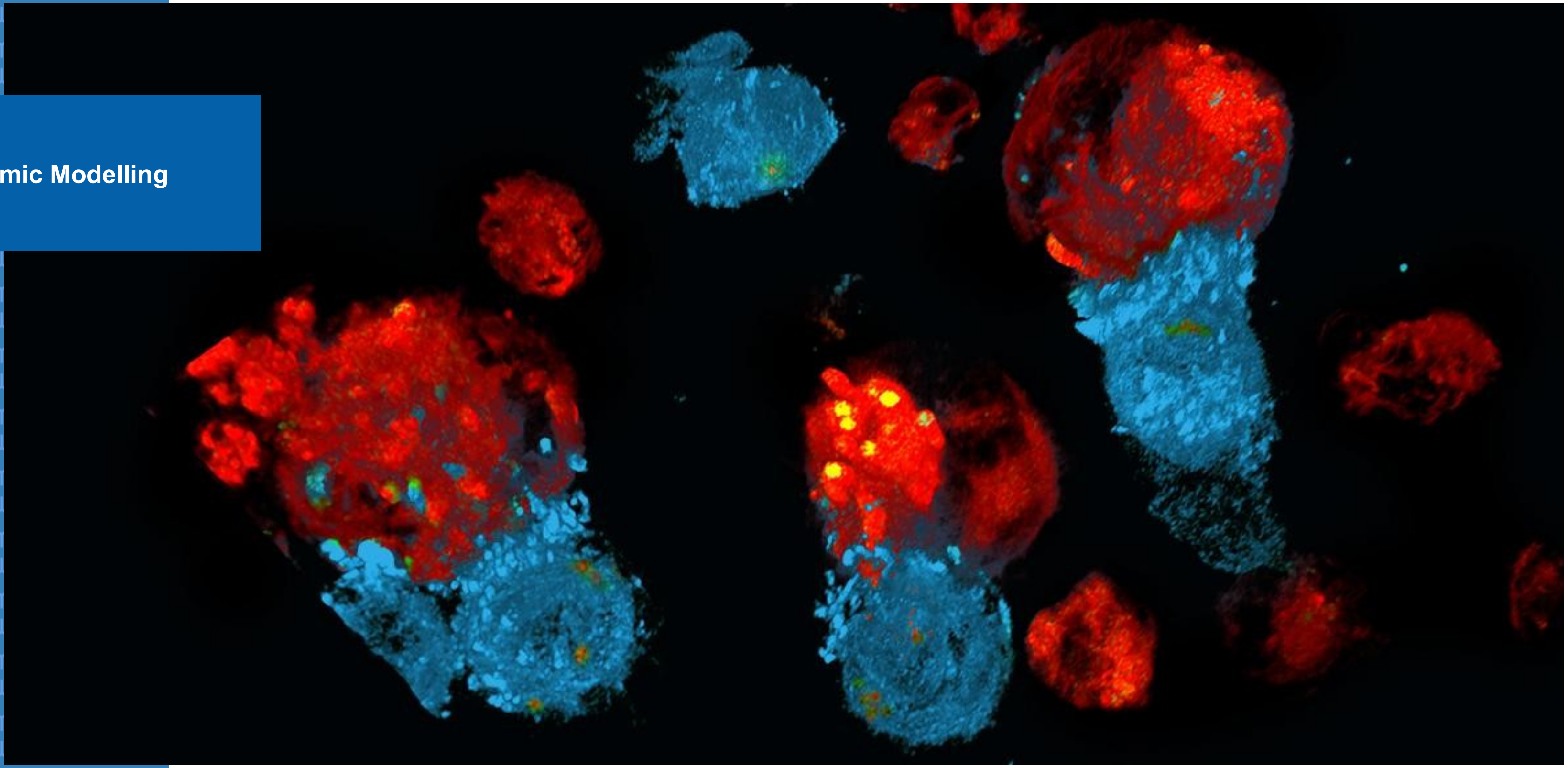
Economic Modelling



Incorporating Clinical Opinion to Survival Extrapolations: An Applied Example

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Background

1. As cited by many authors survival extrapolations are very sensitive to the statistical model used:
   - Exponential ~ Constant Hazard
   - Weibull ~ Monotonically increasing or decreasing Hazards
   - Gompertz ~ Exponentially increasing or decreasing Hazards
   - Log-Normal/Log-Logistic ~ Can initially increase then decrease
2. Give the maturity of the data each model can yield very different extrapolations which may result in different cost effectiveness estimates
3. Extrapolations are based on:
   - Goodness of fit statistics
   - Clinical Opinion
   - External data

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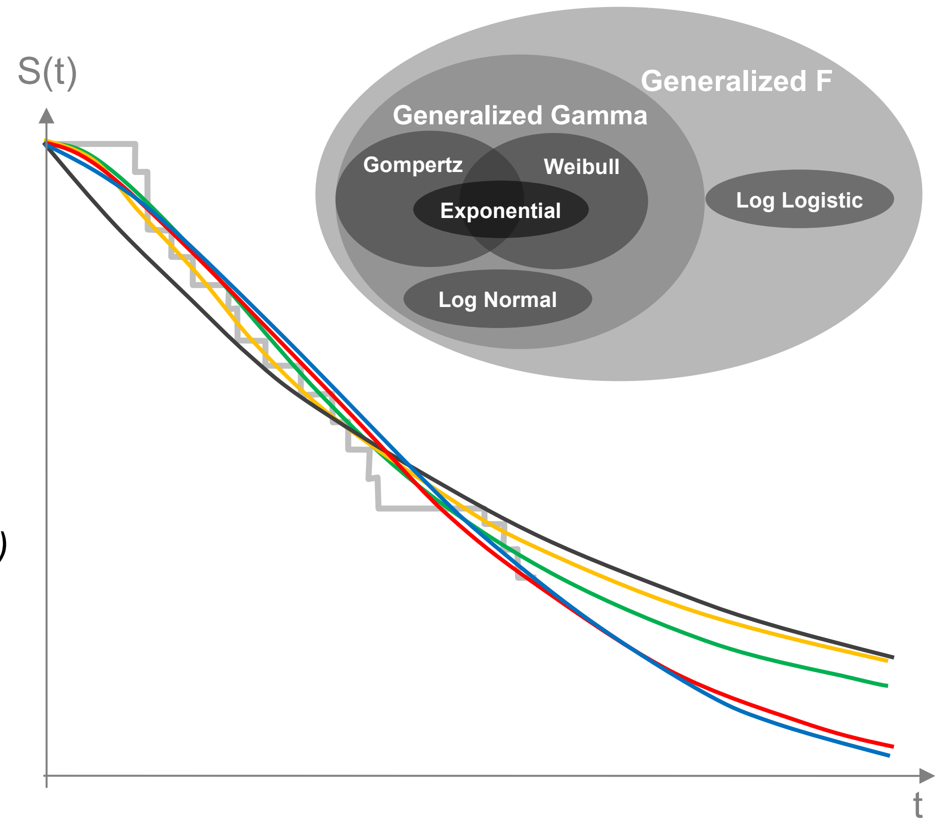
Behaviour of some parametric curves

Distr.	Para-meters	Hazards
Exponential	1	
Weibull, Gompertz	2	
Log Normal	2	
Log Logistic	2	
Generalized Gamma	3	*all above (not LL)*
Generalized F	4	*all above*
... some more ...		



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Extrapolations using Clinical Opinion

1. Acceptance of extrapolations using clinical opinion is generally low:
   a) Elicited in a very ad-hoc and informal manner (open to bias)
   b) Implemented in a very subjective manner (i.e. which extrapolation is closest to the experts opinion)
2. Possible Solution - Bayesian Survival Analysis
3. The expert's opinion can be directly incorporated into the trial level analysis!

N.B. Saw this topic presented at ISPOR 2018 by Dr. Mario Ouwens

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Bayesian Methods

$$p(\theta|data) = \frac{p(data|\theta) \times p(\theta)}{p(data)}$$

- You update your **Prior Belief* (i.e. Clinical Opinion)** with **Data (i.e. Trial Data)** and obtain a **Posterior Belief**
- The $p(data)$ typically has no analytical solution, therefore, software such as BUGS, JAGS or STAN is required
- You can use Goodness of fit measures to see which model fits **both** your data and clinical opinion best!

*About a parameter

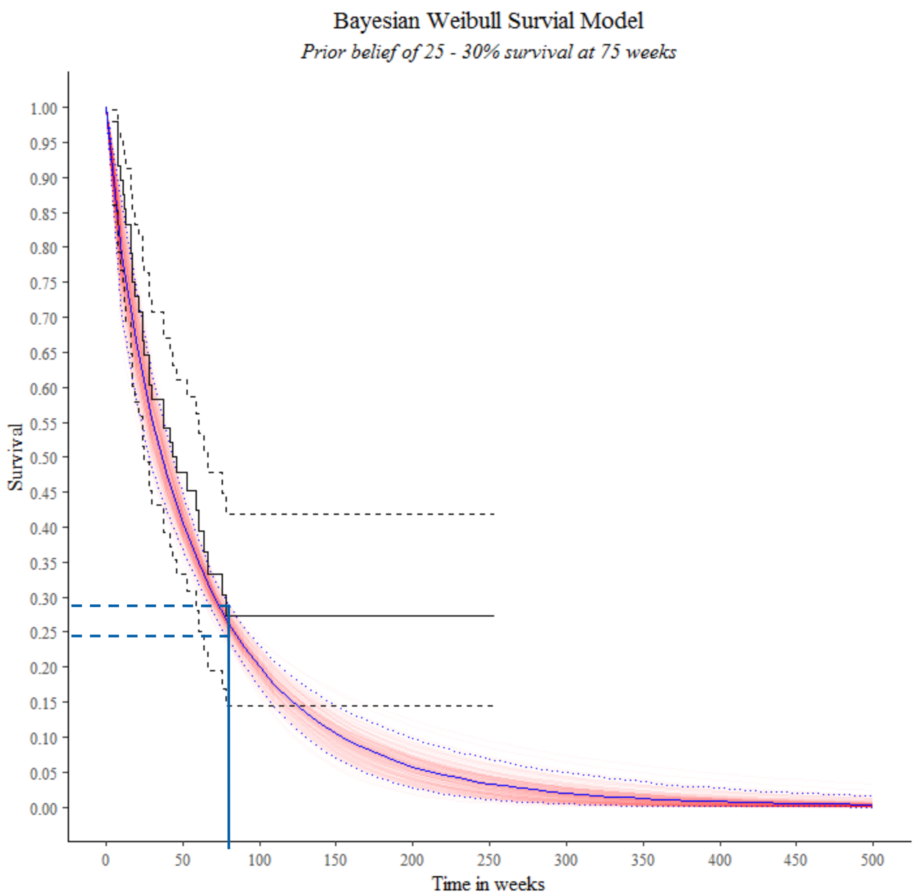
Eliciting the Opinion and Fitting the model

1. Ask an expert to think of the plausible range of survival probabilities at a specific timepoint i.e.:

At 10 years what is the plausible range of survival probabilities for Treatment X?

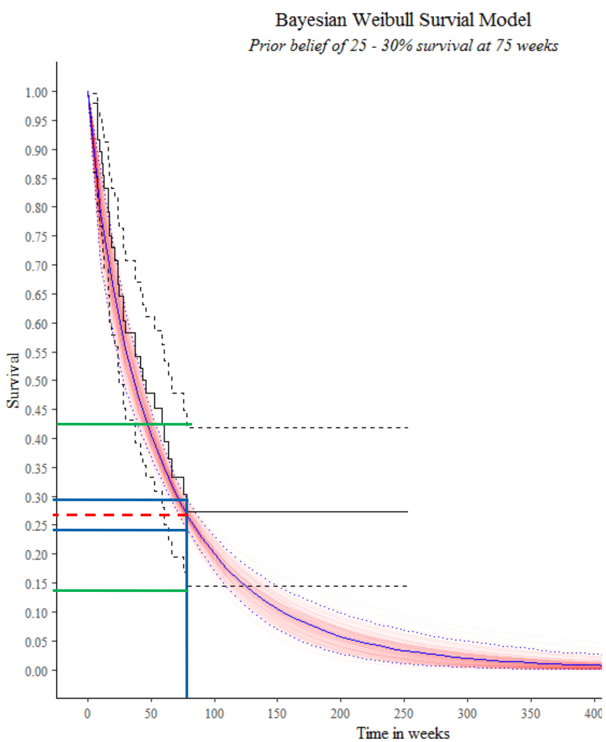
2. *A plausible range means the upper and lower survival probabilities so the expert is 95% sure that the actual survival probability will be within the range*
3. *Through a hierarchical sampling technique the parameters of the survival distribution are selected to cover this distribution*

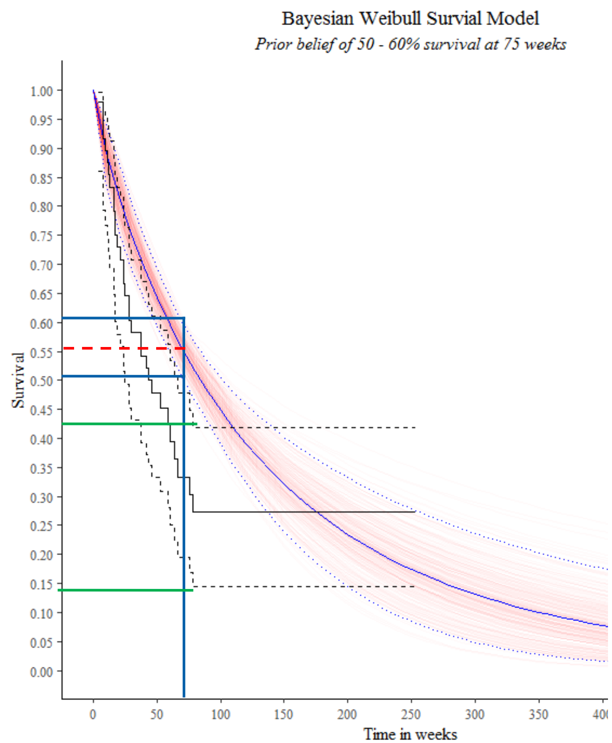
For Illustration: Gastric Cancer Example

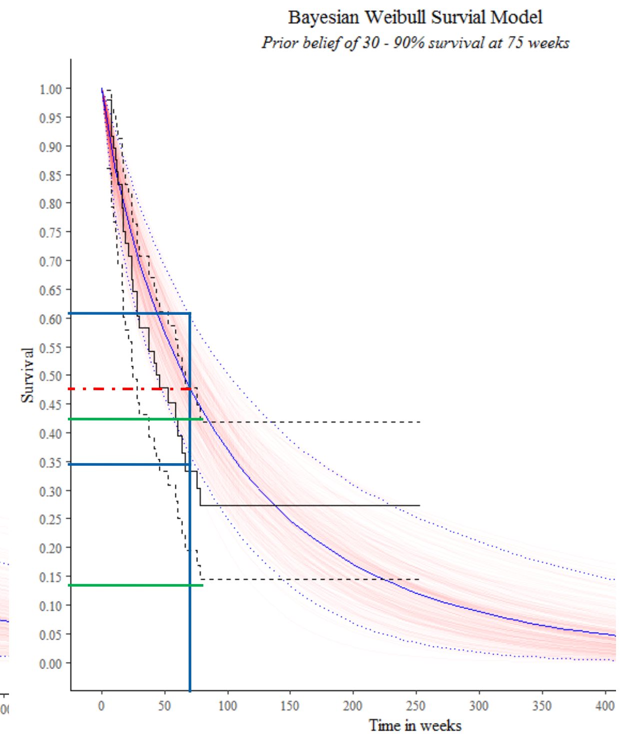


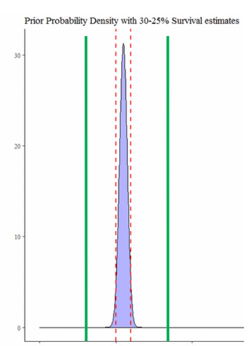
- Dataset available on R, relatively few patients and events (48 and 32)
- For illustration I have constrained the survival at 75 weeks to be between 25-30%
- Exponential, Gompertz, Log-Logistic and Log-Normal all can be fit

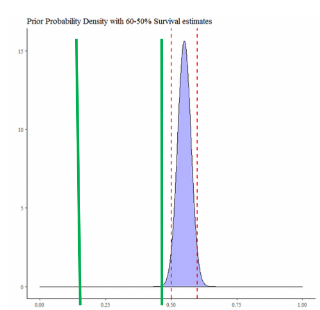
For Illustration: Gastric Cancer Example (2)

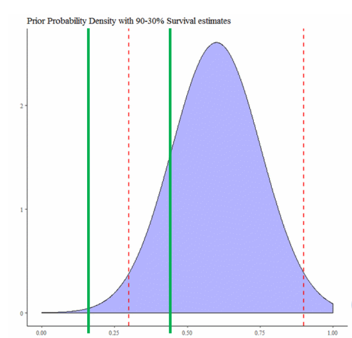












Shiny Tool

The analysis is done in R but it would be potentially easier to elicit opinions if the priors on the survival probabilities could be viewed

Potential Solution =

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Shiny App

Inputs

Outputs

Survival Modelling using Expert Opinion

Expert Opinion on Survival Probabilities

Timepoint

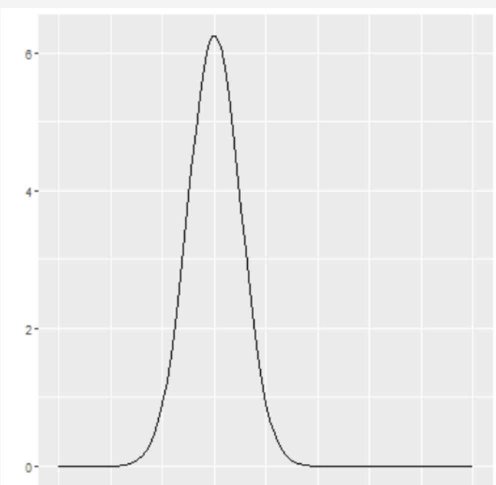
0 200 500

0 50 100 150 200 250 300 350 400 450 500

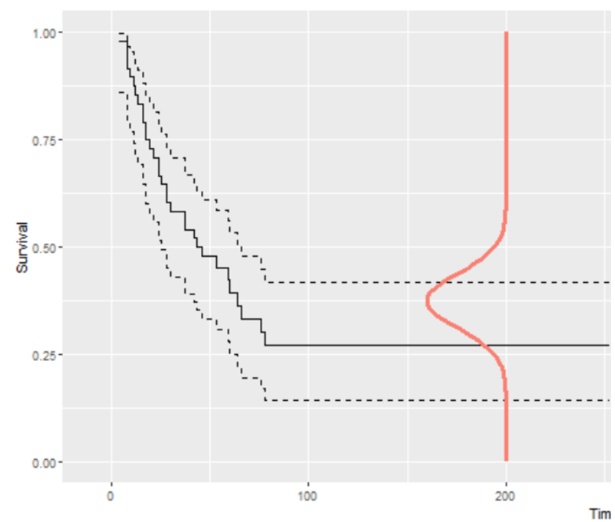
Upper and Lower Survival Probabilities

0 0.25 0.5 1

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1



Kaplan Meier Survival Plot



Choose a survival model

Weibull

Run Analysis

Output of the Bayesian Analysis

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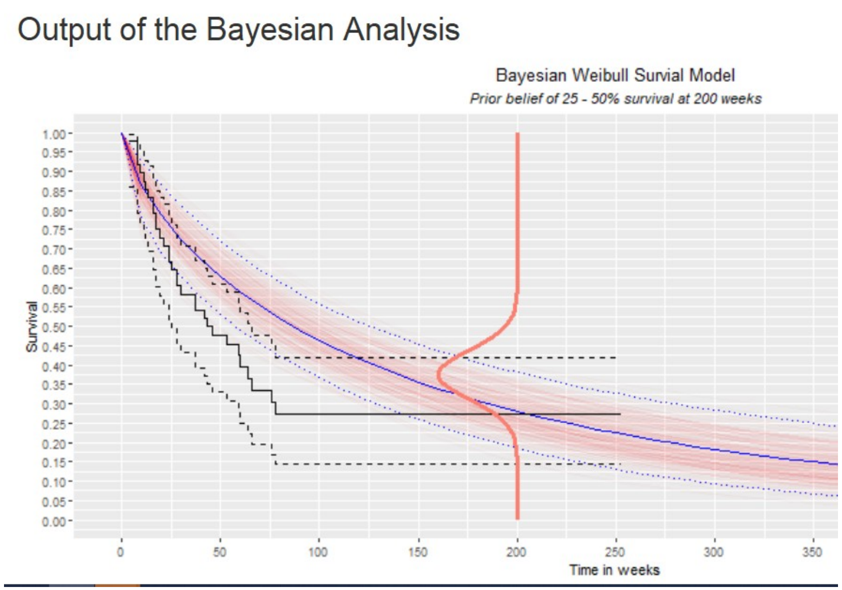
Functionality

We can select the required timepoint & expert’s 95% credible interval and see the output update in real time

We can then select the survival model and run the analysis



Summary

Advantages:

✔ Robust approach to incorporating clinical expert opinion and protects against model misspecification

✔ Demands more formal expert elicitation

Disadvantages:

� Expert elicitation is still the weakest form of evidence; sensitive to overly optimistic/conservative opinions!

� Approach is limited to one timepoint and cannot incorporate belief about the type of model which is most plausible or external evidence (possibly overcome by Bayesian Model Averaging)

� Does not (yet) account for more complex 3 parameter models

Backup-
Mario Ouwens Presentation

How does it work? Bayesian estimation

Construction of a priori distribution for exponential distribution:

Clinician: "At 10 years, placebo survival percentage is between 10 and 15%"

$\exp(-\lambda t)$

Statistician: $\exp(-\lambda t)$

"I can do my magic with the exponential"

$S = \exp(-\lambda t)$

$10\% = \exp(-10\ \lambda_{\text{upper bound}})$
$15\% = \exp(-10\ \lambda_{\text{lower bound}})$

$\lambda_{\text{lower bound}} = 0.19,\ \lambda_{\text{upper bound}} = 0.23$

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How does it work? Bayesian estimation; Challenge: What to do with multiple parameters

But what to do with distributions with more than 1 parameter?

exp???

Distribution	Functional form	Rewritten for S=10% at t = 10
Exponential	S = Exp($-\lambda t$)	λ = -ln(10%) / 10
Weibull	S = Exp($-\lambda t^{\varphi}$)	λ = -ln(10%) / 10^{φ}
Lognormal	S = $1 - \Phi\left(\frac{\log(t)-\mu}{\sigma}\right)$	$\mu = \log(10) - \sigma\, \Phi^{-1}(1 - 10\%)$
Loglogistic	S = $\frac{1}{1+\exp\left(\frac{t}{\beta}\right)^{\varphi}}$	β = 10 – (log((1-10%)/10%))$^{1/\varphi}$
Gompertz	$\exp(-\varphi\,(\exp(\beta t) - 1))$	$\varphi = -\log(10\%)/(\exp(10\beta) - 1)$

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How does it work? Bayesian estimation; Challenge: What to do with multiple parameters

Solution: Sample φ first and compute $\lambda_{upper\ bound}$ and $\lambda_{lower\ bound}$ using S and φ

Distribution	Functional form	Rewritten for S=10% at t = 10
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Gompertz	$exp(-\varphi\,(\exp(\beta t) - 1))$	$\varphi = -\log(10\%)/(\exp(10\beta) - 1)$

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Thank you

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