e+00 0.164585260
#> Theta        -4.7568281e-01 0.022193047
#> beta          0.0000000e+00 0.000000000
#> sigma2_alpha  1.2121724e+00 0.275679610
#> sigma2_theta  4.9303807e-32 0.000000000
#> logitsens     6.0026294e-01 0.164585260
#> sens          6.4571646e-01 0.037651628
#>
#> Sensitivity / specificity
#> -------------------------
#>         spec conflevel  logitsens  Std_Error   CI_Lower   CI_Upper       Sens
#> 1 0.86695447      0.95 0.60026294 0.16458526 0.27768176 0.92284411 0.64571646
#>   SensCI_Lower SensCI_Upper
#> 1   0.56897779   0.71562126
#>
#> Recovered bivariate parameters (Reitsma)
#> ----------------------------------------
#>                        mu_A.sens mu_B.spec sigma2_A.sens sigma2_B.spec
#> Estimate (recovered) 0.76159621 1.7129618    0.30304309    0.30304309
#>                         sigma_AB
#> Estimate (recovered) 0.30304309
```

How do I use the Hoyer model?

The Hoyer model assumes that the diagnostic test measurement arises from a latent continuous variable Y_j, with $j = 0$ for the non-diseased individuals and $j = 1$ for the diseased, which follows

a parametric survival distribution. The observed test results correspond to interval-censored observations of this latent variable due to the use of thresholds.

Which distributions does `dtametaTMB` support?

The latent variable Y_j is assumed to follow a location–scale family:

$$Y_j \sim F(\mu_j, \phi_j),$$

where:

- μ_j is a study-specific location parameter
- ϕ_j is a scale parameter

Common choices for F include:

Weibull distribution

$$f(y; \mu_j, \phi_j) = \mu_j \phi_j y^{\phi_j - 1} \exp(-\mu_j y^{\phi_j})$$

Log-normal distribution

$$f(y; \mu_j, \phi_j) = \frac{1}{\phi_j y} \varphi\left(\frac{\log(y) - \mu_j}{\phi_j} \right)$$

Log-logistic distribution

$$f(y; \mu_j, \phi_j) = \frac{\mu_j \phi_j y^{\phi_j - 1}}{\left(1 + \mu_j y^{\phi_j}\right)^2}$$

Random effects structure

To account for between-study heterogeneity and the correlation between diseased and non-diseased groups, we introduce study-specific random effects:

$$\log(y_{0i}) = \beta_0 + \varepsilon_{0i} + u_{0i}, \quad \log(y_{1i}) = \beta_1 + \varepsilon_{1i} + u_{1i},$$

with

$$\begin{pmatrix} u_{0i} \\ u_{1i} \end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_0^2 & \rho\sigma_0\sigma_1 \\ \rho\sigma_0\sigma_1 & \sigma_1^2 \end{pmatrix} \right).$$

Censoring mechanism

Because only thresholded outcomes (TN,TP,FN,FP) are observed, the latent variable Y_j is subject to censoring.

- Left censoring: $(-\infty, y_k^R]$
- Interval censoring between adjacent thresholds
- Right censoring: $(y_k^L, +\infty)$

where y_k^L and y_k^R denote finite threshold values.

How do I compute sensitivities and specificities?

We can model the ROC curve by predicting sensitivities and specificities (1 - false positive rates) at several threshold values y.

Weibull distribution

$$S_1(y) = \exp\left(-\exp\left(\frac{\log(y) - \beta_1}{\lambda_1}\right)\right), \quad \text{with} \quad \beta_1 = -\log(\mu_1), \quad \lambda_1 = 1/\phi_1,$$

$$S_0(y) = \exp\left(-\exp\left(\frac{\log(y) - \beta_0}{\lambda_0}\right)\right), \quad \text{with} \quad \beta_0 = -\log(\mu_0), \quad \lambda_0 = 1/\phi_0.$$

Log-normal distribution

$$S_1(y) = 1 - \Phi\left(\frac{\log(y) - \beta_1}{\lambda_1}\right), \quad \text{with} \quad \beta_1 = \mu_1, \quad \lambda_1 = \phi_1,$$

$$S_0(y) = 1 - \Phi\left(\frac{\log(y) - \beta_0}{\lambda_0}\right), \quad \text{with} \quad \beta_0 = \mu_0, \quad \lambda_0 = \phi_0.$$

Log-logistic distribution

$$S_1(y) = \left(1 + \exp\left(\frac{\log(y) - \beta_1}{\lambda_1}\right)\right)^{-1}, \quad \text{with} \quad \beta_1 = -\phi_1^{-1}\log(\mu_1), \quad \lambda_1 = 1/\phi_1,$$

$$S_0(y) = \left(1 + \exp\left(\frac{\log(y) - \beta_0}{\lambda_0}\right)\right)^{-1}, \quad \text{with} \quad \beta_0 = -\phi_0^{-1}\log(\mu_0), \quad \lambda_0 = 1/\phi_0.$$

How do I interpret test direction?

For tests where larger values indicate disease (`testdirection = "greater"`):

- $S_1(y)$ corresponds to **sensitivity** at threshold y
- $S_0(y)$ corresponds to the **false positive rate (FPR) = 1 - specificity**

For tests where smaller values indicate disease (`testdirection = "less"`):

- $S_1(y)$ corresponds to the **false negative rate (FNR) = 1 - sensitivity**
- $S_0(y)$ corresponds to **specificity**

In a nutshell

By modelling the diagnostic marker as a latent continuous outcome, the Hoyer model:

- naturally accommodates **multiple thresholds per study**
- provides a unified framework for **interval-censored diagnostic data**
- preserves the correlation between sensitivity and specificity

The following parameters have to be estimated: β_0, β_1, λ_0, λ_1, σ_0^2, σ_1^2, and ρ, where λ_0 and λ_1 are transformations of ϕ_0 and ϕ_1.

To obtain initial values, it is necessary to specify a smallest ($\ll \min y$) and largest ($\gg \max y$) value across all studies, essentially replacing negative and positive infinity for the left and right censored intervals.

How do I fit the Hoyer model?

```
data("diabetes")
head(diabetes)
#>      study threshold  TP   TN   FP  FN   D    H originally_published
#> 1 Study 01       5.9 574 1389  682 262 836 2071                     1
#> 2 Study 02       5.0 617 1005 7735  18 635 8740                     0
#> 3 Study 02       5.1 607 1617 7123  28 635 8740                     0
#> 4 Study 02       5.2 600 2438 6302  35 635 8740                     0
#> 5 Study 02       5.3 581 3409 5331  54 635 8740                     0
#> 6 Study 02       5.4 563 4422 4318  72 635 8740                     0
summary(diabetes$threshold)
#>    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
#>   3.900   5.500   5.800   5.837   6.100   7.600
```

The argument `eval_threshold` specifies the values at which sensitivities and specificities are evaluated after model fitting.

```
hoyer <- fitHoyer(data=diabetes,
                  TP=TP,
                  FP=FP,
                  FN=FN,
                  TN=TN,
                  threshold=threshold,
                  study=study,
                  dist="loglogistic",
                  testdirection="greater",
                  eval_threshold=c(5.0,5.5,6.0,6.5,7.0,7.5),
                  smallest=2,
                  largest=10)
```

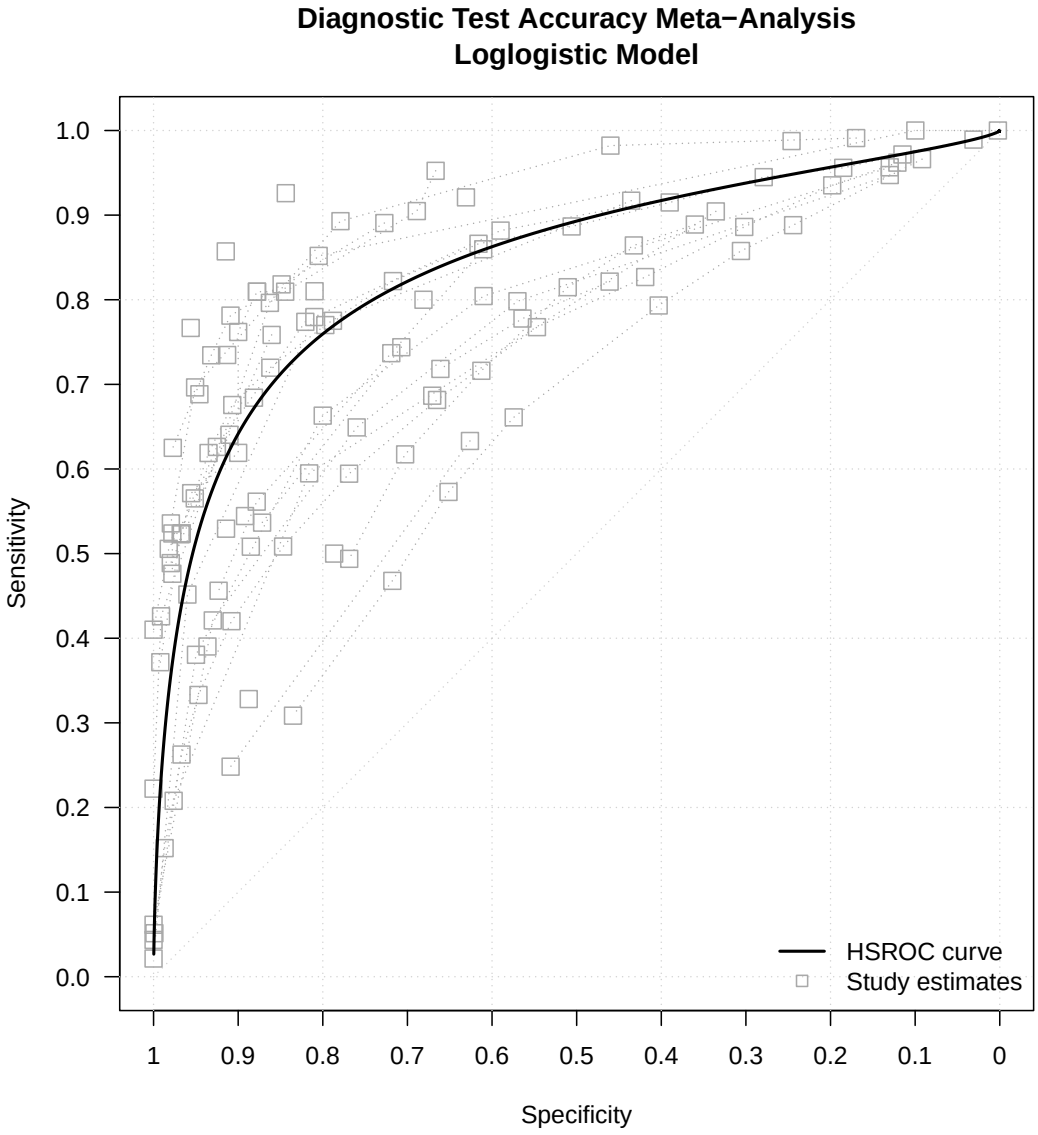
```
hoyer
#>
#> Hoyer Model
#> -----------
#>
#> Number of studies : 38
#> Optimizer         : Converged
#> Hessian           : Positive definite
#> Max |grad|        : 0.06428937
#> -2 log likelihood : 209322 ( df = 7 )
```

```
#> AIC               : 209336
#> BIC               : 209347.4
#>
#> Distribution      : Loglogistic
#> Test direction    : greater
#>
#> Use summary() for parameter estimates.
summary(hoyer)
#>
#> Summary: Hoyer Model
#> --------------------
#>
#> Parameter estimates
#> -------------------
#>                 Estimate    Std. Error
#> beta0       1.7056907000 0.00956289900
#> lambda0     0.0395019340 0.00018572605
#> su0         0.0586479640 0.00677833570
#> beta1       1.8253382000 0.01456523200
#> lambda1     0.0563985690 0.00092447465
#> su1         0.0883203880 0.01095635700
#> rho         0.8630308200 0.04544135200
#> covu0u1     0.0044703365 0.00114169150
#> logitSurv1  3.8281158000 0.26350285000
#> logitSurv1  2.1381761000 0.25933414000
#> logitSurv1  0.5953820900 0.25807847000
#> logitSurv1 -0.8238508600 0.25910685000
#> logitSurv1 -2.1378553000 0.26190416000
#> logitSurv1 -3.3611642000 0.26605379000
#> logitSurv0  2.4366593000 0.24260151000
#> logitSurv0  0.0238614540 0.24208927000
#> logitSurv0 -2.1788504000 0.24208531000
#> logitSurv0 -4.2051488000 0.24247261000
#> logitSurv0 -6.0812082000 0.24316365000
#> logitSurv0 -7.8277776000 0.24409190000
#>
#> Sensitivity / specificity
#> -------------------------
#>   threshold conflevel        Sens SensCI_Lower SensCI_Upper        Spec
#> 1       5.0      0.95 0.978712460  0.964826650  0.987189180 0.080419621
#> 2       5.5      0.95 0.894558700  0.836154650  0.933792570 0.494034920
#> 3       6.0      0.95 0.644599090  0.522374440  0.750486120 0.898334120
```

```
#> 4       6.5      0.95 0.304946840  0.208879800  0.421648260 0.985300730
#> 5       7.0      0.95 0.105471560  0.065916438  0.164580710 0.997719800
#> 6       7.5      0.95 0.033531473  0.020181123  0.055215748 0.999601650
#>   SpecCI_Lower SpecCI_Upper
#> 1  0.051556228   0.12334059
#> 2  0.377929040   0.61078778
#> 3  0.846104860   0.93421587
#> 4  0.976567300   0.99080981
#> 5  0.996332670   0.99858301
#> 6  0.999357410   0.99975308
```

How do I get a summary plot of the Hoyer model?

```
plot(hoyer,
     main="Diagnostic Test Accuracy Meta-Analysis\nLoglogistic Model")
```

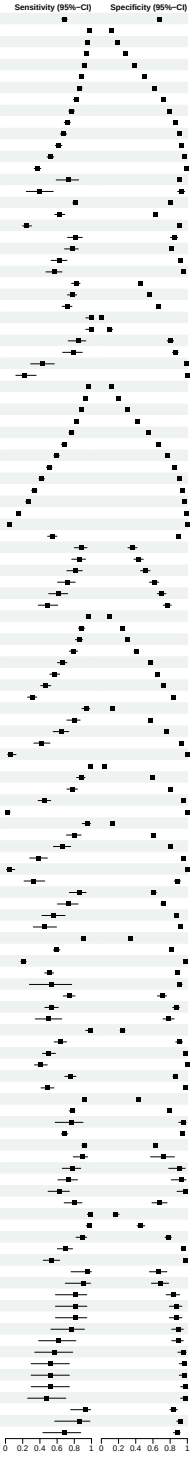


How do I get a coupled forest plot?

Note: Rendering forest plots may take longer in an interactive R session due to the underlying grid graphics. Performance is typically faster when knitting the vignette (e.g. via RMarkdown or Quarto).

```
forest(hoyer)
```

Study	Threshold	TP	FP	FN	TN	Sensitivity (95%−CI)	Specificity (95%−CI)
Study 01	5.9	574	682	262	1389	0.69 [0.65, 0.72]	0.67 [0.65, 0.69]
Study 02	5.0	617	7735	18	1005	0.97 [0.96, 0.98]	0.11 [0.11, 0.12]
	5.1	607	7123	28	1617	0.96 [0.94, 0.97]	0.19 [0.18, 0.19]
	5.2	600	6302	35	2438	0.94 [0.92, 0.96]	0.28 [0.27, 0.29]
	5.3	581	5331	54	3409	0.91 [0.89, 0.94]	0.39 [0.38, 0.40]
	5.4	563	4318	72	4422	0.89 [0.86, 0.91]	0.51 [0.50, 0.52]
	5.5	550	3356	85	5384	0.87 [0.84, 0.89]	0.62 [0.61, 0.63]
	5.6	522	2473	113	6267	0.82 [0.79, 0.85]	0.72 [0.71, 0.73]
	5.7	489	1774	146	6966	0.77 [0.74, 0.80]	0.80 [0.79, 0.81]
	5.8	457	1206	178	7534	0.72 [0.68, 0.75]	0.86 [0.85, 0.87]
	5.9	429	813	206	7927	0.68 [0.64, 0.71]	0.91 [0.90, 0.91]
	6.0	393	568	242	8172	0.62 [0.58, 0.66]	0.94 [0.93, 0.94]
	6.2	332	280	303	8460	0.52 [0.48, 0.56]	0.97 [0.96, 0.97]
	6.6	236	70	399	8670	0.37 [0.33, 0.41]	0.99 [0.99, 0.99]
Study 03	6.2	36	95	13	998	0.73 [0.59, 0.85]	0.91 [0.89, 0.93]
Study 04	6.0	16	10	25	147	0.39 [0.24, 0.55]	0.94 [0.89, 0.97]
Study 05	6.1	644	286	151	1217	0.81 [0.78, 0.84]	0.81 [0.79, 0.83]
Study 06	5.6	176	768	102	1286	0.63 [0.57, 0.69]	0.63 [0.60, 0.65]
	6.5	69	187	209	1867	0.25 [0.20, 0.30]	0.91 [0.90, 0.92]
Study 07	6.1	72	46	16	258	0.82 [0.72, 0.89]	0.85 [0.80, 0.89]
Study 08	5.3	89	302	26	1382	0.77 [0.69, 0.85]	0.82 [0.80, 0.84]
	5.5	72	126	43	1558	0.63 [0.53, 0.71]	0.93 [0.91, 0.94]
	5.6	65	82	50	1602	0.57 [0.47, 0.66]	0.95 [0.94, 0.96]
Study 09	5.8	207	3161	45	2704	0.82 [0.77, 0.87]	0.46 [0.45, 0.47]
	5.9	196	2557	56	3308	0.78 [0.72, 0.83]	0.56 [0.55, 0.58]
	6.0	181	1988	71	3877	0.72 [0.66, 0.77]	0.66 [0.65, 0.67]
Study 10	3.9	54	450	0	1	1.00 [0.93, 1.00]	0.00 [0.00, 0.01]
	4.7	54	406	0	45	1.00 [0.93, 1.00]	0.10 [0.07, 0.13]
	5.6	46	88	8	363	0.85 [0.73, 0.93]	0.80 [0.77, 0.84]
	5.7	43	62	11	389	0.80 [0.66, 0.89]	0.86 [0.83, 0.89]
	6.2	23	4	31	447	0.43 [0.29, 0.57]	0.99 [0.98, 1.00]
	6.8	12	0	42	451	0.22 [0.12, 0.36]	1.00 [0.99, 1.00]
Study 11	5.0	861	4439	34	611	0.96 [0.95, 0.97]	0.12 [0.11, 0.13]
	5.1	837	4050	58	1000	0.94 [0.92, 0.95]	0.20 [0.19, 0.21]
	5.2	793	3525	102	1525	0.89 [0.86, 0.91]	0.30 [0.29, 0.31]
	5.3	740	2934	155	2116	0.83 [0.80, 0.85]	0.42 [0.41, 0.43]
	5.4	687	2288	208	2762	0.77 [0.74, 0.79]	0.55 [0.53, 0.56]
	5.5	610	1692	285	3358	0.68 [0.65, 0.71]	0.66 [0.65, 0.68]
	5.6	532	1167	363	3883	0.59 [0.56, 0.63]	0.77 [0.76, 0.78]
	5.7	455	773	440	4277	0.51 [0.48, 0.54]	0.85 [0.84, 0.86]
	5.8	376	465	519	4585	0.42 [0.39, 0.45]	0.91 [0.90, 0.92]
	5.9	298	268	597	4782	0.33 [0.30, 0.36]	0.95 [0.94, 0.95]
	6.0	235	167	660	4883	0.26 [0.23, 0.29]	0.97 [0.96, 0.97]
	6.2	136	66	759	4984	0.15 [0.13, 0.18]	0.99 [0.98, 0.99]
	6.6	46	5	849	5045	0.05 [0.04, 0.07]	1.00 [1.00, 1.00]
Study 12	5.7	184	638	154	5265	0.54 [0.49, 0.60]	0.89 [0.88, 0.90]
Study 13	5.5	72	213	9	120	0.89 [0.80, 0.95]	0.36 [0.31, 0.41]
	5.6	70	189	11	144	0.86 [0.77, 0.93]	0.43 [0.38, 0.49]
	5.7	66	163	15	170	0.81 [0.71, 0.89]	0.51 [0.46, 0.57]
	5.8	58	129	23	204	0.72 [0.60, 0.81]	0.61 [0.56, 0.67]
	5.9	50	99	31	234	0.62 [0.50, 0.72]	0.70 [0.65, 0.75]
	6.0	40	77	41	256	0.49 [0.38, 0.61]	0.77 [0.72, 0.81]
Study 14	4.8	285	1532	10	155	0.97 [0.94, 0.98]	0.09 [0.08, 0.11]
	5.1	262	1275	33	412	0.89 [0.85, 0.92]	0.24 [0.22, 0.27]
	5.2	253	1171	42	516	0.86 [0.81, 0.90]	0.31 [0.28, 0.33]
	5.3	234	1007	61	680	0.79 [0.74, 0.84]	0.40 [0.38, 0.43]
	5.5	195	718	100	969	0.66 [0.60, 0.71]	0.57 [0.55, 0.60]
	5.6	169	588	126	1099	0.57 [0.51, 0.63]	0.65 [0.63, 0.67]
	5.7	138	476	157	1211	0.47 [0.41, 0.53]	0.72 [0.70, 0.74]
	5.9	91	278	204	1409	0.31 [0.26, 0.36]	0.84 [0.82, 0.85]
Study 15	5.0	108	4190	6	626	0.95 [0.89, 0.98]	0.13 [0.12, 0.14]
	5.5	91	2071	23	2745	0.80 [0.71, 0.87]	0.57 [0.56, 0.58]
	5.7	74	1156	40	3660	0.65 [0.55, 0.74]	0.76 [0.75, 0.77]
	6.0	48	337	66	4479	0.42 [0.33, 0.52]	0.93 [0.92, 0.94]
	6.4	7	0	107	4816	0.06 [0.03, 0.12]	1.00 [1.00, 1.00]
Study 16	5.0	184	5645	2	181	0.99 [0.96, 1.00]	0.03 [0.03, 0.04]
	5.5	164	2389	22	3437	0.88 [0.83, 0.92]	0.59 [0.58, 0.60]
	5.7	145	1107	41	4719	0.78 [0.71, 0.84]	0.81 [0.80, 0.82]
	6.0	84	233	102	5593	0.45 [0.38, 0.53]	0.96 [0.95, 0.96]
	6.4	4	0	182	5826	0.02 [0.01, 0.05]	1.00 [1.00, 1.00]
Study 17	5.0	88	3212	4	480	0.96 [0.89, 0.99]	0.13 [0.12, 0.14]
	5.5	74	1440	18	2252	0.80 [0.71, 0.88]	0.61 [0.59, 0.63]
	5.7	61	738	31	2954	0.66 [0.56, 0.76]	0.80 [0.79, 0.81]
	6.0	35	185	57	3507	0.38 [0.28, 0.49]	0.95 [0.94, 0.96]
	6.4	4	0	88	3692	0.04 [0.01, 0.11]	1.00 [1.00, 1.00]
Study 18	5.7	21	36	43	284	0.33 [0.22, 0.46]	0.89 [0.85, 0.92]
Study 19	5.1	49	441	8	691	0.86 [0.74, 0.94]	0.61 [0.58, 0.64]
	5.2	42	318	15	814	0.74 [0.60, 0.84]	0.72 [0.69, 0.75]
	5.3	32	138	25	994	0.56 [0.42, 0.69]	0.88 [0.86, 0.90]
	5.4	26	87	31	1045	0.46 [0.32, 0.59]	0.92 [0.91, 0.94]
Study 20	5.0	596	4083	63	2062	0.90 [0.88, 0.93]	0.34 [0.32, 0.35]
	5.5	392	1130	267	5015	0.59 [0.56, 0.63]	0.82 [0.81, 0.83]
	6.0	137	146	522	5999	0.21 [0.18, 0.24]	0.98 [0.97, 0.98]
Study 21	5.5	187	1112	181	8562	0.51 [0.46, 0.56]	0.89 [0.88, 0.89]
Study 22	5.8	9	37	8	395	0.53 [0.28, 0.77]	0.91 [0.88, 0.94]
Study 23	5.5	122	89	42	215	0.74 [0.67, 0.81]	0.71 [0.65, 0.76]
	5.7	88	39	76	265	0.54 [0.46, 0.61]	0.87 [0.83, 0.91]
Study 24	6.1	22	35	22	129	0.50 [0.35, 0.65]	0.79 [0.72, 0.85]
Study 25	6.6	79	665	1	217	0.99 [0.93, 1.00]	0.25 [0.22, 0.28]
Study 26	6.9	114	20	64	203	0.64 [0.57, 0.71]	0.91 [0.86, 0.94]
	7.4	90	4	88	219	0.51 [0.43, 0.58]	0.98 [0.95, 1.00]
	7.6	73	0	105	223	0.41 [0.34, 0.49]	1.00 [0.98, 1.00]
Study 27	5.9	135	96	43	592	0.76 [0.69, 0.82]	0.86 [0.83, 0.89]
	6.5	87	14	91	674	0.49 [0.41, 0.56]	0.98 [0.97, 0.99]
Study 28	5.5	575	1270	52	980	0.92 [0.89, 0.94]	0.44 [0.41, 0.46]
	6.1	486	477	141	1773	0.78 [0.74, 0.81]	0.79 [0.77, 0.80]
Study 29	6.1	23	5	7	109	0.77 [0.58, 0.90]	0.96 [0.90, 0.99]
Study 30	6.0	424	121	192	2112	0.69 [0.65, 0.72]	0.95 [0.94, 0.95]
Study 31	5.7	338	2376	29	4060	0.92 [0.89, 0.95]	0.63 [0.62, 0.64]
Study 32	6.0	57	12	7	32	0.89 [0.79, 0.95]	0.73 [0.57, 0.85]
	6.4	50	4	14	40	0.78 [0.66, 0.87]	0.91 [0.78, 0.97]
	6.5	47	3	17	41	0.73 [0.61, 0.84]	0.93 [0.81, 0.99]
	7.0	40	1	24	43	0.62 [0.50, 0.74]	0.98 [0.88, 1.00]
Study 33	5.6	52	37	13	79	0.80 [0.68, 0.89]	0.68 [0.59, 0.76]
Study 34	5.0	111	406	1	83	0.99 [0.95, 1.00]	0.17 [0.14, 0.21]
	5.5	110	264	2	225	0.98 [0.94, 1.00]	0.46 [0.42, 0.51]
	6.0	100	108	12	381	0.89 [0.82, 0.94]	0.78 [0.74, 0.82]
	6.5	78	24	34	465	0.70 [0.60, 0.78]	0.95 [0.93, 0.97]
	7.0	60	10	52	479	0.54 [0.44, 0.63]	0.98 [0.96, 0.99]
Study 35	5.9	20	30	1	60	0.95 [0.76, 1.00]	0.67 [0.56, 0.76]
	6.0	19	28	2	62	0.90 [0.70, 0.99]	0.69 [0.58, 0.78]
	6.1	17	14	4	76	0.81 [0.58, 0.95]	0.84 [0.75, 0.91]
	6.2	17	11	4	79	0.81 [0.58, 0.95]	0.88 [0.79, 0.94]
	6.3	17	11	4	79	0.81 [0.58, 0.95]	0.88 [0.79, 0.94]
	6.4	16	9	5	81	0.76 [0.53, 0.92]	0.90 [0.82, 0.95]
	6.5	13	9	8	81	0.62 [0.38, 0.82]	0.90 [0.82, 0.95]
	6.6	12	4	9	86	0.57 [0.34, 0.78]	0.96 [0.89, 0.99]
	6.7	11	3	10	87	0.52 [0.30, 0.74]	0.97 [0.91, 0.99]
	6.8	11	3	10	87	0.52 [0.30, 0.74]	0.97 [0.91, 0.99]
	6.9	11	2	10	88	0.52 [0.30, 0.74]	0.98 [0.92, 1.00]
	7.0	10	2	11	88	0.48 [0.26, 0.70]	0.98 [0.92, 1.00]
Study 36	5.9	25	45	2	243	0.93 [0.76, 0.99]	0.84 [0.80, 0.88]
Study 37	5.9	12	25	2	268	0.86 [0.57, 0.98]	0.91 [0.88, 0.94]
Study 38	5.9	13	35	6	260	0.68 [0.43, 0.87]	0.88 [0.84, 0.92]

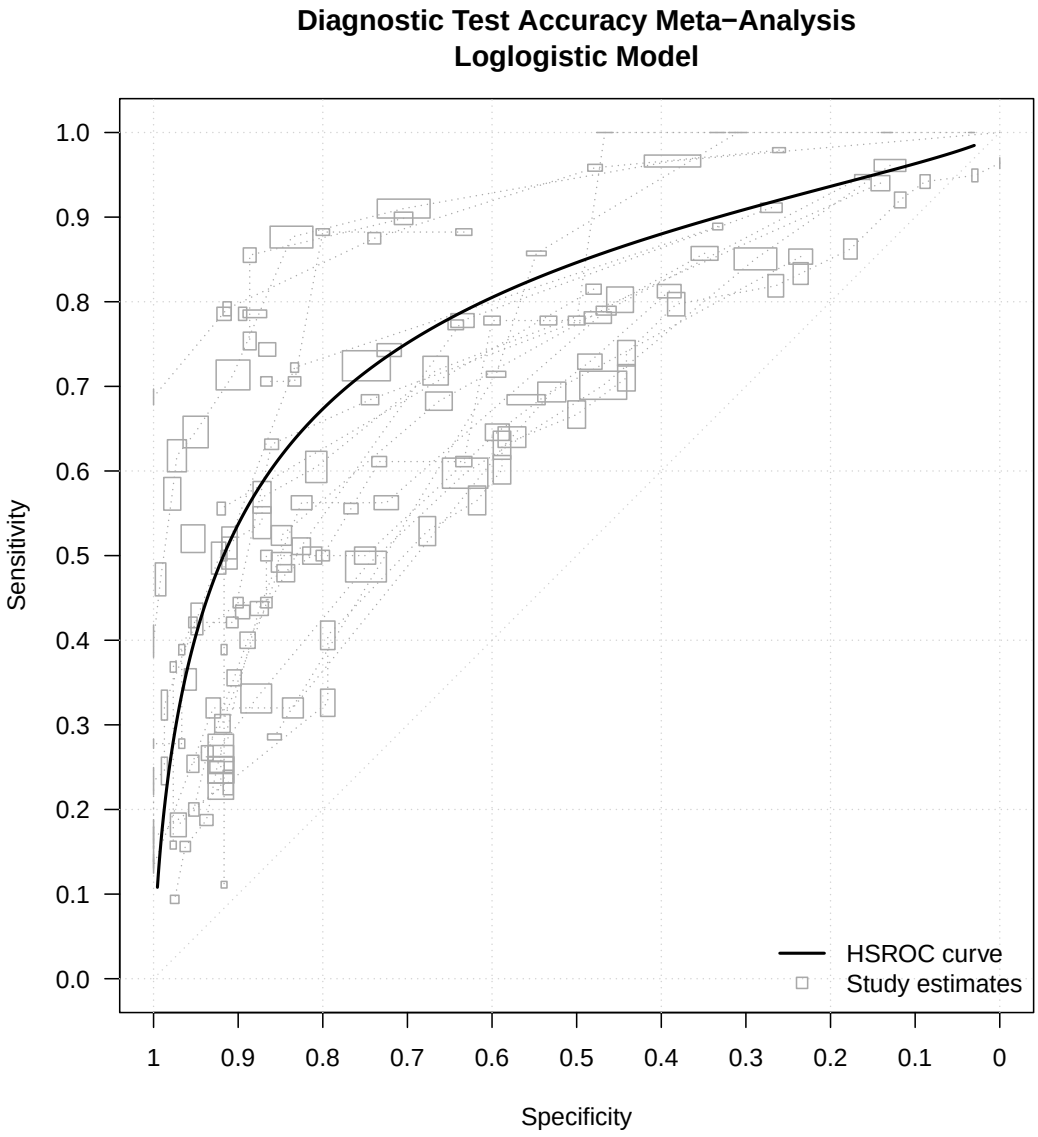


How do I fit the Hoyer model to the FeNO dataset?

Note: The FeNO data are reproduced from the original source and the supplementary material accompanying the Cochrane Handbook. However, the study 'Schneider 2013' contains inconsistent diseased counts (TP + FN). To illustrate the Hoyer analysis, we modify the TP counts in rows 118–120 from 39 to 38, restoring a constant total of 154 diseased individuals. Other corrections restoring internal consistency are also conceivable.

```
data("FENO")
head(FENO)
#>        study study_id cutoff  TP FN FP TN
#> 1 Arora 2006        1      6 133  5 34  0
#> 2 Arora 2006        1      7 131  7 33  1
#> 3 Arora 2006        1      8 130  8 31  3
#> 4 Arora 2006        1      9 127 11 30  4
#> 5 Arora 2006        1     10 119 19 28  6
#> 6 Arora 2006        1     11 115 23 26  8
summary(FENO$cutoff)
#>    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
#>    5.00   16.00   25.00   31.05   40.75  100.00
# feno <- fitHoyer(data=FENO,
#                  TP=TP,
#                  FP=FP,
#                  FN=FN,
#                  TN=TN,
#                  threshold=cutoff,
#                  study=study,
#                  dist="loglogistic",
#                  testdirection="greater",
#                  eval_threshold=seq(16,40,1),
#                  smallest=2,
#                  largest=120)
#Error in `FUN()`:
#! Inconsistent diseased counts (TP+FN) within study 'Schneider 2013'.
#Rows: 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122
#Counts: 154, 155
#
# Let's check the Schneider 2013 study
check_schneider    <- FENO[110:122,]
check_schneider$n1 <- with(check_schneider,TP+FN)
check_schneider$n0 <- with(check_schneider,TN+FP)
check_schneider
#>              study study_id cutoff  TP  FN  FP  TN  n1  n0
```

```
#> 110 Schneider 2013       11      9 148   6 208  31 154 239
#> 111 Schneider 2013       11     12 131  23 170  69 154 239
#> 112 Schneider 2013       11     16 108  46 127 112 154 239
#> 113 Schneider 2013       11     20  92  62  88 151 154 239
#> 114 Schneider 2013       11     25  75  79  60 179 154 239
#> 115 Schneider 2013       11     35  51 103  29 210 154 239
#> 116 Schneider 2013       11     41  42 112  19 220 154 239
#> 117 Schneider 2013       11     42  40 114  19 220 154 239
#> 118 Schneider 2013       11     43  39 116  19 220 155 239
#> 119 Schneider 2013       11     44  39 116  19 220 155 239
#> 120 Schneider 2013       11     45  39 116  19 220 155 239
#> 121 Schneider 2013       11     46  35 119  19 220 154 239
#> 122 Schneider 2013       11     71  28 126   7 232 154 239
# Inspection suggests that the TP and/or FN counts
# in rows 118, 119, 120 may need to be changed.
# Let's reduce the TP counts from 39 to 38.
# But other corrections are conceivable as well.
FENO[118:120,"TP"] <- 38
### Let's try again
feno <- fitHoyer(data=FENO,
                 TP=TP,
                 FP=FP,
                 FN=FN,
                 TN=TN,
                 threshold=cutoff,
                 study=study,
                 dist="loglogistic",
                 testdirection="greater",
                 eval_threshold=seq(16,40,1),
                 smallest=2,
                 largest=120)
plot(feno,size="se",scale=0.03,
     main="Diagnostic Test Accuracy Meta-Analysis\nLoglogistic Model")
```



How does `testdirection="less"` work?

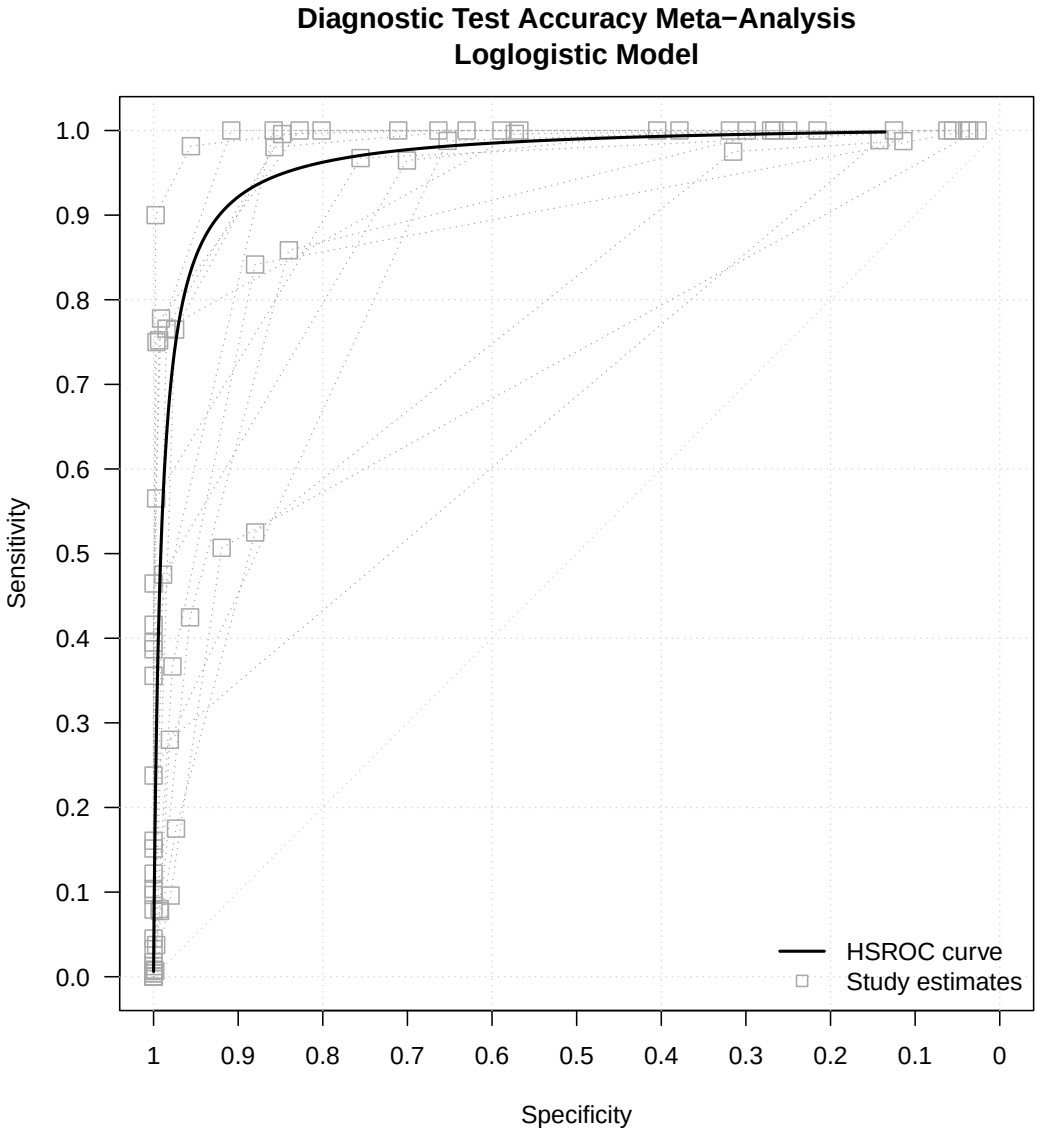
We use the synthetic anaemia data set. Smaller values in haemoglobin indicate disease.

```
data("anaemia")
summary(anaemia$threshold)
#>    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
#>    7.00    8.00   10.00   10.33   13.00   14.00
```

```r
less <-  fitHoyer(data=anaemia,
                  TP=TP,
                  FP=FP,
                  FN=FN,
                  TN=TN,
                  threshold=threshold,
                  study=study,
                  dist="loglogistic",
                  testdirection="less",
                  eval_threshold=c(8,9,10,11,12,13),
                  smallest=5,
                  largest=17)
```

```r
less
#>
#> Hoyer Model
#> -----------
#>
#> Number of studies : 15
#> Optimizer         : Converged
#> Hessian           : Positive definite
#> Max |grad|        : 0.03477329
#> -2 log likelihood : 19708.9 ( df = 7 )
#> AIC               : 19722.9
#> BIC               : 19727.86
#>
#> Distribution      : Loglogistic
#> Test direction    : less
#>
#> Use summary() for parameter estimates.
summary(less)
#>
#> Summary: Hoyer Model
#> --------------------
#>
#> Parameter estimates
#> -------------------
#>                 Estimate   Std. Error
#> beta0       2.5310712000 0.0169254100
#> lambda0     0.0583099970 0.0007979991
#> su0         0.0652667800 0.0120139560
#> beta1       2.2538212000 0.0147254380
```

```
#> lambda1     0.0605300340 0.0012263705
#> su1         0.0562794810 0.0105351710
#> rho        -0.4117582600 0.2194120800
#> covu0u1    -0.0015124624 0.0010422566
#> logitSurv1  2.8808784000 0.2497852800
#> logitSurv1  0.9350173500 0.2438804400
#> logitSurv1 -0.8056146700 0.2439346900
#> logitSurv1 -2.3802079000 0.2483362300
#> logitSurv1 -3.8176988000 0.2557856900
#> logitSurv1 -5.1400623000 0.2652905600
#> logitSurv0  7.7453210000 0.3083465400
#> logitSurv0  5.7253751000 0.3001481600
#> logitSurv0  3.9184720000 0.2948244800
#> logitSurv0  2.2839293000 0.2917357100
#> logitSurv0  0.7917087700 0.2903955800
#> logitSurv0 -0.5810010800 0.2904281500
#>
#> Sensitivity / specificity
#> -------------------------
#>   threshold conflevel        Sens SensCI_Lower SensCI_Upper       Spec
#> 1         8      0.95 0.053106947  0.033231895  0.083837892 0.99956742
#> 2         9      0.95 0.281907910  0.195759070  0.387692890 0.99674848
#> 3        10      0.95 0.691174230  0.581153750  0.783081980 0.98051575
#> 4        11      0.95 0.915305550  0.869151560  0.946187650 0.90753730
#> 5        12      0.95 0.978494340  0.964986080  0.986862110 0.68819812
#> 6        13      0.95 0.994176780  0.990244320  0.996529650 0.35870228
#>   SpecCI_Lower SpecCI_Upper
#> 1   0.99920865   0.99976358
#> 2   0.99415958   0.99819187
#> 3   0.96579655   0.98897297
#> 4   0.84711337   0.94561365
#> 5   0.55540748   0.79590165
#> 6   0.24044711   0.49705694
plot(less,main="Diagnostic Test Accuracy Meta-Analysis\nLoglogistic Model")
```



How does `fitHoyer` work internally? – Optional advanced workflow

Most users should use the high-level `fitHoyer` function. The lower-level functions are provided for advanced use and transparency.

Step 1: How do we restructure the data set?

```
res <- restructure_data(
    data = diabetes,
    TP = TP,
    FP = FP,
    FN = FN,
    TN = TN,
    study = study,
    threshold = threshold,
    testdirection = "greater",
    smallest = 2,
    largest = 10)
res
#> $restructured
#>                study  TP   TN   D    H threshold lowerB upperB events1 events0
#> Study 01.1  Study 01 574 1389 836 2071       5.9     NA    5.9     262    1389
#> Study 01.2  Study 01 574 1389 836 2071       5.9    5.9     NA     574     682
#> Study 02.1  Study 02 617 1005 635 8740       5.0     NA    5.0      18    1005
#> Study 02.2  Study 02 607 1617 635 8740       5.1    5.0    5.1      10     612
#> Study 02.3  Study 02 600 2438 635 8740       5.2    5.1    5.2       7     821
#> Study 02.4  Study 02 581 3409 635 8740       5.3    5.2    5.3      19     971
#> Study 02.5  Study 02 563 4422 635 8740       5.4    5.3    5.4      18    1013
#> Study 02.6  Study 02 550 5384 635 8740       5.5    5.4    5.5      13     962
#> Study 02.7  Study 02 522 6267 635 8740       5.6    5.5    5.6      28     883
#> Study 02.8  Study 02 489 6966 635 8740       5.7    5.6    5.7      33     699
#> Study 02.9  Study 02 457 7534 635 8740       5.8    5.7    5.8      32     568
#> Study 02.10 Study 02 429 7927 635 8740       5.9    5.8    5.9      28     393
#> Study 02.11 Study 02 393 8172 635 8740       6.0    5.9    6.0      36     245
#> Study 02.12 Study 02 332 8460 635 8740       6.2    6.0    6.2      61     288
#> Study 02.13 Study 02 236 8670 635 8740       6.6    6.2    6.6      96     210
#> Study 02.14 Study 02 236 8670 635 8740       6.6    6.6     NA     236      70
#> Study 03.1  Study 03  36  998  49 1093       6.2     NA    6.2      13     998
#> Study 03.2  Study 03  36  998  49 1093       6.2    6.2     NA      36      95
#> Study 04.1  Study 04  16  147  41  157       6.0     NA    6.0      25     147
#> Study 04.2  Study 04  16  147  41  157       6.0    6.0     NA      16      10
#> Study 05.1  Study 05 644 1217 795 1503       6.1     NA    6.1     151    1217
#> Study 05.2  Study 05 644 1217 795 1503       6.1    6.1     NA     644     286
#> Study 06.1  Study 06 176 1286 278 2054       5.6     NA    5.6     102    1286
#> Study 06.2  Study 06  69 1867 278 2054       6.5    5.6    6.5     107     581
#> Study 06.3  Study 06  69 1867 278 2054       6.5    6.5     NA      69     187
#> Study 07.1  Study 07  72  258  88  304       6.1     NA    6.1      16     258
```

```
#> Study 07.2  Study 07  72  258  88  304       6.1    6.1     NA      72      46
#> Study 08.1  Study 08  89 1382 115 1684       5.3     NA    5.3      26    1382
#> Study 08.2  Study 08  72 1558 115 1684       5.5    5.3    5.5      17     176
#> Study 08.3  Study 08  65 1602 115 1684       5.6    5.5    5.6       7      44
#> Study 08.4  Study 08  65 1602 115 1684       5.6    5.6     NA      65      82
#> Study 09.1  Study 09 207 2704 252 5865       5.8     NA    5.8      45    2704
#> Study 09.2  Study 09 196 3308 252 5865       5.9    5.8    5.9      11     604
#> Study 09.3  Study 09 181 3877 252 5865       6.0    5.9    6.0      15     569
#> Study 09.4  Study 09 181 3877 252 5865       6.0    6.0     NA     181    1988
#> Study 10.1  Study 10  54    1  54  451       3.9     NA    3.9       0       1
#> Study 10.2  Study 10  54   45  54  451       4.7    3.9    4.7       0      44
#> Study 10.3  Study 10  46  363  54  451       5.6    4.7    5.6       8     318
#> Study 10.4  Study 10  43  389  54  451       5.7    5.6    5.7       3      26
#> Study 10.5  Study 10  23  447  54  451       6.2    5.7    6.2      20      58
#> Study 10.6  Study 10  12  451  54  451       6.8    6.2    6.8      11       4
#> Study 10.7  Study 10  12  451  54  451       6.8    6.8     NA      12       0
#> Study 11.1  Study 11 861  611 895 5050       5.0     NA    5.0      34     611
#> Study 11.2  Study 11 837 1000 895 5050       5.1    5.0    5.1      24     389
#> Study 11.3  Study 11 793 1525 895 5050       5.2    5.1    5.2      44     525
#> Study 11.4  Study 11 740 2116 895 5050       5.3    5.2    5.3      53     591
#> Study 11.5  Study 11 687 2762 895 5050       5.4    5.3    5.4      53     646
#> Study 11.6  Study 11 610 3358 895 5050       5.5    5.4    5.5      77     596
#> Study 11.7  Study 11 532 3883 895 5050       5.6    5.5    5.6      78     525
#> Study 11.8  Study 11 455 4277 895 5050       5.7    5.6    5.7      77     394
#> Study 11.9  Study 11 376 4585 895 5050       5.8    5.7    5.8      79     308
#> Study 11.10 Study 11 298 4782 895 5050       5.9    5.8    5.9      78     197
#> Study 11.11 Study 11 235 4883 895 5050       6.0    5.9    6.0      63     101
#> Study 11.12 Study 11 136 4984 895 5050       6.2    6.0    6.2      99     101
#> Study 11.13 Study 11  46 5045 895 5050       6.6    6.2    6.6      90      61
#> Study 11.14 Study 11  46 5045 895 5050       6.6    6.6     NA      46       5
#> Study 12.1  Study 12 184 5265 338 5903       5.7     NA    5.7     154    5265
#> Study 12.2  Study 12 184 5265 338 5903       5.7    5.7     NA     184     638
#> Study 13.1  Study 13  72  120  81  333       5.5     NA    5.5       9     120
#> Study 13.2  Study 13  70  144  81  333       5.6    5.5    5.6       2      24
#> Study 13.3  Study 13  66  170  81  333       5.7    5.6    5.7       4      26
#> Study 13.4  Study 13  58  204  81  333       5.8    5.7    5.8       8      34
#> Study 13.5  Study 13  50  234  81  333       5.9    5.8    5.9       8      30
#> Study 13.6  Study 13  40  256  81  333       6.0    5.9    6.0      10      22
#> Study 13.7  Study 13  40  256  81  333       6.0    6.0     NA      40      77
#> Study 14.1  Study 14 285  155 295 1687       4.8     NA    4.8      10     155
#> Study 14.2  Study 14 262  412 295 1687       5.1    4.8    5.1      23     257
#> Study 14.3  Study 14 253  516 295 1687       5.2    5.1    5.2       9     104
```

```
#> Study 14.4  Study 14 234  680 295 1687       5.3    5.2    5.3      19     164
#> Study 14.5  Study 14 195  969 295 1687       5.5    5.3    5.5      39     289
#> Study 14.6  Study 14 169 1099 295 1687       5.6    5.5    5.6      26     130
#> Study 14.7  Study 14 138 1211 295 1687       5.7    5.6    5.7      31     112
#> Study 14.8  Study 14  91 1409 295 1687       5.9    5.7    5.9      47     198
#> Study 14.9  Study 14  91 1409 295 1687       5.9    5.9     NA      91     278
#> Study 15.1  Study 15 108  626 114 4816       5.0     NA    5.0       6     626
#> Study 15.2  Study 15  91 2745 114 4816       5.5    5.0    5.5      17    2119
#> Study 15.3  Study 15  74 3660 114 4816       5.7    5.5    5.7      17     915
#> Study 15.4  Study 15  48 4479 114 4816       6.0    5.7    6.0      26     819
#> Study 15.5  Study 15   7 4816 114 4816       6.4    6.0    6.4      41     337
#> Study 15.6  Study 15   7 4816 114 4816       6.4    6.4     NA       7       0
#> Study 16.1  Study 16 184  181 186 5826       5.0     NA    5.0       2     181
#> Study 16.2  Study 16 164 3437 186 5826       5.5    5.0    5.5      20    3256
#> Study 16.3  Study 16 145 4719 186 5826       5.7    5.5    5.7      19    1282
#> Study 16.4  Study 16  84 5593 186 5826       6.0    5.7    6.0      61     874
#> Study 16.5  Study 16   4 5826 186 5826       6.4    6.0    6.4      80     233
#> Study 16.6  Study 16   4 5826 186 5826       6.4    6.4     NA       4       0
#> Study 17.1  Study 17  88  480  92 3692       5.0     NA    5.0       4     480
#> Study 17.2  Study 17  74 2252  92 3692       5.5    5.0    5.5      14    1772
#> Study 17.3  Study 17  61 2954  92 3692       5.7    5.5    5.7      13     702
#> Study 17.4  Study 17  35 3507  92 3692       6.0    5.7    6.0      26     553
#> Study 17.5  Study 17   4 3692  92 3692       6.4    6.0    6.4      31     185
#> Study 17.6  Study 17   4 3692  92 3692       6.4    6.4     NA       4       0
#> Study 18.1  Study 18  21  284  64  320       5.7     NA    5.7      43     284
#> Study 18.2  Study 18  21  284  64  320       5.7    5.7     NA      21      36
#> Study 19.1  Study 19  49  691  57 1132       5.1     NA    5.1       8     691
#> Study 19.2  Study 19  42  814  57 1132       5.2    5.1    5.2       7     123
#> Study 19.3  Study 19  32  994  57 1132       5.3    5.2    5.3      10     180
#> Study 19.4  Study 19  26 1045  57 1132       5.4    5.3    5.4       6      51
#> Study 19.5  Study 19  26 1045  57 1132       5.4    5.4     NA      26      87
#> Study 20.1  Study 20 596 2062 659 6145       5.0     NA    5.0      63    2062
#> Study 20.2  Study 20 392 5015 659 6145       5.5    5.0    5.5     204    2953
#> Study 20.3  Study 20 137 5999 659 6145       6.0    5.5    6.0     255     984
#> Study 20.4  Study 20 137 5999 659 6145       6.0    6.0     NA     137     146
#> Study 21.1  Study 21 187 8562 368 9674       5.5     NA    5.5     181    8562
#> Study 21.2  Study 21 187 8562 368 9674       5.5    5.5     NA     187    1112
#> Study 22.1  Study 22   9  395  17  432       5.8     NA    5.8       8     395
#> Study 22.2  Study 22   9  395  17  432       5.8    5.8     NA       9      37
#> Study 23.1  Study 23 122  215 164  304       5.5     NA    5.5      42     215
#> Study 23.2  Study 23  88  265 164  304       5.7    5.5    5.7      34      50
#> Study 23.3  Study 23  88  265 164  304       5.7    5.7     NA      88      39
```

```
#> Study 24.1  Study 24  22  129  44  164       6.1    NA    6.1     22     129
#> Study 24.2  Study 24  22  129  44  164       6.1   6.1     NA     22      35
#> Study 25.1  Study 25  79  217  80  882       6.6    NA    6.6      1     217
#> Study 25.2  Study 25  79  217  80  882       6.6   6.6     NA     79     665
#> Study 26.1  Study 26 114  203 178  223       6.9    NA    6.9     64     203
#> Study 26.2  Study 26  90  219 178  223       7.4   6.9    7.4     24      16
#> Study 26.3  Study 26  73  223 178  223       7.6   7.4    7.6     17       4
#> Study 26.4  Study 26  73  223 178  223       7.6   7.6     NA     73       0
#> Study 27.1  Study 27 135  592 178  688       5.9    NA    5.9     43     592
#> Study 27.2  Study 27  87  674 178  688       6.5   5.9    6.5     48      82
#> Study 27.3  Study 27  87  674 178  688       6.5   6.5     NA     87      14
#> Study 28.1  Study 28 575  980 627 2250       5.5    NA    5.5     52     980
#> Study 28.2  Study 28 486 1773 627 2250       6.1   5.5    6.1     89     793
#> Study 28.3  Study 28 486 1773 627 2250       6.1   6.1     NA    486     477
#> Study 29.1  Study 29  23  109  30  114       6.1    NA    6.1      7     109
#> Study 29.2  Study 29  23  109  30  114       6.1   6.1     NA     23       5
#> Study 30.1  Study 30 424 2112 616 2233       6.0    NA    6.0    192    2112
#> Study 30.2  Study 30 424 2112 616 2233       6.0   6.0     NA    424     121
#> Study 31.1  Study 31 338 4060 367 6436       5.7    NA    5.7     29    4060
#> Study 31.2  Study 31 338 4060 367 6436       5.7   5.7     NA    338    2376
#> Study 32.1  Study 32  57   32  64   44       6.0    NA    6.0      7      32
#> Study 32.2  Study 32  50   40  64   44       6.4   6.0    6.4      7       8
#> Study 32.3  Study 32  47   41  64   44       6.5   6.4    6.5      3       1
#> Study 32.4  Study 32  40   43  64   44       7.0   6.5    7.0      7       2
#> Study 32.5  Study 32  40   43  64   44       7.0   7.0     NA     40       1
#> Study 33.1  Study 33  52   79  65  116       5.6    NA    5.6     13      79
#> Study 33.2  Study 33  52   79  65  116       5.6   5.6     NA     52      37
#> Study 34.1  Study 34 111   83 112  489       5.0    NA    5.0      1      83
#> Study 34.2  Study 34 110  225 112  489       5.5   5.0    5.5      1     142
#> Study 34.3  Study 34 100  381 112  489       6.0   5.5    6.0     10     156
#> Study 34.4  Study 34  78  465 112  489       6.5   6.0    6.5     22      84
#> Study 34.5  Study 34  60  479 112  489       7.0   6.5    7.0     18      14
#> Study 34.6  Study 34  60  479 112  489       7.0   7.0     NA     60      10
#> Study 35.1  Study 35  20   60  21   90       5.9    NA    5.9      1      60
#> Study 35.2  Study 35  19   62  21   90       6.0   5.9    6.0      1       2
#> Study 35.3  Study 35  17   76  21   90       6.1   6.0    6.1      2      14
#> Study 35.4  Study 35  17   79  21   90       6.2   6.1    6.2      0       3
#> Study 35.5  Study 35  17   79  21   90       6.3   6.2    6.3      0       0
#> Study 35.6  Study 35  16   81  21   90       6.4   6.3    6.4      1       2
#> Study 35.7  Study 35  13   81  21   90       6.5   6.4    6.5      3       0
#> Study 35.8  Study 35  12   86  21   90       6.6   6.5    6.6      1       5
#> Study 35.9  Study 35  11   87  21   90       6.7   6.6    6.7      1       1
```

```
#> Study 35.10 Study 35  11   87  21   90       6.8    6.7    6.8       0       0
#> Study 35.11 Study 35  11   88  21   90       6.9    6.8    6.9       0       1
#> Study 35.12 Study 35  10   88  21   90       7.0    6.9    7.0       1       0
#> Study 35.13 Study 35  10   88  21   90       7.0    7.0     NA      10       2
#> Study 36.1  Study 36  25  243  27  288       5.9     NA    5.9       2     243
#> Study 36.2  Study 36  25  243  27  288       5.9    5.9     NA      25      45
#> Study 37.1  Study 37  12  268  14  293       5.9     NA    5.9       2     268
#> Study 37.2  Study 37  12  268  14  293       5.9    5.9     NA      12      25
#> Study 38.1  Study 38  13  260  19  295       5.9     NA    5.9       6     260
#> Study 38.2  Study 38  13  260  19  295       5.9    5.9     NA      13      35
#>             ctype lcutmean
#> Study 01.1      1 1.234050
#> Study 01.2      3 2.038769
#> Study 02.1      1 1.151293
#> Study 02.2      2 1.619339
#> Study 02.3      2 1.638950
#> Study 02.4      2 1.658183
#> Study 02.5      2 1.677053
#> Study 02.6      2 1.695574
#> Study 02.7      2 1.713757
#> Study 02.8      2 1.731616
#> Study 02.9      2 1.749162
#> Study 02.10     2 1.766405
#> Study 02.11     2 1.783356
#> Study 02.12     2 1.808154
#> Study 02.13     2 1.855809
#> Study 02.14     3 2.094827
#> Study 03.1      1 1.258848
#> Study 03.2      3 2.063567
#> Study 04.1      1 1.242453
#> Study 04.2      3 2.047172
#> Study 05.1      1 1.250718
#> Study 05.2      3 2.055437
#> Study 06.1      1 1.207957
#> Study 06.2      2 1.797284
#> Study 06.3      3 2.087194
#> Study 07.1      1 1.250718
#> Study 07.2      3 2.055437
#> Study 08.1      1 1.180427
#> Study 08.2      2 1.686227
#> Study 08.3      2 1.713757
#> Study 08.4      3 2.012676
```

```
#> Study 09.1      1 1.225503
#> Study 09.2      2 1.766405
#> Study 09.3      2 1.783356
#> Study 09.4      3 2.047172
#> Study 10.1      1 1.027062
#> Study 10.2      2 1.454270
#> Study 10.3      2 1.635165
#> Study 10.4      2 1.731616
#> Study 10.5      2 1.782508
#> Study 10.6      2 1.870736
#> Study 10.7      3 2.109754
#> Study 11.1      1 1.151293
#> Study 11.2      2 1.619339
#> Study 11.3      2 1.638950
#> Study 11.4      2 1.658183
#> Study 11.5      2 1.677053
#> Study 11.6      2 1.695574
#> Study 11.7      2 1.713757
#> Study 11.8      2 1.731616
#> Study 11.9      2 1.749162
#> Study 11.10     2 1.766405
#> Study 11.11     2 1.783356
#> Study 11.12     2 1.808154
#> Study 11.13     2 1.855809
#> Study 11.14     3 2.094827
#> Study 12.1      1 1.216807
#> Study 12.2      3 2.021526
#> Study 13.1      1 1.198948
#> Study 13.2      2 1.713757
#> Study 13.3      2 1.731616
#> Study 13.4      2 1.749162
#> Study 13.5      2 1.766405
#> Study 13.6      2 1.783356
#> Study 13.7      3 2.047172
#> Study 14.1      1 1.130882
#> Study 14.2      2 1.598928
#> Study 14.3      2 1.638950
#> Study 14.4      2 1.658183
#> Study 14.5      2 1.686227
#> Study 14.6      2 1.713757
#> Study 14.7      2 1.731616
#> Study 14.8      2 1.757709
```

```
#> Study 14.9      3 2.038769
#> Study 15.1      1 1.151293
#> Study 15.2      2 1.657093
#> Study 15.3      2 1.722607
#> Study 15.4      2 1.766113
#> Study 15.5      2 1.824029
#> Study 15.6      3 2.079442
#> Study 16.1      1 1.151293
#> Study 16.2      2 1.657093
#> Study 16.3      2 1.722607
#> Study 16.4      2 1.766113
#> Study 16.5      2 1.824029
#> Study 16.6      3 2.079442
#> Study 17.1      1 1.151293
#> Study 17.2      2 1.657093
#> Study 17.3      2 1.722607
#> Study 17.4      2 1.766113
#> Study 17.5      2 1.824029
#> Study 17.6      3 2.079442
#> Study 18.1      1 1.216807
#> Study 18.2      3 2.021526
#> Study 19.1      1 1.161194
#> Study 19.2      2 1.638950
#> Study 19.3      2 1.658183
#> Study 19.4      2 1.677053
#> Study 19.5      3 1.994492
#> Study 20.1      1 1.151293
#> Study 20.2      2 1.657093
#> Study 20.3      2 1.748254
#> Study 20.4      3 2.047172
#> Study 21.1      1 1.198948
#> Study 21.2      3 2.003667
#> Study 22.1      1 1.225503
#> Study 22.2      3 2.030222
#> Study 23.1      1 1.198948
#> Study 23.2      2 1.722607
#> Study 23.3      3 2.021526
#> Study 24.1      1 1.250718
#> Study 24.2      3 2.055437
#> Study 25.1      1 1.290108
#> Study 25.2      3 2.094827
#> Study 26.1      1 1.312334
```

```
#> Study 26.2      2 1.966501
#> Study 26.3      2 2.014814
#> Study 26.4      3 2.165367
#> Study 27.1      1 1.234050
#> Study 27.2      2 1.823377
#> Study 27.3      3 2.087194
#> Study 28.1      1 1.198948
#> Study 28.2      2 1.756518
#> Study 28.3      3 2.055437
#> Study 29.1      1 1.250718
#> Study 29.2      3 2.055437
#> Study 30.1      1 1.242453
#> Study 30.2      3 2.047172
#> Study 31.1      1 1.216807
#> Study 31.2      3 2.021526
#> Study 32.1      1 1.242453
#> Study 32.2      2 1.824029
#> Study 32.3      2 1.864050
#> Study 32.4      2 1.908856
#> Study 32.5      3 2.124248
#> Study 33.1      1 1.207957
#> Study 33.2      3 2.012676
#> Study 34.1      1 1.151293
#> Study 34.2      2 1.657093
#> Study 34.3      2 1.748254
#> Study 34.4      2 1.831781
#> Study 34.5      2 1.908856
#> Study 34.6      3 2.124248
#> Study 35.1      1 1.234050
#> Study 35.2      2 1.783356
#> Study 35.3      2 1.800024
#> Study 35.4      2 1.816419
#> Study 35.5      2 1.832549
#> Study 35.6      2 1.848424
#> Study 35.7      2 1.864050
#> Study 35.8      2 1.879436
#> Study 35.9      2 1.894589
#> Study 35.10     2 1.909515
#> Study 35.11     2 1.924222
#> Study 35.12     2 1.938716
#> Study 35.13     3 2.124248
#> Study 36.1      1 1.234050
```

```
#> Study 36.2      3 2.038769
#> Study 37.1      1 1.234050
#> Study 37.2      3 2.038769
#> Study 38.1      1 1.234050
#> Study 38.2      3 2.038769
#>
#> $original
#>        study  TP   TN   FP  FN threshold  n1   n0 testdirection       sens
#> 1   Study 01 574 1389  682 262       5.9 836 2071       greater 0.68660287
#> 2   Study 02 617 1005 7735  18        5.0 635 8740       greater 0.97165354
#> 3   Study 02 607 1617 7123  28        5.1 635 8740       greater 0.95590551
#> 4   Study 02 600 2438 6302  35        5.2 635 8740       greater 0.94488189
#> 5   Study 02 581 3409 5331  54        5.3 635 8740       greater 0.91496063
#> 6   Study 02 563 4422 4318  72        5.4 635 8740       greater 0.88661417
#> 7   Study 02 550 5384 3356  85        5.5 635 8740       greater 0.86614173
#> 8   Study 02 522 6267 2473 113        5.6 635 8740       greater 0.82204724
#> 9   Study 02 489 6966 1774 146        5.7 635 8740       greater 0.77007874
#> 10  Study 02 457 7534 1206 178        5.8 635 8740       greater 0.71968504
#> 11  Study 02 429 7927  813 206        5.9 635 8740       greater 0.67559055
#> 12  Study 02 393 8172  568 242        6.0 635 8740       greater 0.61889764
#> 13  Study 02 332 8460  280 303        6.2 635 8740       greater 0.52283465
#> 14  Study 02 236 8670   70 399        6.6 635 8740       greater 0.37165354
#> 15  Study 03  36  998   95  13        6.2  49 1093       greater 0.73469388
#> 16  Study 04  16  147   10  25        6.0  41  157       greater 0.39024390
#> 17  Study 05 644 1217  286 151        6.1 795 1503       greater 0.81006289
#> 18  Study 06 176 1286  768 102        5.6 278 2054       greater 0.63309353
#> 19  Study 06  69 1867  187 209        6.5 278 2054       greater 0.24820144
#> 20  Study 07  72  258   46  16        6.1  88  304       greater 0.81818182
#> 21  Study 08  89 1382  302  26        5.3 115 1684       greater 0.77391304
#> 22  Study 08  72 1558  126  43        5.5 115 1684       greater 0.62608696
#> 23  Study 08  65 1602   82  50        5.6 115 1684       greater 0.56521739
#> 24  Study 09 207 2704 3161  45        5.8 252 5865       greater 0.82142857
#> 25  Study 09 196 3308 2557  56        5.9 252 5865       greater 0.77777778
#> 26  Study 09 181 3877 1988  71        6.0 252 5865       greater 0.71825397
#> 27  Study 10  54    1  450   0        3.9  54  451       greater 1.00000000
#> 28  Study 10  54   45  406   0        4.7  54  451       greater 1.00000000
#> 29  Study 10  46  363   88   8        5.6  54  451       greater 0.85185185
#> 30  Study 10  43  389   62  11        5.7  54  451       greater 0.79629630
#> 31  Study 10  23  447    4  31        6.2  54  451       greater 0.42592593
#> 32  Study 10  12  451    0  42        6.8  54  451       greater 0.22222222
#> 33  Study 11 861  611 4439  34        5.0 895 5050       greater 0.96201117
#> 34  Study 11 837 1000 4050  58        5.1 895 5050       greater 0.93519553
```

```
#> 35  Study 11 793 1525 3525 102       5.2 895 5050       greater 0.88603352
#> 36  Study 11 740 2116 2934 155       5.3 895 5050       greater 0.82681564
#> 37  Study 11 687 2762 2288 208       5.4 895 5050       greater 0.76759777
#> 38  Study 11 610 3358 1692 285       5.5 895 5050       greater 0.68156425
#> 39  Study 11 532 3883 1167 363       5.6 895 5050       greater 0.59441341
#> 40  Study 11 455 4277  773 440       5.7 895 5050       greater 0.50837989
#> 41  Study 11 376 4585  465 519       5.8 895 5050       greater 0.42011173
#> 42  Study 11 298 4782  268 597       5.9 895 5050       greater 0.33296089
#> 43  Study 11 235 4883  167 660       6.0 895 5050       greater 0.26256983
#> 44  Study 11 136 4984   66 759       6.2 895 5050       greater 0.15195531
#> 45  Study 11  46 5045    5 849       6.6 895 5050       greater 0.05139665
#> 46  Study 12 184 5265  638 154       5.7 338 5903       greater 0.54437870
#> 47  Study 13  72  120  213   9       5.5  81  333       greater 0.88888889
#> 48  Study 13  70  144  189  11       5.6  81  333       greater 0.86419753
#> 49  Study 13  66  170  163  15       5.7  81  333       greater 0.81481481
#> 50  Study 13  58  204  129  23       5.8  81  333       greater 0.71604938
#> 51  Study 13  50  234   99  31       5.9  81  333       greater 0.61728395
#> 52  Study 13  40  256   77  41       6.0  81  333       greater 0.49382716
#> 53  Study 14 285  155 1532  10       4.8 295 1687       greater 0.96610169
#> 54  Study 14 262  412 1275  33       5.1 295 1687       greater 0.88813559
#> 55  Study 14 253  516 1171  42       5.2 295 1687       greater 0.85762712
#> 56  Study 14 234  680 1007  61       5.3 295 1687       greater 0.79322034
#> 57  Study 14 195  969  718 100       5.5 295 1687       greater 0.66101695
#> 58  Study 14 169 1099  588 126       5.6 295 1687       greater 0.57288136
#> 59  Study 14 138 1211  476 157       5.7 295 1687       greater 0.46779661
#> 60  Study 14  91 1409  278 204       5.9 295 1687       greater 0.30847458
#> 61  Study 15 108  626 4190   6       5.0 114 4816       greater 0.94736842
#> 62  Study 15  91 2745 2071  23       5.5 114 4816       greater 0.79824561
#> 63  Study 15  74 3660 1156  40       5.7 114 4816       greater 0.64912281
#> 64  Study 15  48 4479  337  66       6.0 114 4816       greater 0.42105263
#> 65  Study 15   7 4816    0 107       6.4 114 4816       greater 0.06140351
#> 66  Study 16 184  181 5645   2       5.0 186 5826       greater 0.98924731
#> 67  Study 16 164 3437 2389  22       5.5 186 5826       greater 0.88172043
#> 68  Study 16 145 4719 1107  41       5.7 186 5826       greater 0.77956989
#> 69  Study 16  84 5593  233 102       6.0 186 5826       greater 0.45161290
#> 70  Study 16   4 5826    0 182       6.4 186 5826       greater 0.02150538
#> 71  Study 17  88  480 3212   4       5.0  92 3692       greater 0.95652174
#> 72  Study 17  74 2252 1440  18       5.5  92 3692       greater 0.80434783
#> 73  Study 17  61 2954  738  31       5.7  92 3692       greater 0.66304348
#> 74  Study 17  35 3507  185  57       6.0  92 3692       greater 0.38043478
#> 75  Study 17   4 3692    0  88       6.4  92 3692       greater 0.04347826
#> 76  Study 18  21  284   36  43       5.7  64  320       greater 0.32812500
```

```
#> 77  Study 19  49  691  441   8       5.1  57 1132       greater 0.85964912
#> 78  Study 19  42  814  318  15       5.2  57 1132       greater 0.73684211
#> 79  Study 19  32  994  138  25       5.3  57 1132       greater 0.56140351
#> 80  Study 19  26 1045   87  31       5.4  57 1132       greater 0.45614035
#> 82  Study 20 596 2062 4083  63       5.0 659 6145       greater 0.90440061
#> 81  Study 20 392 5015 1130 267       5.5 659 6145       greater 0.59484067
#> 83  Study 20 137 5999  146 522       6.0 659 6145       greater 0.20789074
#> 84  Study 21 187 8562 1112 181       5.5 368 9674       greater 0.50815217
#> 85  Study 22   9  395   37   8       5.8  17  432       greater 0.52941176
#> 86  Study 23 122  215   89  42       5.5 164  304       greater 0.74390244
#> 87  Study 23  88  265   39  76       5.7 164  304       greater 0.53658537
#> 88  Study 24  22  129   35  22       6.1  44  164       greater 0.50000000
#> 89  Study 25  79  217  665   1       6.6  80  882       greater 0.98750000
#> 90  Study 26 114  203   20  64       6.9 178  223       greater 0.64044944
#> 91  Study 26  90  219    4  88       7.4 178  223       greater 0.50561798
#> 92  Study 26  73  223    0 105       7.6 178  223       greater 0.41011236
#> 93  Study 27 135  592   96  43       5.9 178  688       greater 0.75842697
#> 94  Study 27  87  674   14  91       6.5 178  688       greater 0.48876404
#> 95  Study 28 575  980 1270  52       5.5 627 2250       greater 0.91706539
#> 96  Study 28 486 1773  477 141       6.1 627 2250       greater 0.77511962
#> 97  Study 29  23  109    5   7       6.1  30  114       greater 0.76666667
#> 98  Study 30 424 2112  121 192       6.0 616 2233       greater 0.68831169
#> 99  Study 31 338 4060 2376  29       5.7 367 6436       greater 0.92098093
#> 100 Study 32  57   32   12   7       6.0  64   44       greater 0.89062500
#> 101 Study 32  50   40    4  14       6.4  64   44       greater 0.78125000
#> 102 Study 32  47   41    3  17       6.5  64   44       greater 0.73437500
#> 103 Study 32  40   43    1  24       7.0  64   44       greater 0.62500000
#> 104 Study 33  52   79   37  13       5.6  65  116       greater 0.80000000
#> 105 Study 34 111   83  406   1       5.0 112  489       greater 0.99107143
#> 106 Study 34 110  225  264   2       5.5 112  489       greater 0.98214286
#> 107 Study 34 100  381  108  12       6.0 112  489       greater 0.89285714
#> 108 Study 34  78  465   24  34       6.5 112  489       greater 0.69642857
#> 109 Study 34  60  479   10  52       7.0 112  489       greater 0.53571429
#> 110 Study 35  20   60   30   1       5.9  21   90       greater 0.95238095
#> 111 Study 35  19   62   28   2       6.0  21   90       greater 0.90476190
#> 112 Study 35  17   76   14   4       6.1  21   90       greater 0.80952381
#> 113 Study 35  17   79   11   4       6.2  21   90       greater 0.80952381
#> 114 Study 35  17   79   11   4       6.3  21   90       greater 0.80952381
#> 115 Study 35  16   81    9   5       6.4  21   90       greater 0.76190476
#> 116 Study 35  13   81    9   8       6.5  21   90       greater 0.61904762
#> 117 Study 35  12   86    4   9       6.6  21   90       greater 0.57142857
#> 118 Study 35  11   87    3  10       6.7  21   90       greater 0.52380952
```

```
#> 119 Study 35  11   87    3  10       6.8  21   90       greater 0.52380952
#> 120 Study 35  11   88    2  10       6.9  21   90       greater 0.52380952
#> 121 Study 35  10   88    2  11       7.0  21   90       greater 0.47619048
#> 122 Study 36  25  243   45   2       5.9  27  288       greater 0.92592593
#> 123 Study 37  12  268   25   2       5.9  14  293       greater 0.85714286
#> 124 Study 38  13  260   35   6       5.9  19  295       greater 0.68421053
#>            spec         fpr
#> 1   0.670690488 0.329309512
#> 2   0.114988558 0.885011442
#> 3   0.185011442 0.814988558
#> 4   0.278947368 0.721052632
#> 5   0.390045767 0.609954233
#> 6   0.505949657 0.494050343
#> 7   0.616018307 0.383981693
#> 8   0.717048055 0.282951945
#> 9   0.797025172 0.202974828
#> 10  0.862013730 0.137986270
#> 11  0.906979405 0.093020595
#> 12  0.935011442 0.064988558
#> 13  0.967963387 0.032036613
#> 14  0.991990847 0.008009153
#> 15  0.913083257 0.086916743
#> 16  0.936305732 0.063694268
#> 17  0.809713906 0.190286094
#> 18  0.626095424 0.373904576
#> 19  0.908958130 0.091041870
#> 20  0.848684211 0.151315789
#> 21  0.820665083 0.179334917
#> 22  0.925178147 0.074821853
#> 23  0.951306413 0.048693587
#> 24  0.461040068 0.538959932
#> 25  0.564023870 0.435976130
#> 26  0.661040068 0.338959932
#> 27  0.002217295 0.997782705
#> 28  0.099778271 0.900221729
#> 29  0.804878049 0.195121951
#> 30  0.862527716 0.137472284
#> 31  0.991130820 0.008869180
#> 32  1.000000000 0.000000000
#> 33  0.120990099 0.879009901
#> 34  0.198019802 0.801980198
#> 35  0.301980198 0.698019802
```

```
#> 36  0.419009901 0.580990099
#> 37  0.546930693 0.453069307
#> 38  0.664950495 0.335049505
#> 39  0.768910891 0.231089109
#> 40  0.846930693 0.153069307
#> 41  0.907920792 0.092079208
#> 42  0.946930693 0.053069307
#> 43  0.966930693 0.033069307
#> 44  0.986930693 0.013069307
#> 45  0.999009901 0.000990099
#> 46  0.891919363 0.108080637
#> 47  0.360360360 0.639639640
#> 48  0.432432432 0.567567568
#> 49  0.510510511 0.489489489
#> 50  0.612612613 0.387387387
#> 51  0.702702703 0.297297297
#> 52  0.768768769 0.231231231
#> 53  0.091879075 0.908120925
#> 54  0.244220510 0.755779490
#> 55  0.305868405 0.694131595
#> 56  0.403082395 0.596917605
#> 57  0.574392413 0.425607587
#> 58  0.651452282 0.348547718
#> 59  0.717842324 0.282157676
#> 60  0.835210433 0.164789567
#> 61  0.129983389 0.870016611
#> 62  0.569975083 0.430024917
#> 63  0.759966777 0.240033223
#> 64  0.930024917 0.069975083
#> 65  1.000000000 0.000000000
#> 66  0.031067628 0.968932372
#> 67  0.589941641 0.410058359
#> 68  0.809989701 0.190010299
#> 69  0.960006866 0.039993134
#> 70  1.000000000 0.000000000
#> 71  0.130010834 0.869989166
#> 72  0.609967497 0.390032503
#> 73  0.800108342 0.199891658
#> 74  0.949891658 0.050108342
#> 75  1.000000000 0.000000000
#> 76  0.887500000 0.112500000
#> 77  0.610424028 0.389575972
```

```
#> 78  0.719081272 0.280918728
#> 79  0.878091873 0.121908127
#> 80  0.923144876 0.076855124
#> 82  0.335557364 0.664442636
#> 81  0.816110659 0.183889341
#> 83  0.976240846 0.023759154
#> 84  0.885052719 0.114947281
#> 85  0.914351852 0.085648148
#> 86  0.707236842 0.292763158
#> 87  0.871710526 0.128289474
#> 88  0.786585366 0.213414634
#> 89  0.246031746 0.753968254
#> 90  0.910313901 0.089686099
#> 91  0.982062780 0.017937220
#> 92  1.000000000 0.000000000
#> 93  0.860465116 0.139534884
#> 94  0.979651163 0.020348837
#> 95  0.435555556 0.564444444
#> 96  0.788000000 0.212000000
#> 97  0.956140351 0.043859649
#> 98  0.945812808 0.054187192
#> 99  0.630826600 0.369173400
#> 100 0.727272727 0.272727273
#> 101 0.909090909 0.090909091
#> 102 0.931818182 0.068181818
#> 103 0.977272727 0.022727273
#> 104 0.681034483 0.318965517
#> 105 0.169734151 0.830265849
#> 106 0.460122699 0.539877301
#> 107 0.779141104 0.220858896
#> 108 0.950920245 0.049079755
#> 109 0.979550102 0.020449898
#> 110 0.666666667 0.333333333
#> 111 0.688888889 0.311111111
#> 112 0.844444444 0.155555556
#> 113 0.877777778 0.122222222
#> 114 0.877777778 0.122222222
#> 115 0.900000000 0.100000000
#> 116 0.900000000 0.100000000
#> 117 0.955555556 0.044444444
#> 118 0.966666667 0.033333333
#> 119 0.966666667 0.033333333
```

```
#> 120 0.977777778 0.022222222
#> 121 0.977777778 0.022222222
#> 122 0.843750000 0.156250000
#> 123 0.914675768 0.085324232
#> 124 0.881355932 0.118644068
```

Step 2: How do we get initial values?

```
init <- initHoyerAFT(res$restructured,
                     dist="loglogistic")
init
#>               beta0_init lambda0_init beta1_init lambda1_init  su0_init
#> Initial value   1.681153   0.04964348   1.815414   0.08091965 0.1552818
#>                su1_init coru0u1_init distcode
#> Initial value 0.1284618    0.3948626        3
```

Step 3: How do we fit the model?

```
hoyerAFT <- fitHoyerAFT(data=res,
                        init=init,
                        eval_threshold=c(5.0,5.5,6.0,6.5,7.0,7.5))
```

```
hoyerAFT
#>
#> Hoyer Model
#> -----------
#>
#> Number of studies : 38
#> Optimizer         : Converged
#> Hessian           : Positive definite
#> Max |grad|        : 0.06428937
#> -2 log likelihood : 209322 ( df = 7 )
#> AIC               : 209336
#> BIC               : 209347.4
#>
#> Distribution      : Loglogistic
#> Test direction    : greater
#>
```

```
#> Use summary() for parameter estimates.
summary(hoyerAFT)
#>
#> Summary: Hoyer Model
#> --------------------
#>
#> Parameter estimates
#> -------------------
#>                 Estimate    Std. Error
#> beta0       1.7056907000 0.00956289900
#> lambda0     0.0395019340 0.00018572605
#> su0         0.0586479640 0.00677833570
#> beta1       1.8253382000 0.01456523200
#> lambda1     0.0563985690 0.00092447465
#> su1         0.0883203880 0.01095635700
#> rho         0.8630308200 0.04544135200
#> covu0u1     0.0044703365 0.00114169150
#> logitSurv1  3.8281158000 0.26350285000
#> logitSurv1  2.1381761000 0.25933414000
#> logitSurv1  0.5953820900 0.25807847000
#> logitSurv1 -0.8238508600 0.25910685000
#> logitSurv1 -2.1378553000 0.26190416000
#> logitSurv1 -3.3611642000 0.26605379000
#> logitSurv0  2.4366593000 0.24260151000
#> logitSurv0  0.0238614540 0.24208927000
#> logitSurv0 -2.1788504000 0.24208531000
#> logitSurv0 -4.2051488000 0.24247261000
#> logitSurv0 -6.0812082000 0.24316365000
#> logitSurv0 -7.8277776000 0.24409190000
#>
#> Sensitivity / specificity
#> -------------------------
#>   threshold conflevel        Sens SensCI_Lower SensCI_Upper        Spec
#> 1       5.0      0.95 0.978712460  0.964826650  0.987189180 0.080419621
#> 2       5.5      0.95 0.894558700  0.836154650  0.933792570 0.494034920
#> 3       6.0      0.95 0.644599090  0.522374440  0.750486120 0.898334120
#> 4       6.5      0.95 0.304946840  0.208879800  0.421648260 0.985300730
#> 5       7.0      0.95 0.105471560  0.065916438  0.164580710 0.997719800
#> 6       7.5      0.95 0.033531473  0.020181123  0.055215748 0.999601650
#>   SpecCI_Lower SpecCI_Upper
#> 1  0.051556228   0.12334059
#> 2  0.377929040   0.61078778
```

```
#> 3  0.846104860   0.93421587
#> 4  0.976567300   0.99080981
#> 5  0.996332670   0.99858301
#> 6  0.999357410   0.99975308
```

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