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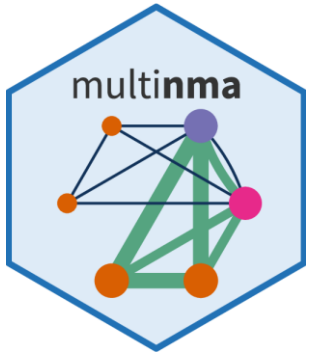

multinma

A comprehensive R package for network meta-analysis of survival outcomes with aggregate data, individual patient data, or a mixture of both

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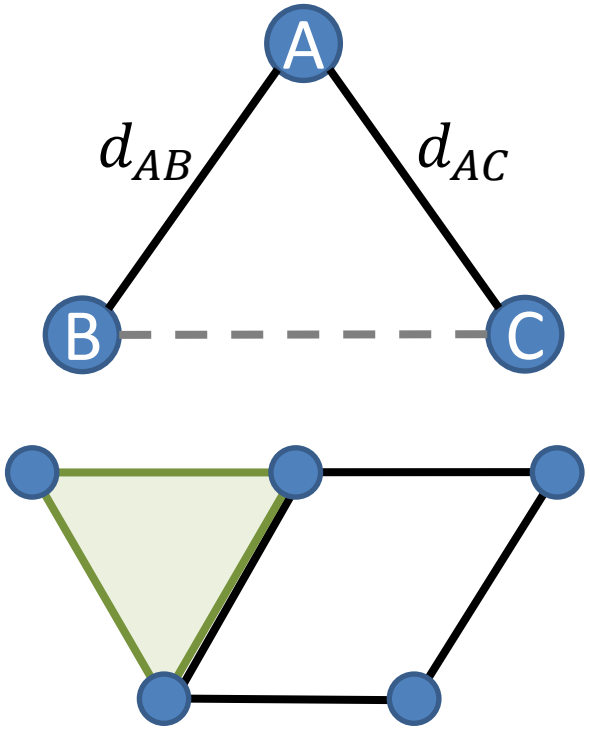
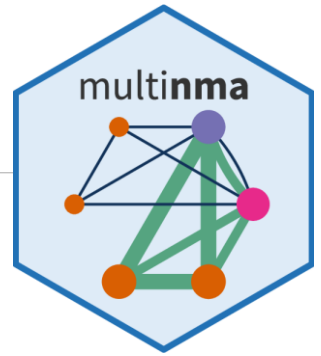
Background

We wish to compare multiple treatments, but not all are studied in the same trial

- Network meta-analysis (NMA) combines evidence on multiple treatments from several studies
- Survival outcomes are common, e.g. oncology
  - Synthesise log hazard ratios (HRs)
    - Restricted to proportional hazards (PH) assumption
  - Synthesise KM data
    - Assess and relax PH assumption
    - Covariate adjustment with individual participant data (IPD)
    - Requires complex bespoke modelling code



The multinma R package

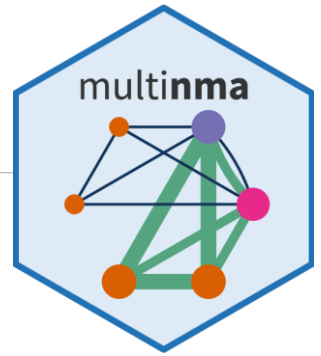


A user-friendly and comprehensive suite of tools for performing

- Aggregate data (AgD) NMA
- Individual participant data (IPD) NMA
- Multilevel network meta-regression with mixed IPD and AgD

- Models fitted in a Bayesian framework using Stan
- First released June 2020, with regular updates and new features since
  - Survival analysis features added in v0.6.0 (January 2024)

The multinma R package



Outcomes, likelihoods, link functions:

- **Binary/count** –Bernoulli/binomial (logit, probit, cloglog)
- **Rate** – Poisson (log)
- **Ordered categorical** – Multinomial (logit, probit, cloglog)
- **Continuous** – Normal (identity, log)
- **Survival** – Exponential (PH/AFT), Weibull (PH/AFT), Gompertz, log-Normal, log-Logistic, Gamma, Generalised Gamma, M-spline, piecewise exponential

Outline of NMA in multinma

Data Long ("tidy") format

- One row per arm/contrast in each AgD study, or per individual in IPD
- One row per event time for survival outcomes

Network setup

- `set_agd_arm()` `set_agd_contrast()` `set_agd_surv()` `set_ipd()`
- `combine_network()`

Fitting Specify model and prior distributions, run analysis

- `nma()`

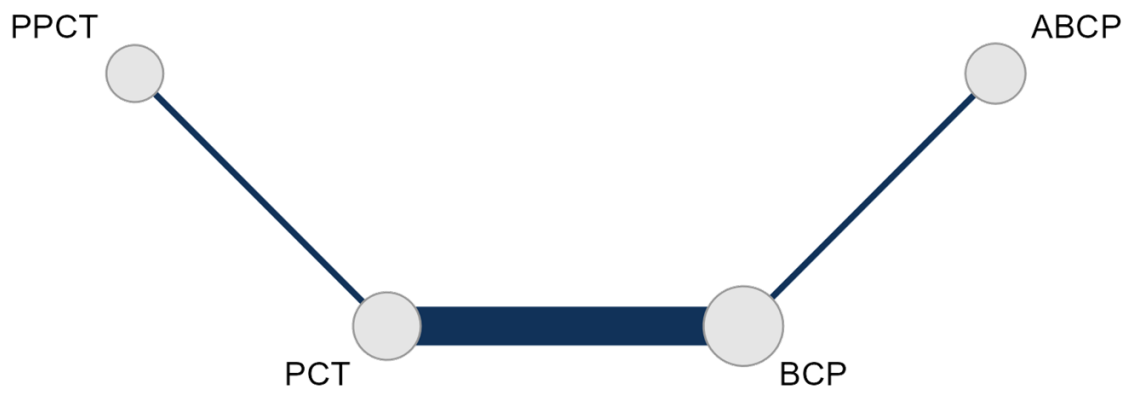
Posterior analysis Checking convergence, model fit and comparison, results

- `dic()` `loo::loo()` `loo::waic()`
- `relative_effects()` `predict()` `marginal_effects()` } `plot()`
- `posterior_ranks()` `posterior_rank_probs()`

Example: Non-small cell lung cancer

Four studies comparing first-line treatments for NSCLC

- PCT = platinum chemotherapy
- PPCT = pembrolizumab + platinum chemotherapy
- BCP = bevacizumab, carboplatin, paclitaxel
- ABCP = atezolizumab + bevacizumab, carboplatin, paclitaxel

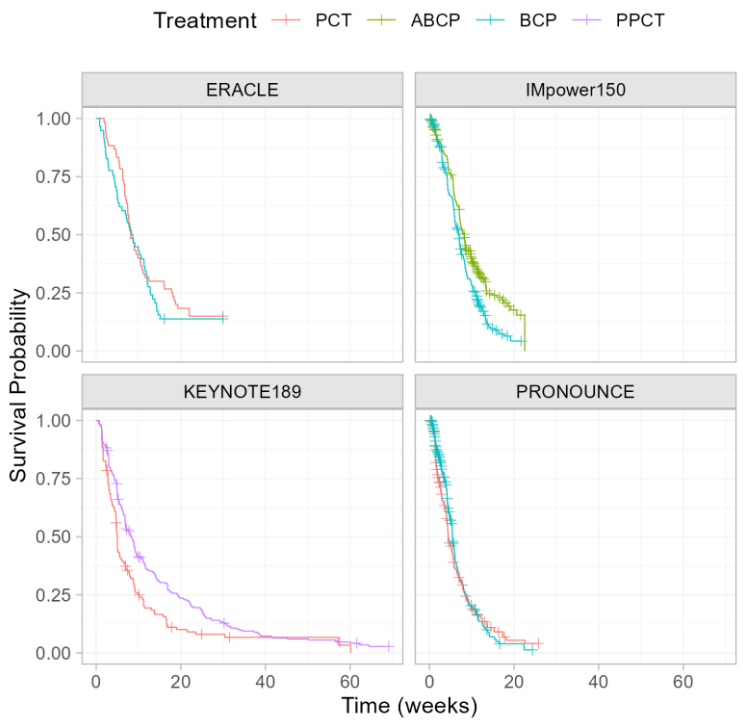



```
plot(nsclc_net)
```

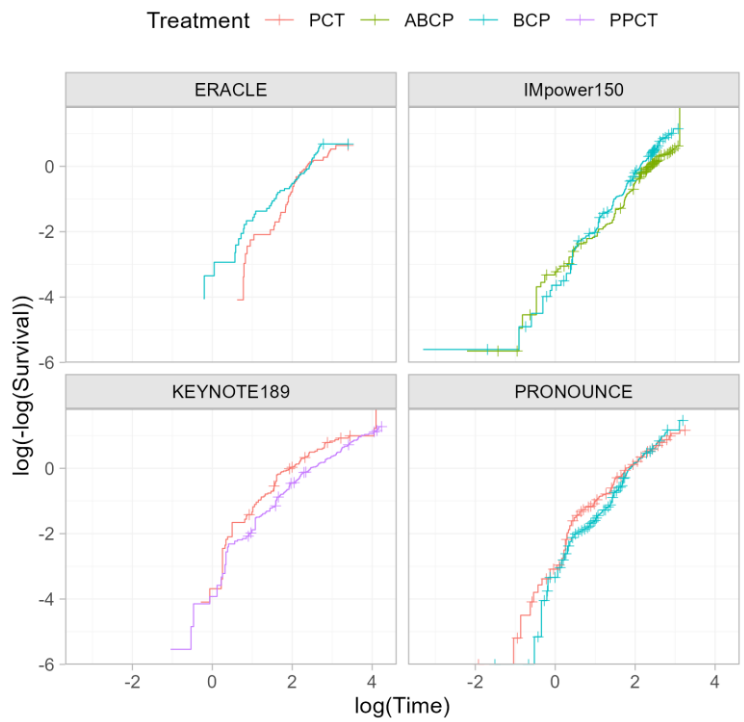
Example: Non-small cell lung cancer

- Survival and censoring times digitised from KM plots
- Evidence for non-proportional hazards

`geom_km()`



`geom_km(transform = "cloglog")`



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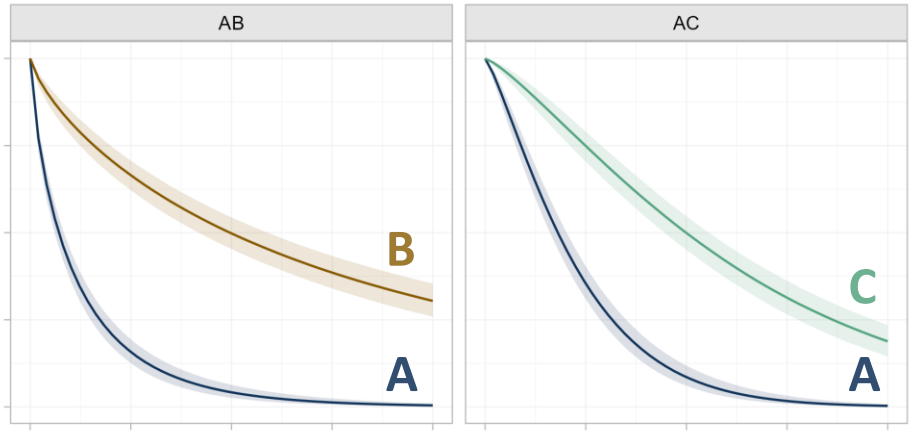
M-spline baseline hazards model

Phillippo et al. (2024)

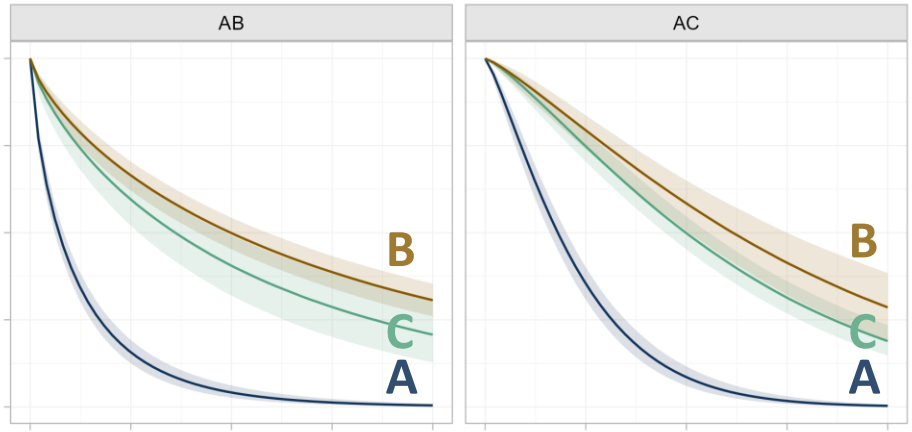
- Flexible M-spline baseline hazard model
- Avoids overfitting with a novel random walk prior on spline coefficients
  - Shrinks towards a prior constant baseline hazard
  - Random walk constructed to be invariant to the number and location of knots, and to the timescale
  - Does provide appropriate shrinkage, unlike other priors
    - No shrinkage with Dirichlet (rstanarm, Brilleman 2020)
    - Insufficient shrinkage with random effects (survextrap, Jackson 2024)
  - Avoids the need to fit multiple models (Fractional Polynomials)

Options for modelling non-PH in multinma

- Stratify shape parameters by treatment arm
  - `aux_by = c(.study, .trt)`
  - Fewest assumptions
  - No predictions for unobserved treatment arms



- Treatment effects on shape parameters
  - `aux_regression = ~.trt`
  - Predictions for any treatment in any population



- IPD covariates in NMA model
  - `regression = ~(x1 + x2)*.trt`

NSCLC analysis: network setup

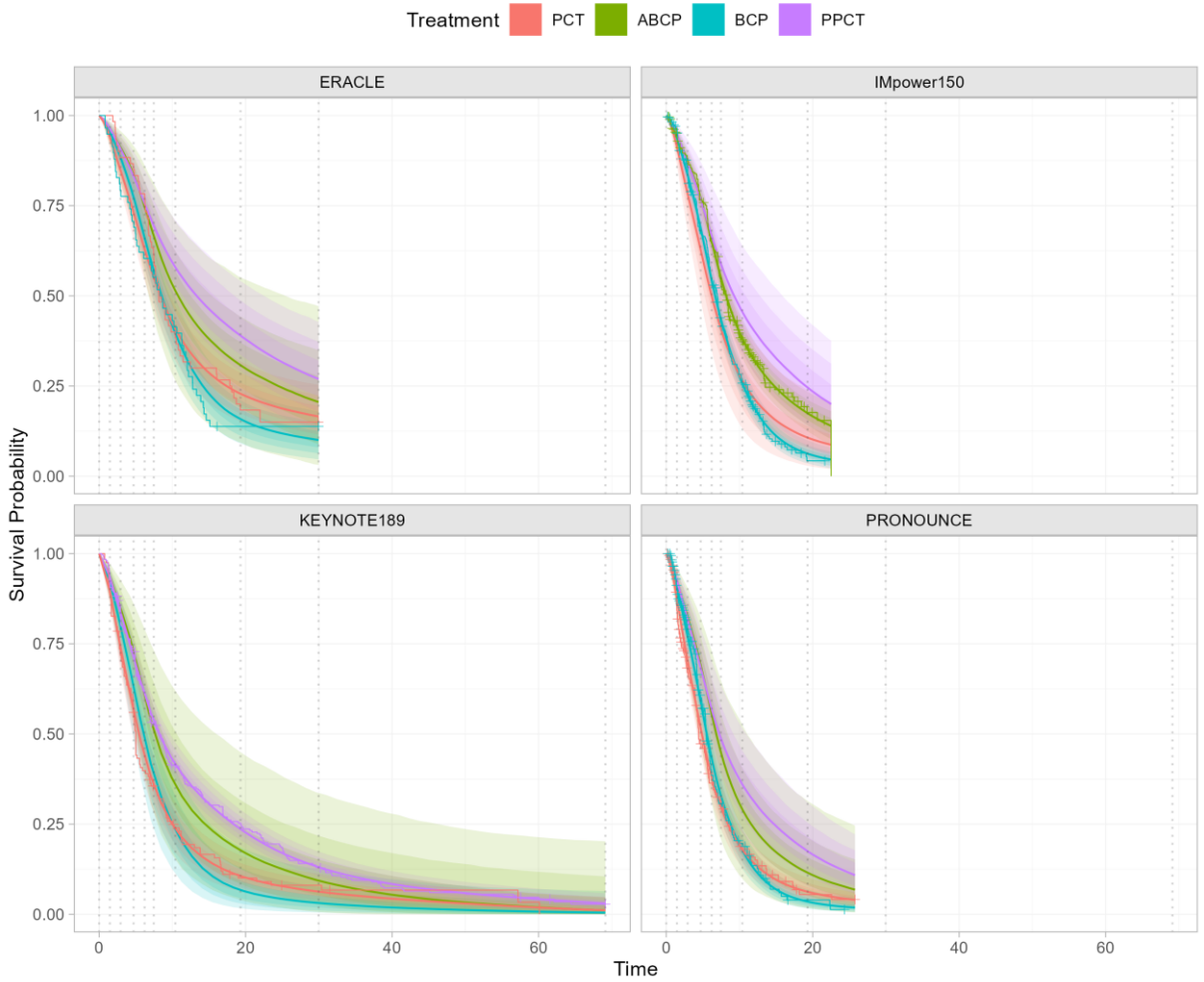
```
# Set up network
nsclc_net <- set_agd_surv(
  nsclc_dat,
  study = studyc,
  trt = trtc,
  Surv = Surv(eventtime, status))
```

NSCLC analysis: model fitting

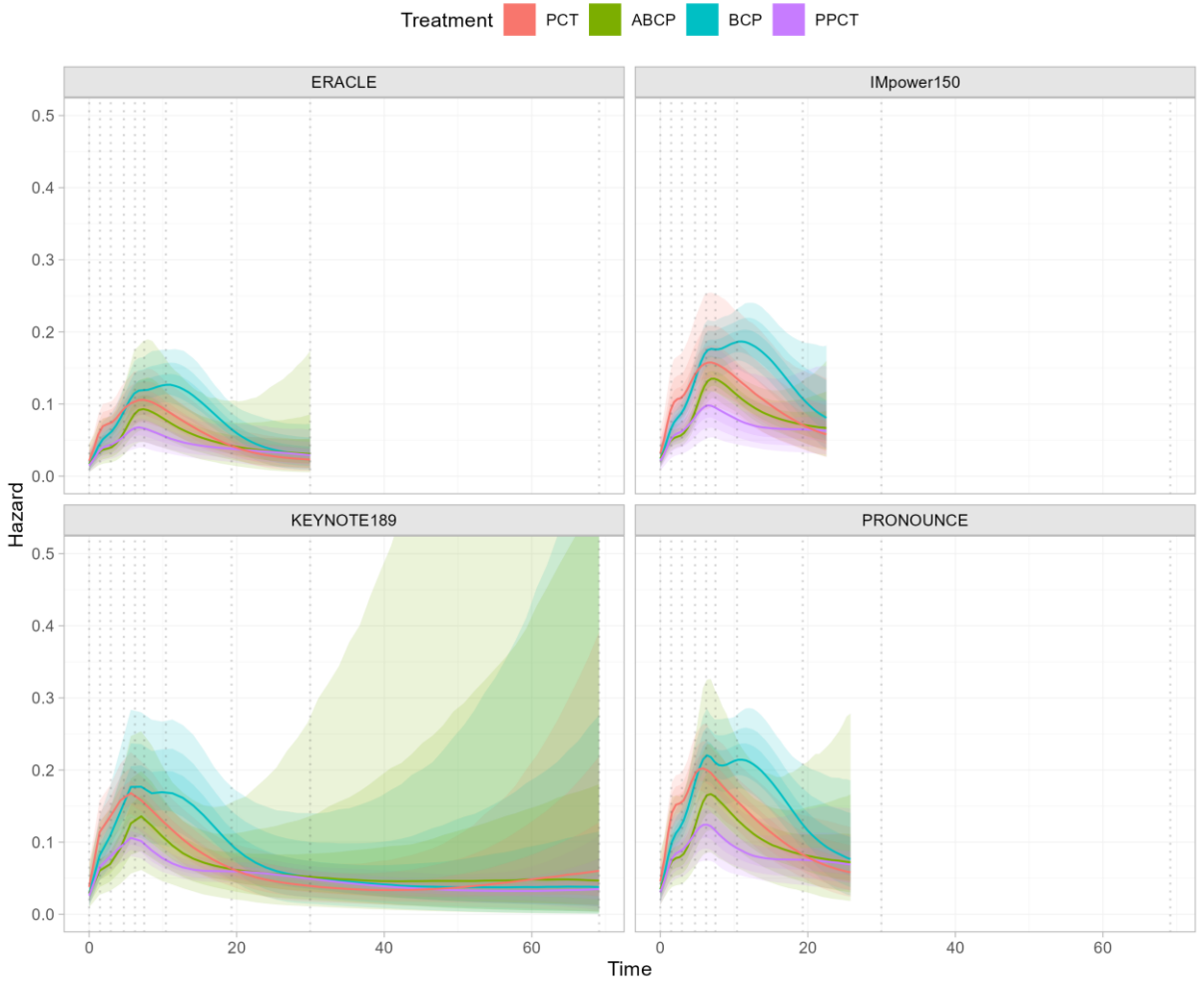
```
# Fit non-PH M-spline NMA
nsclc_fit <- nma(nsclc_net,
  likelihood = "mspline",       # M-spline likelihood
  aux_regression = ~.trt,       # Regression on spline coefs
  prior_intercept = normal(scale = 100),  # Priors
  prior_trt = normal(scale = 10),
  prior_aux = half_normal(1),
  prior_aux_reg = half_normal(1))
```

NSCLC analysis: fitted survival and hazard curves

```
plot(predict(nsclc_fit, type = "survival"))
```




```
plot(predict(nsclc_fit, type = "hazard"))
```



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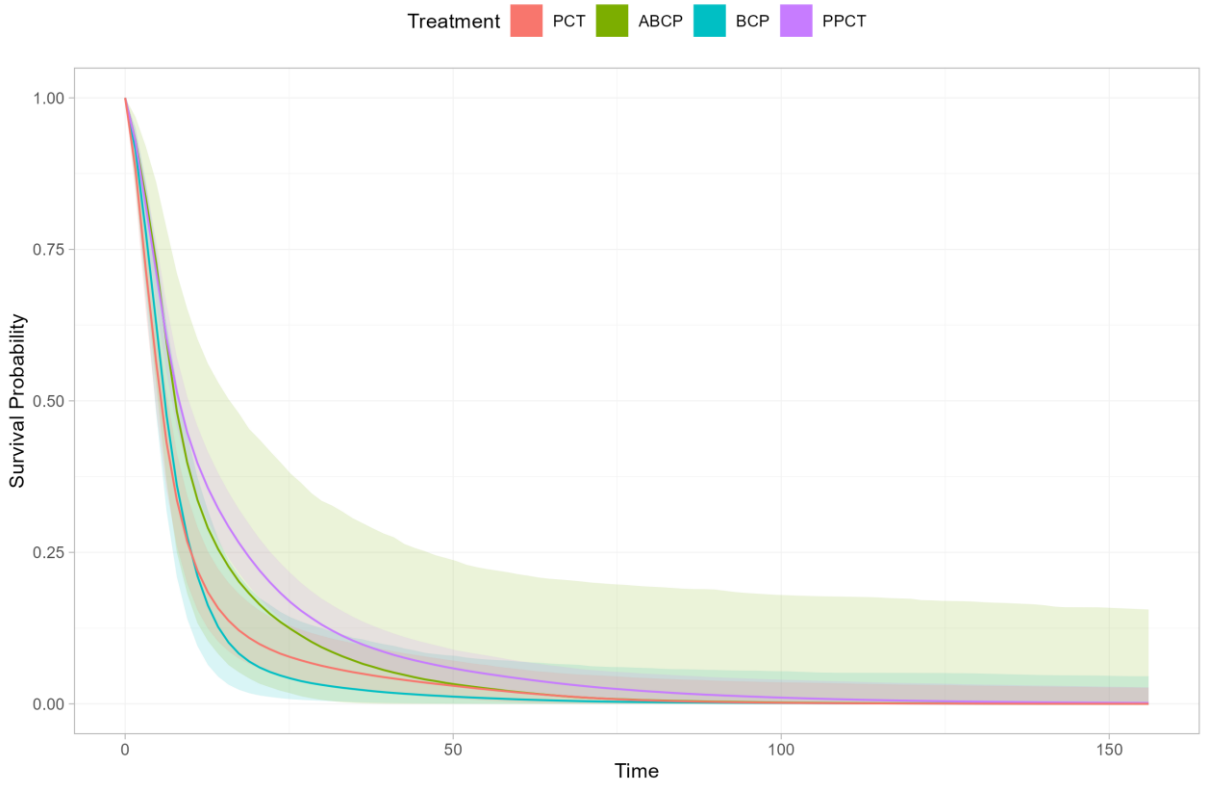
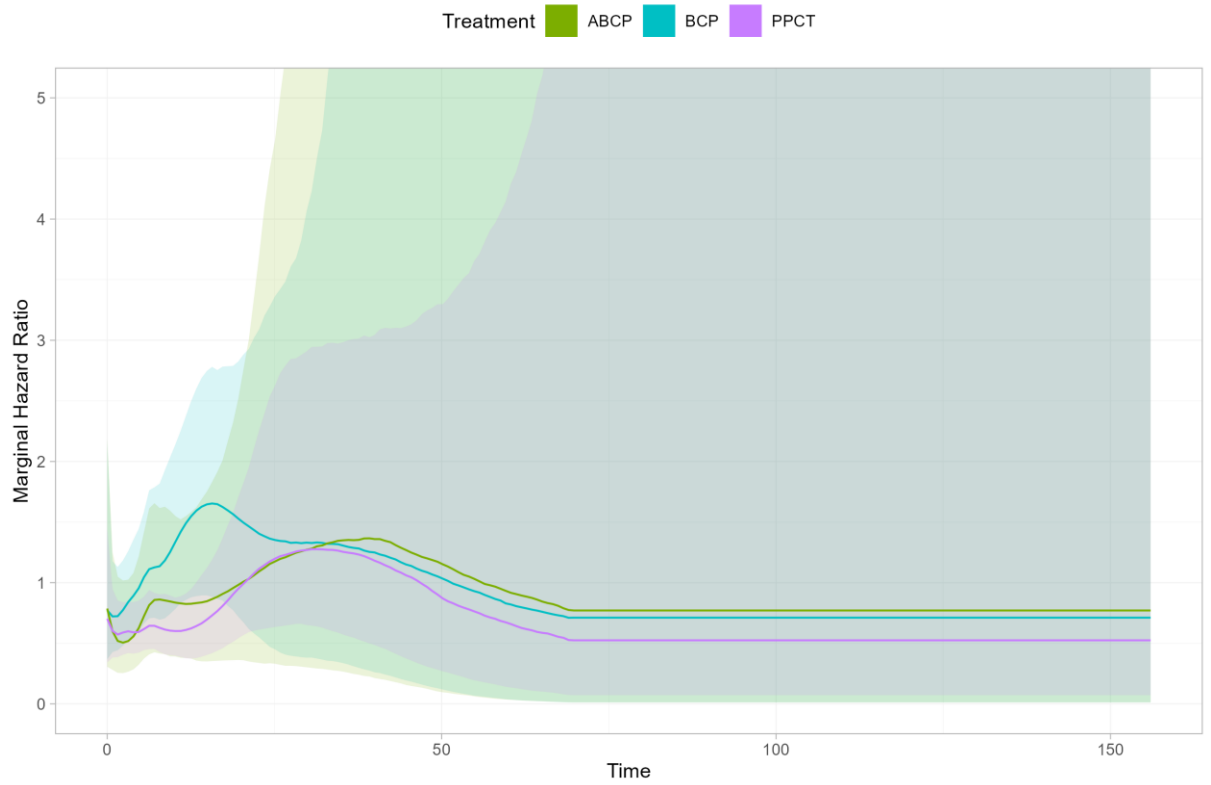
NSCLC analysis: 3-year survival extrapolations and HRs for KEYNOTE

```
plot(predict(nsclc_fit, type = "survival",
  times = seq(0, 52 * 3, length.out = 100),
  baseline="KEYNOTE189", aux="KEYNOTE189"))
```




```
plot(marginal_effects(nsclc_fit,
  type = "hazard", mtype = "ratio",
  times = seq(0, 52 * 3, length.out = 100),
  baseline="KEYNOTE189", aux="KEYNOTE189"))
```



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Other summary quantities

Phillippo et al. (2024)

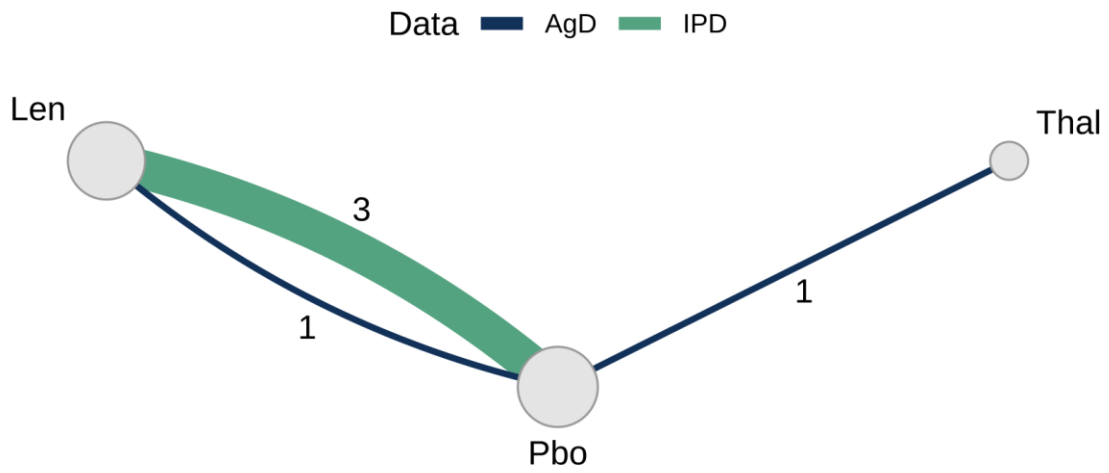
- The `predict()` function can produce:
  - Survival curves
  - Hazard and cumulative hazard curves
  - Median and quantiles of survival times
  - Mean and restricted mean survival times

- The `marginal_effects()` function produces differences or ratios of these, e.g.
  - Time-varying marginal hazard ratios
  - Relative survival ratios over time
  - Differences in RMST or median survival times

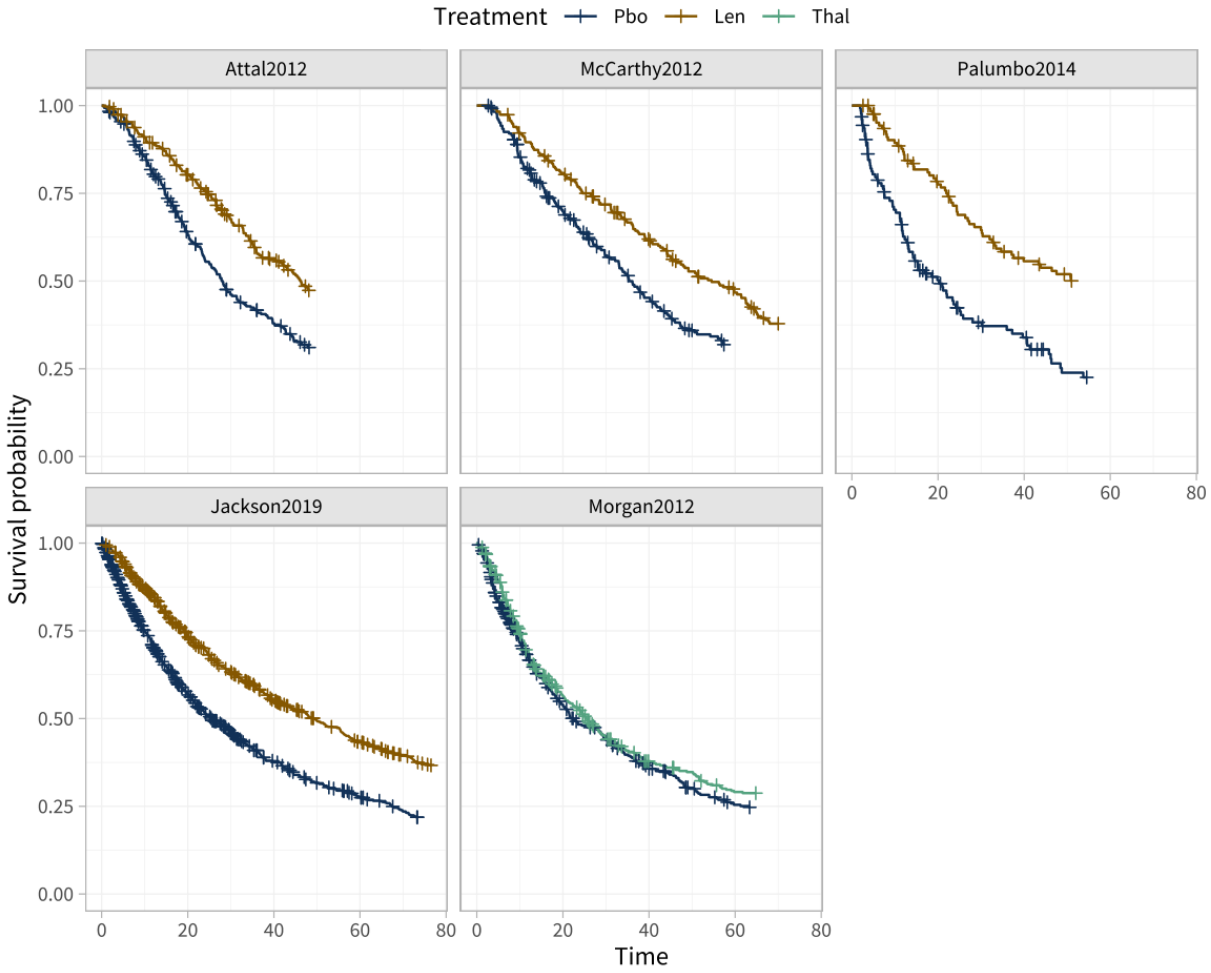
Example: Newly-diagnosed multiple myeloma

- Lenalidomide, Thalidomide, Placebo
- 3 IPD studies, 2 AgD studies
- Four potentially effect-modifying covariates
  - Age, ISS stage, response category, sex

```
plot(ndmm_net)
```




```
geom_km()
```



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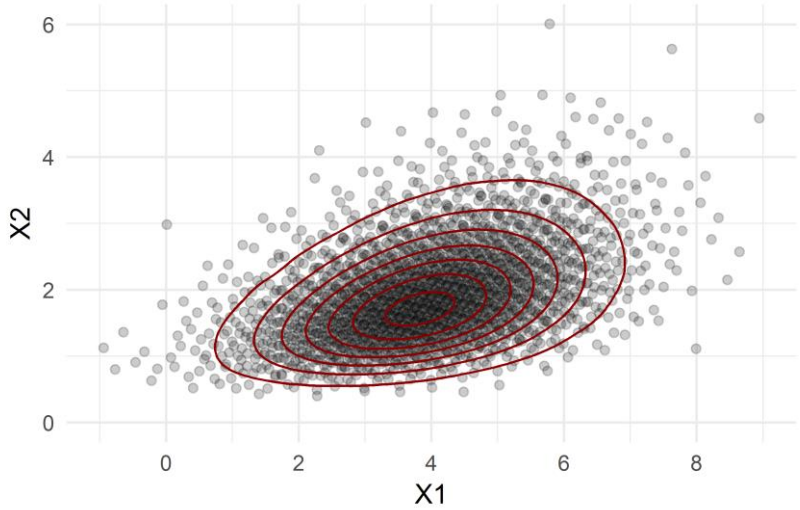
Multilevel network meta-regression (ML-NMR)

Phillippo et al. (2020, 2024)

Extends full-IPD NMA to coherently incorporate AgD

- Avoids aggregation bias by integrating the individual-level model over the aggregate populations
  - Using numerical integration



- Adjust for differences in effect-modifying covariates between populations
- Produce estimates in a target population of interest for decision making

Outline of ML-NMR in multinma

Data Long ("tidy") format

Network setup

- `set_*()` `combine_network()`

Numerical integration setup

- `add_integration()` `distr()`

Fitting Specify model and prior distributions, run analysis

- `nma()`

Posterior analysis Checking convergence, model fit and comparison, results

- `dic()` `loo::loo()` `loo::waic()`
- `relative_effects()` `predict()` `marginal_effects()` ⎫
- `posterior_ranks()` `posterior_rank_probs()` ⎭ `plot()`

NDMM analysis code

```
# Set up network
ndmm_net <- combine_network(
  set_ipd(ndmm_ipd, study = studyc, trt = trtc,
          Surv = Surv(eventtime, status), trt_class = trtclass),
  set_agd_surv(ndmm_agd, study = studyc, trt = trtc,
               Surv = Surv(eventtime, status), trt_class = trtclass,
               covariates = ndmm_agd_covs))

# Add integration
ndmm_net <- add_integration(ndmm_net,
  age = distr(qgamma, mean = age_mean, sd = age_sd),
  iss_stage3 = distr(qbern, iss_stage3),
  response = distr(qbern, response),
  male = distr(qbern, male))

# Fit M-spline ML-NMR model in Stan
ndmm_fit <- nma(ndmm_net,
  likelihood = "mspline",                          # M-spline model
  regression = ~(age + iss_stage3 + response + male)*.trt,      # Regression
  prior_intercept = normal(scale = 100),           # Priors
  prior_trt = normal(scale = 10),
  prior_reg = normal(scale = 10),
  prior_aux = half_normal(1))
```

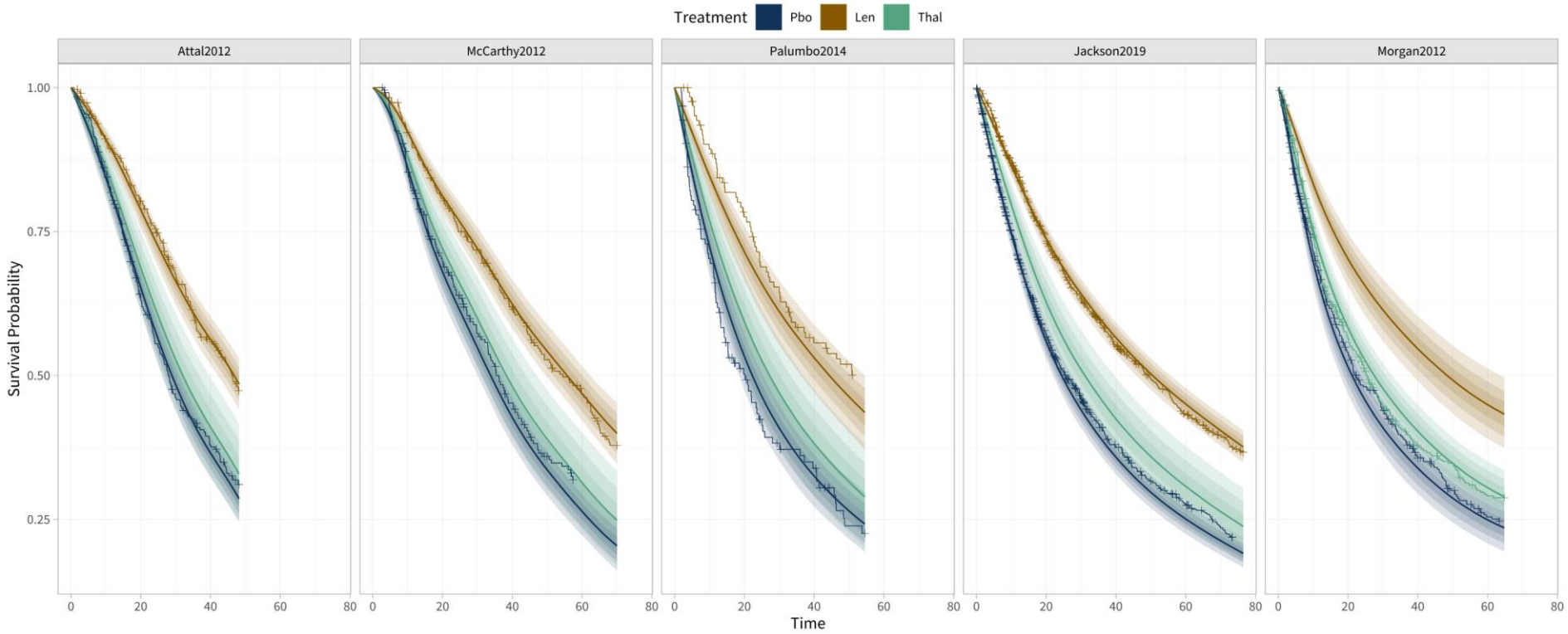
set_ipd()
set_agd_surv()
combine_network()

add_integration()

nma()

Population-average survival curves

```
plot(predict(ndmm_fit, type = "survival"))
```

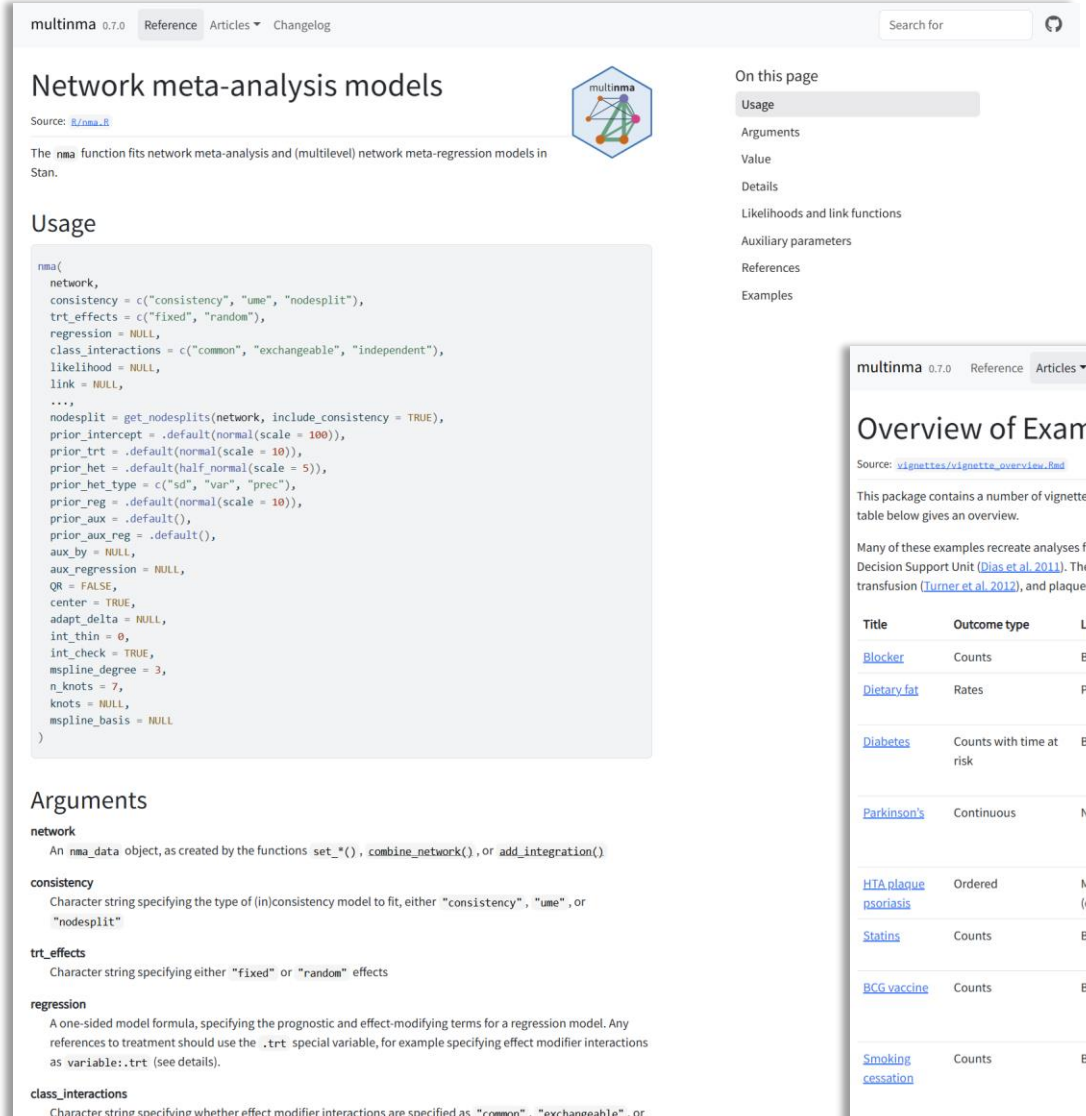


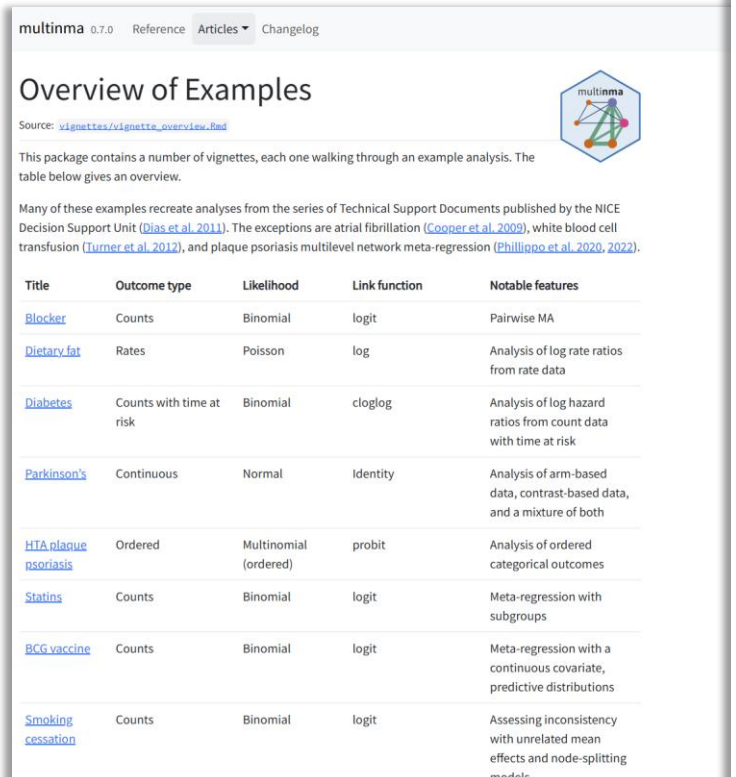
- Median survival estimates vary by up to a year across populations:

  Placebo 20.75 to 33.30 months Thalidomide 26.55 to 38.44 months Lenalidomide 44.95 to 55.92 months
- Evidence of non-PH in unadjusted model, removed by covariate adjustment

Package website

dmphillippo.github.io/multinma





Summary

- multinma is a comprehensive suite of tools for NMA and ML-NMR with AgD, IPD, or mixtures of both
- Now with survival analysis features
  - Parametric and flexible models, non-PH modelling
  - Without complex bespoke modelling code
- ML-NMR coherently combines IPD and AgD, produces population-adjusted estimates in specific target populations for decision making
- M-spline baseline hazards are a novel approach with advantages over alternative flexible methods
  - Provide appropriate shrinkage via random walk prior
  - Closed form likelihood, single model fit (unlike Fractional Polynomials)

Funding and References

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Phillippo, DM et al. (2020) Multilevel Network Meta-Regression for population-adjusted treatment comparisons. *Journal of the Royal Statistical Society: Series A*, 183(3):1189-1210. DOI: 10.1111/rssa.12579.

Phillippo DM et al. (2023) Validating the assumptions of population adjustment: application of multilevel network meta-regression to a network of treatments for plaque psoriasis. *Medical Decision Making*, 43(1):53-67. DOI: 10.1177/0272989X221117162.

Phillippo DM et al. (2024) Multilevel network meta-regression for general likelihoods: synthesis of individual and aggregate data with applications to survival analysis. Preprint, *arXiv*:2401.12640 [stat.ME]

Phillippo DM (2024). *multinma: Bayesian Network Meta-Analysis of Individual and Aggregate Data*. R package version 0.7.0. DOI: 10.5281/zenodo.3904454. URL: dmphillippo.github.io/multinma. CRAN: cran.r-project.org/package=multinma