# 1. Time-dependence (cont.)
# 2. Uncertainty

Ivy Tsai

20231031

# Agenda 20231031

- 1st hour: quick review and R package – time-varying values
- 2nd hour: video and self-study
- 3rd hour: discussion –  uncertainty/heterogeneity

Homework for 20231107:

Exercise 3.5 Hip Fracture **(MUST)**

Videos **(if no time to read Briggs and Edlin)**

# Exercise 3.5 Hip Fracture

- Page 67-75

https://www.herc.ox.ac.uk/downloads/decision-modelling-for-health-economic-evaluation

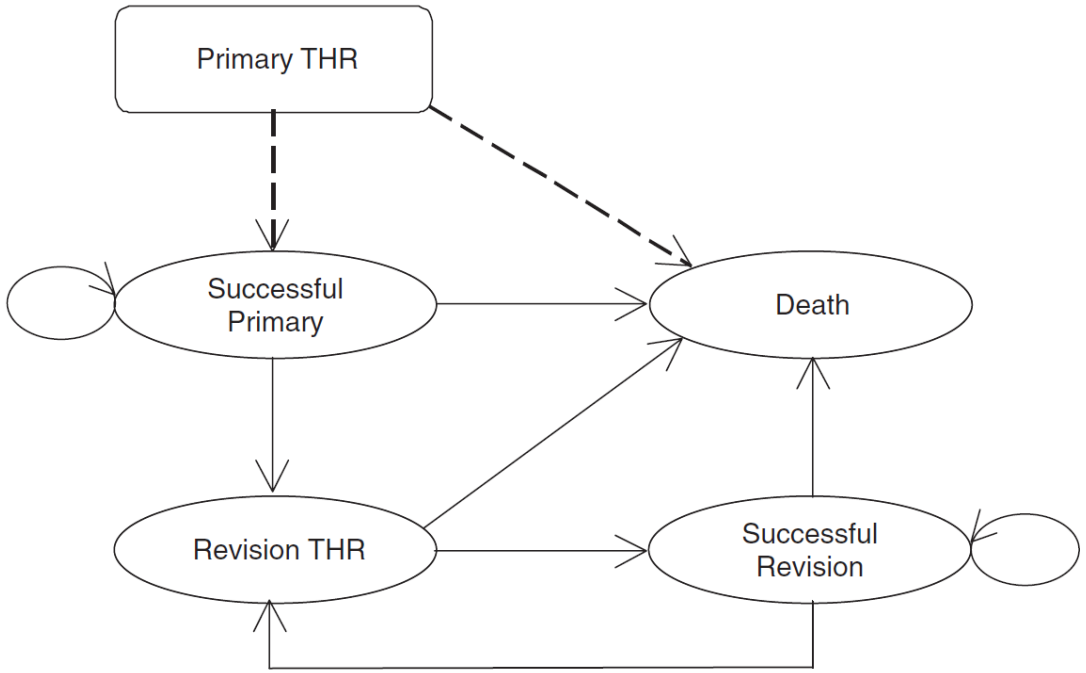
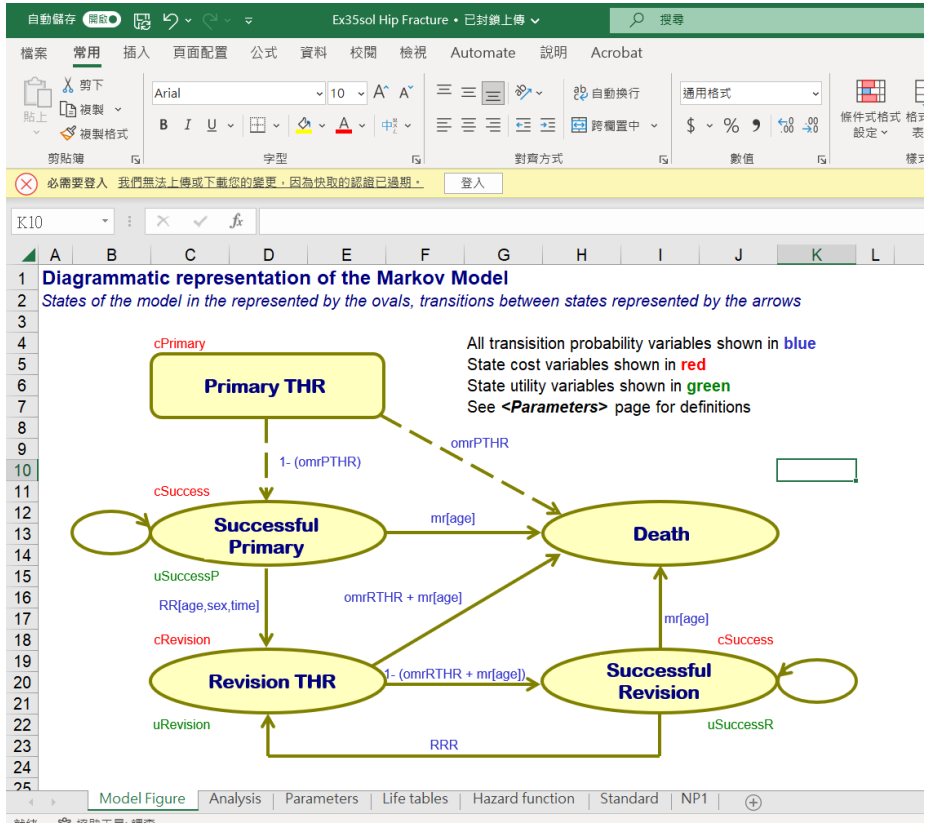
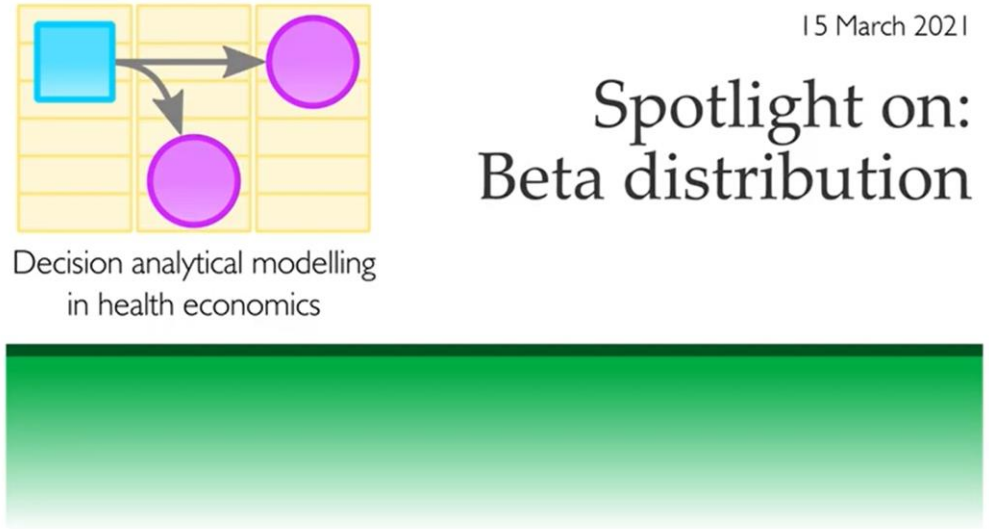
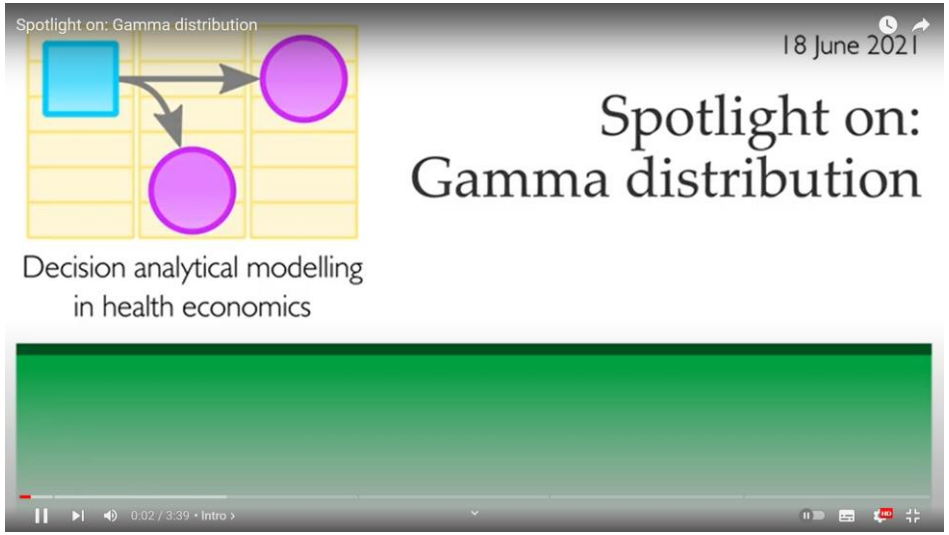



**Fig. 3.7** Diagram showing the structure of the model (Briggs *et al*. 2004, Fig. 1).

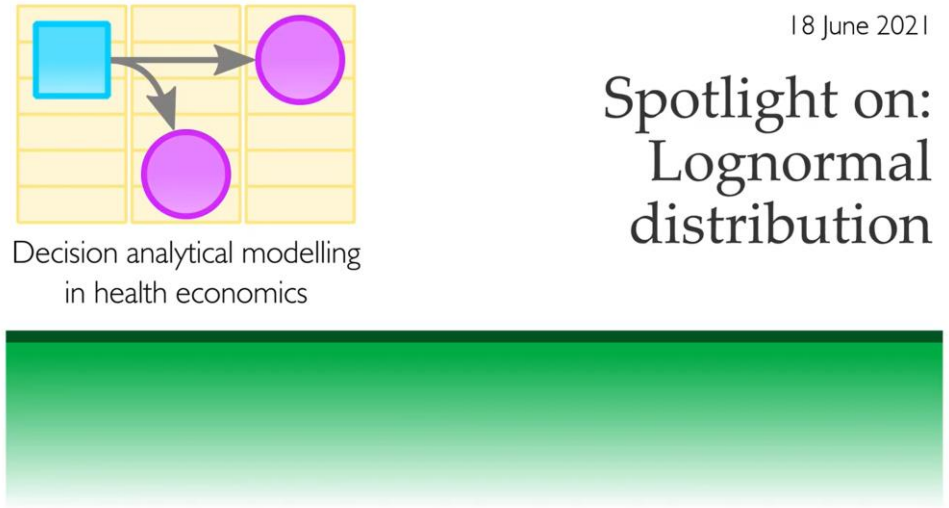




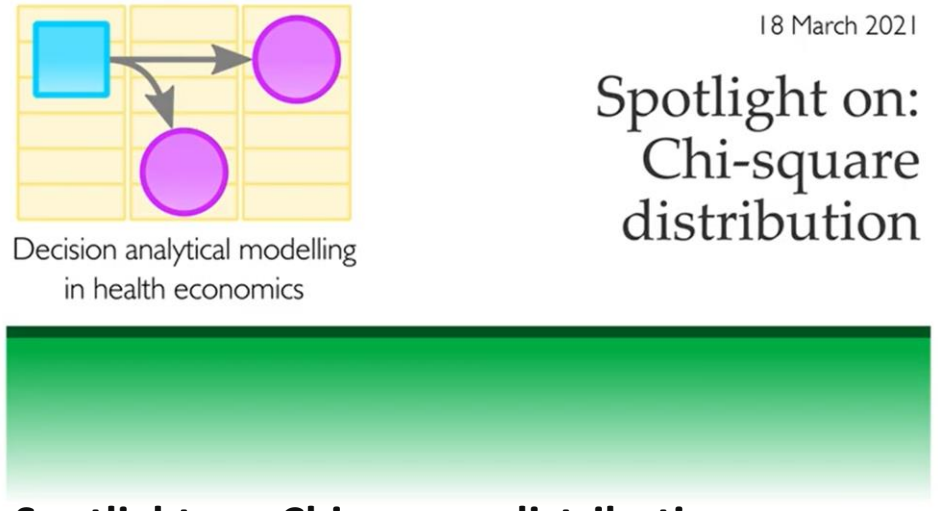

**Spotlight on: Beta distribution**
https://www.youtube.com/watch?v=i8KvU-ODqgA




**Spotlight on: Gamma distribution**
https://www.youtube.com/watch?v=-pIIVcwq6NI




**Spotlight on: Lognormal distribution**
https://www.youtube.com/watch?v=qxQ2GC1uYjs




**Spotlight on: Chi-square distribution**
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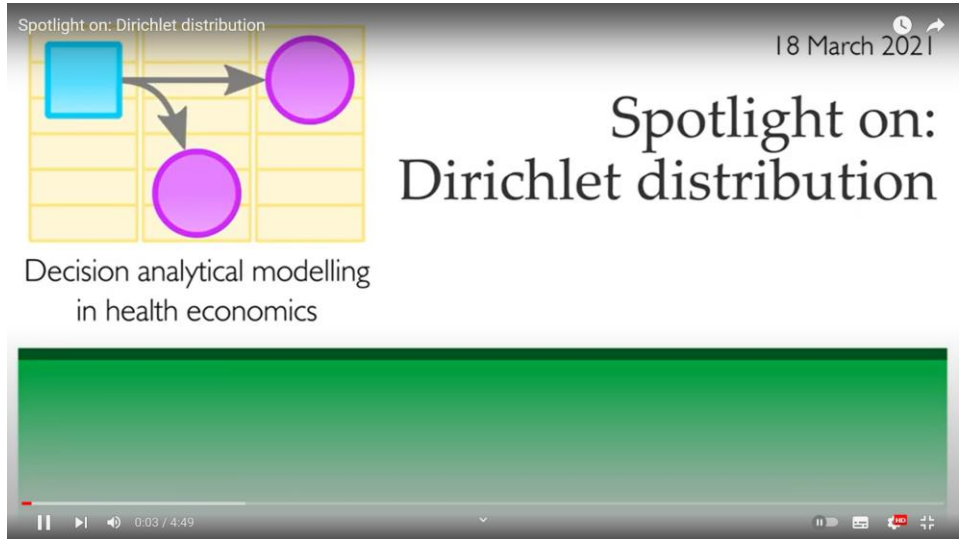
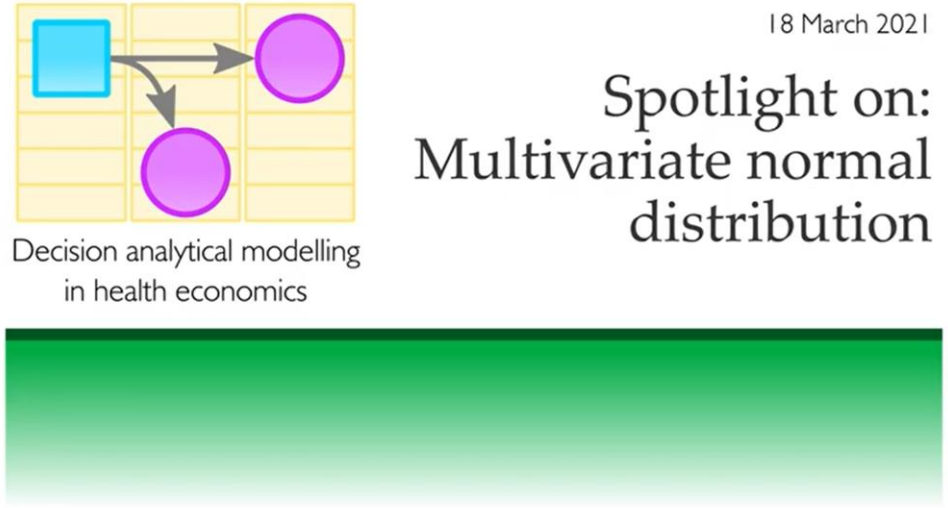
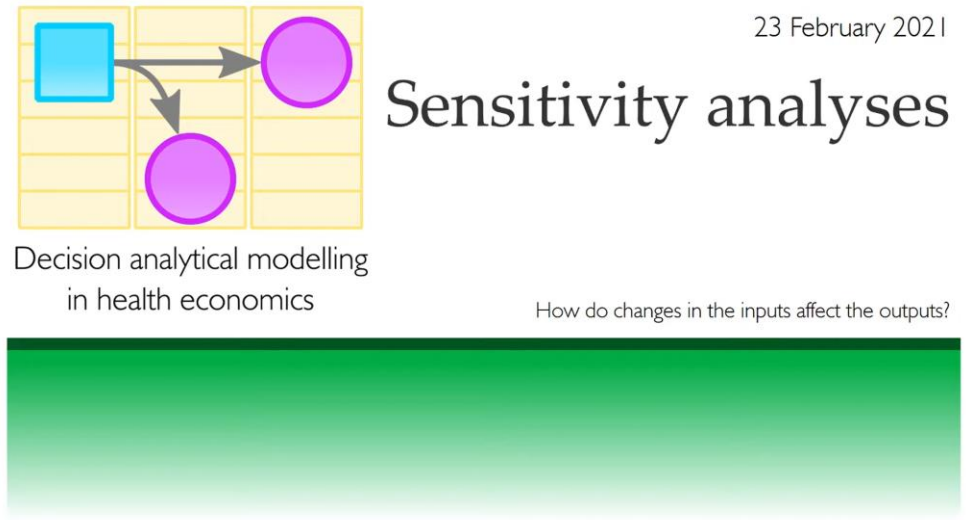


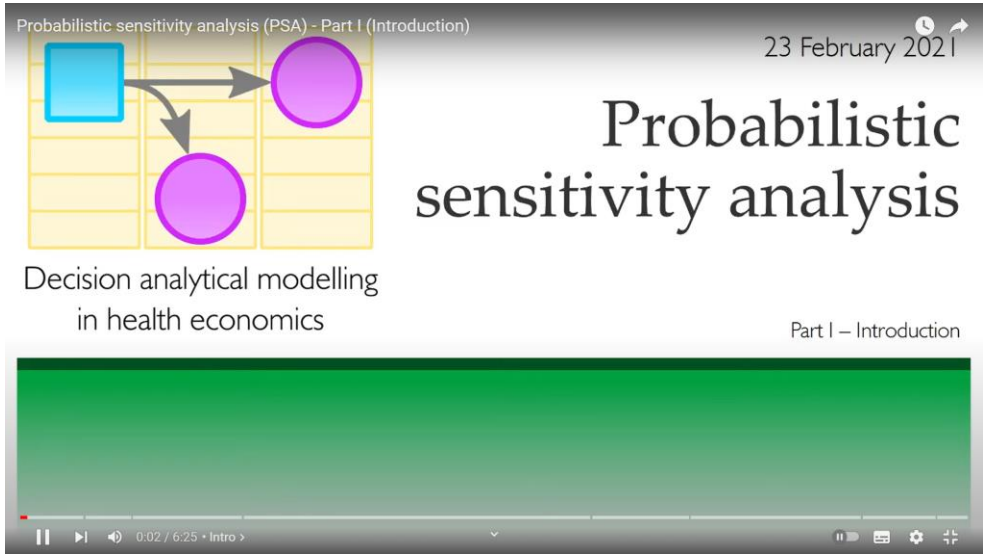

**Spotlight on: Dirichlet distribution**
https://www.youtube.com/watch?v=eOOzVyBDHjc



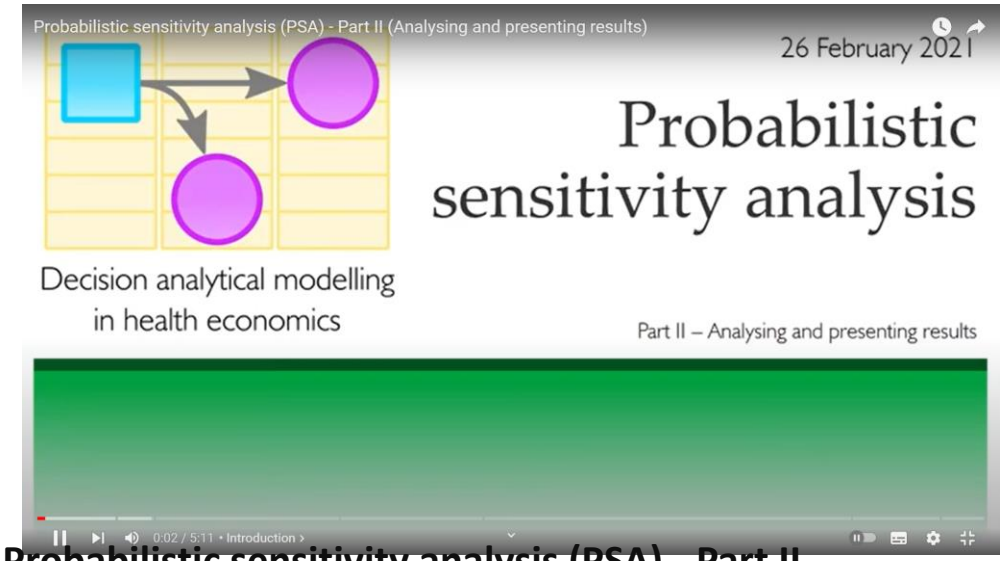

**Spotlight on: Multivariate normal distribution**
https://www.youtube.com/watch?v=X3sbaqJ2tcY




**Sensitivity analyses in cost-effectiveness modelling**
https://www.youtube.com/watch?v=1txk9FUsIbw&list=PLIT7NqYN7YT3LNYOoTEFchRXX7crLfYa5&index=10




**Probabilistic sensitivity analysis (PSA) - Part I (Introduction)**
https://www.youtube.com/watch?v=Mnftc8V0pU4




**Probabilistic sensitivity analysis (PSA) - Part II (Analysing and presenting results)**
https://www.youtube.com/watch?v=cTEceyHOqQQ

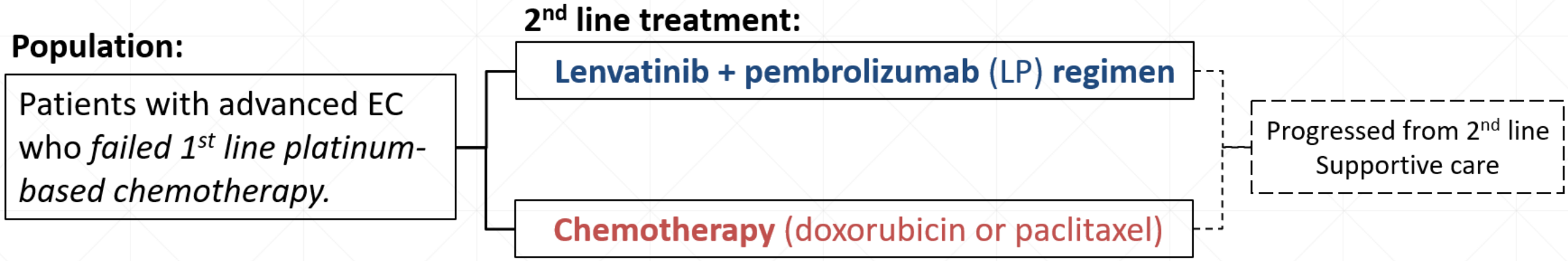
# Uncertainty in decision model

- York Materials

# 2.1. Analytic Framework of Cost-Effectiveness Analysis (2/6)

Case 1

## 1. Define the elements of decision problem




- **Cycle length:** 3 weeks
- **Time horizon (t):** 20 years
- **Discount rate (r):** 3% per year
- **Outcome variables:**
  - **Effectiveness** ($E_I$ and $E_C$)
    → Life years (Lys), quality-adjusted life years (QALYs = Life year × quality of life).
  - **Directed medical costs** ($C_I$ and $C_C$)
    → Medical cost reimbursed by NHI and NHI listing price.

# 2.1. Analytic Framework of Cost-Effectiveness Analysis (4/6)

Case 1

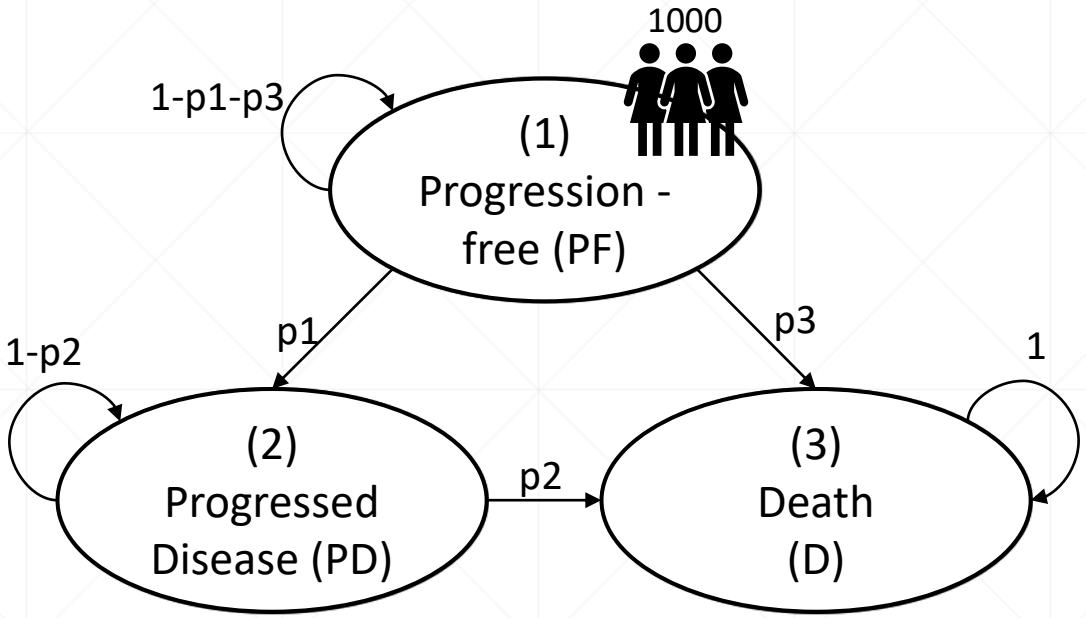
## 2. Analytical Model building

- **Decision analytical model:** Cohort-based Markov model
- **Disease model:** 3 health states

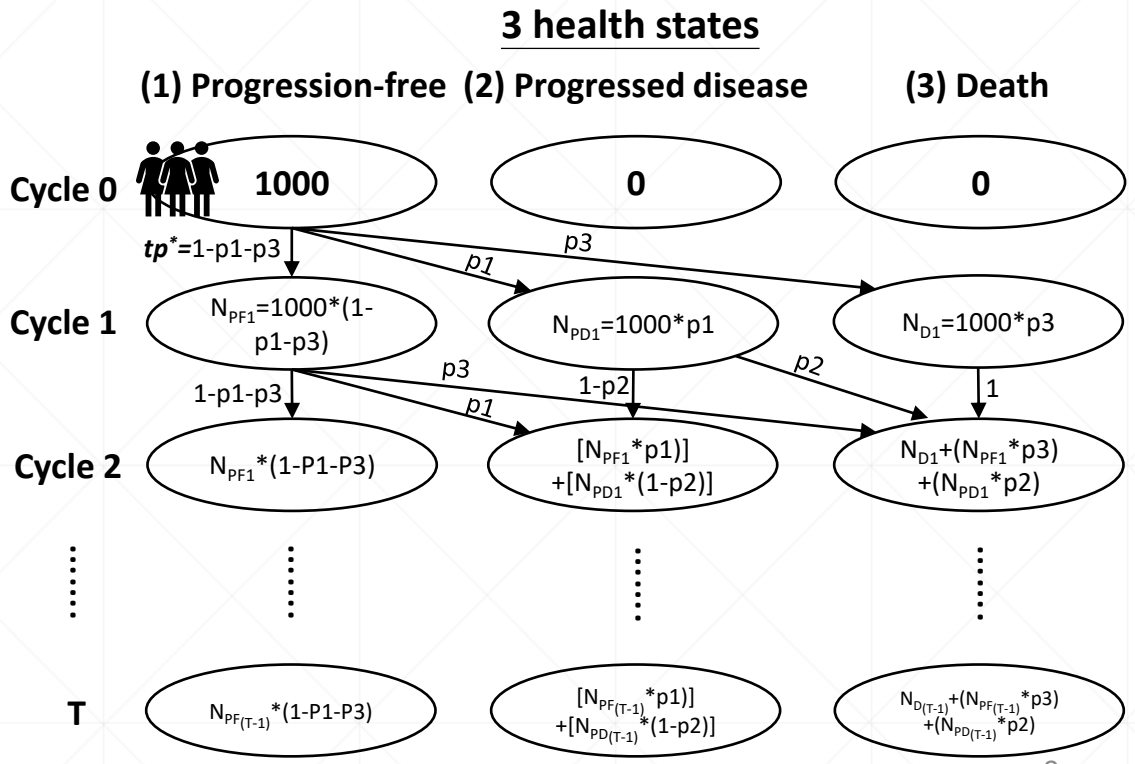
  (1) Progression-free (PF): Disease stable and keep current treatment.

  (2) Progressed disease (PD): Disease progressed and shift to supportive care.

  (3) Death (D)




p = probability




*tp* = transition probability

# 2.1. Analytic Framework of Cost-Effectiveness Analysis (4/6)

Case 1

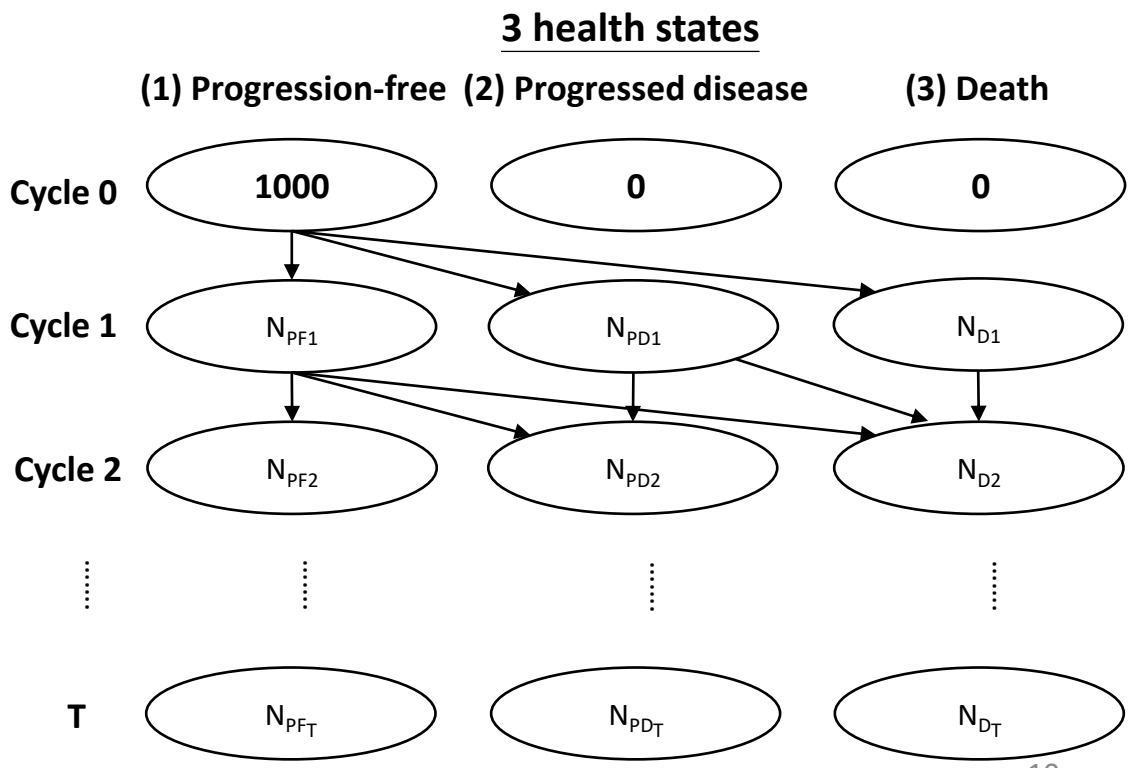
## 2. Analytical Model building

- **Decision analytical model:** Cohort-based Markov model
- **Cumulated outputs**: $E_I$, $E_C$, $C_I$, and $C_C$

$$E = \sum_{0}^{T} \frac{1}{(1+r)^t} E_t \qquad C = \sum_{0}^{T} \frac{1}{(1+r)^t} C_t$$

| Cycle | Effectiveness (E) (Unit: LYs, QALYs*) | Cost (C) (Unit: NTD) |
|---|---|---|
| 0 | $E_0 = E_{PF0}$ | $C_0 = C_{PF0}$ |
| 1 | $E_1 = E_{PF1} + E_{PD1}$ | $C_1 = C_{PF1} + C_{PD1} + C_{D1}$ |
| 2 | $E_2 = E_{PF2} + E_{PD2}$ | $C_2 = C_{PF2} + C_{PD2} + C_{D2}$ |
| ⋮ | ⋮ | ⋮ |
| T | $E_T = E_{PFT} + E_{PDT}$ | $C_T = C_{PFT} + C_{PDT} + C_{DT}$ |

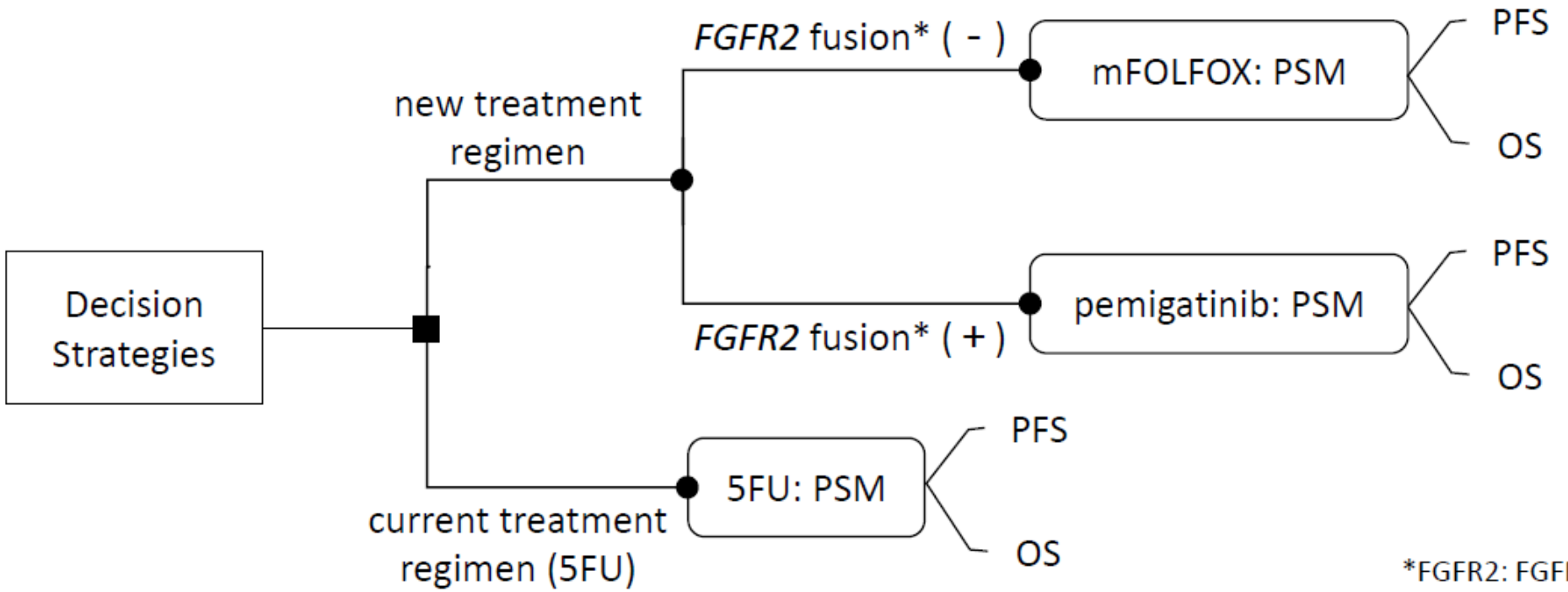
*LYs = life years, QALYs = quality-adjusted life years.



# 3-1. Study Design

Case 2

- **Target population:** advanced ICC patients who failed their 1st line treatment
- **Treatment regimens:** 2nd line treatment for advanced ICC patients
  - Intervention: new treatment regimen (mFOLFOX and pemigatinib)
  - Comparator: current treatment regimen (5FU)




*FGFR2: FGFR2 gene fusion/rearrangement

This study is approved by the Institutional Review Board of National Yang Ming Chiao Tung University (YM111012E).

# 3-2. Building the Decision Analytical Model

Case 2

- **Decision analytical model**
  - Partitioned survival analysis (PartSA) model

- **Model structure**
  - 3 Health states
    1. **Progression free (PF)**
       - Clinical performance: stable
       - Treatment: 2nd line new or current regimen
    2. **Progressed disease (PD)**
       - Clinical performance: tumor progressed
       - Treatment: supportive care
    3. **Death**
  - Cycle length: 1 month
  - Time horizon: 5 years
  - Discounting rate: 3% (CDE, 2014)

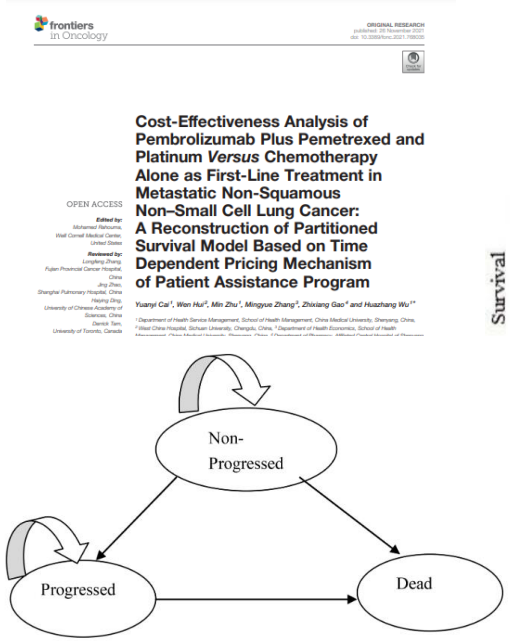
- **Perspective**
  - National Health Insurance Administration, Taiwan

- **Outcomes**
  - Life years, quality-adjusted life years (QALYs), direct medical costs, cost-effectiveness results

- **Parameters**
  - Proportion of ICC patients with FGFR2 gene fusion
    - Taiwan: 7.7% (Chiang et al., 2021)
  - Willingness-to-pay (WTP, λ) = 3 times GDP per capita
  - Clinical efficacy
  - Utility
  - Direct medical costs

Case 2

# Partitioned Survival Model

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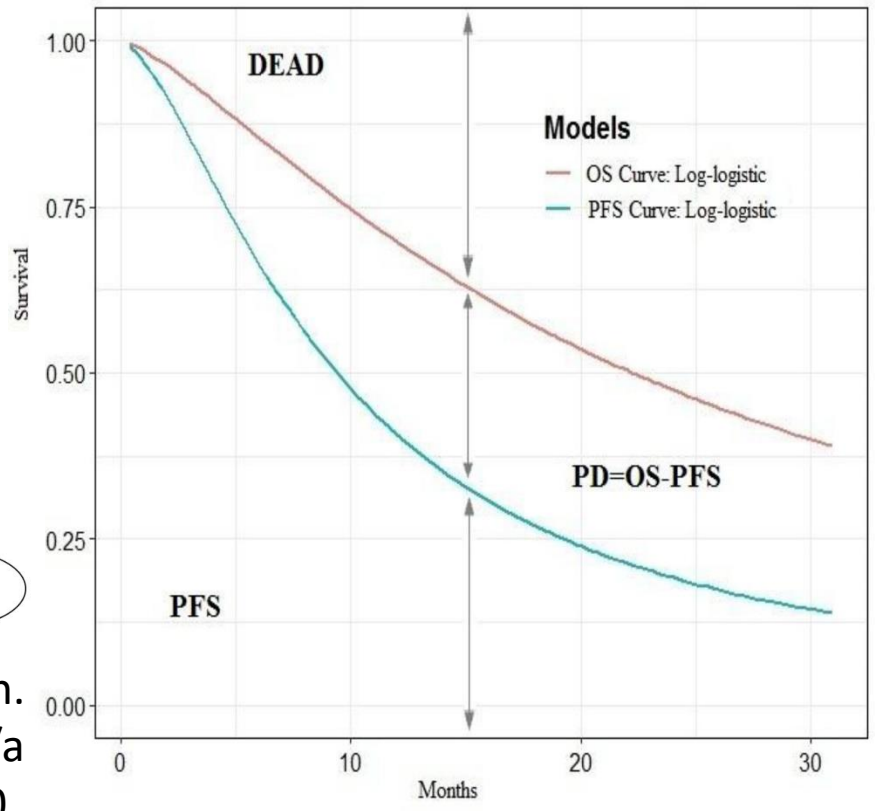
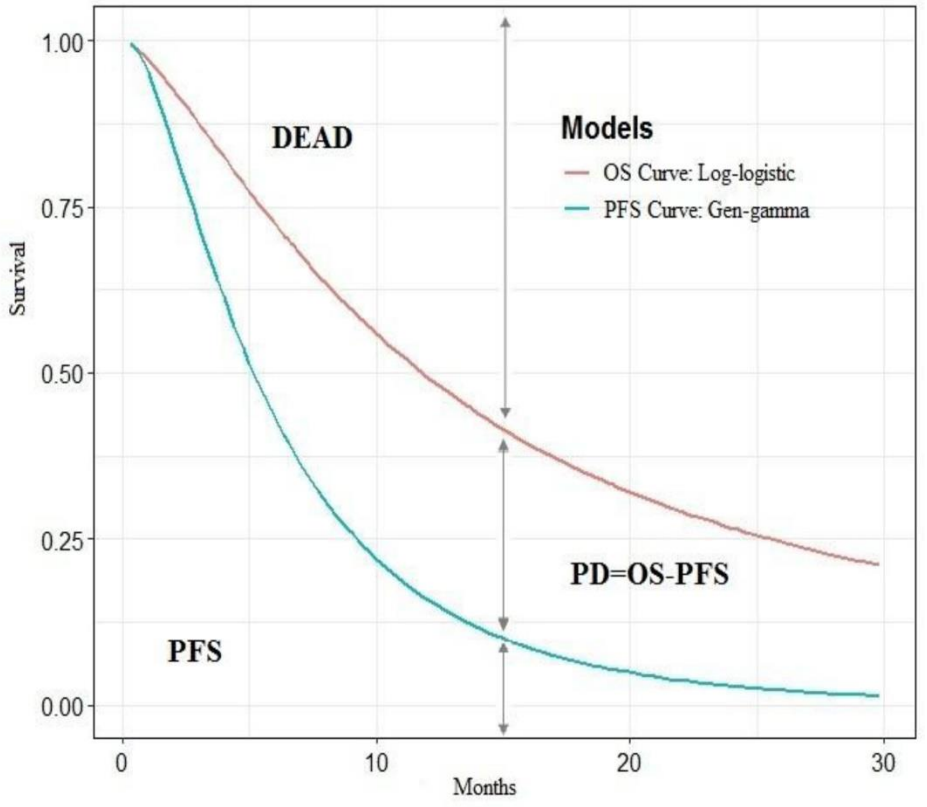
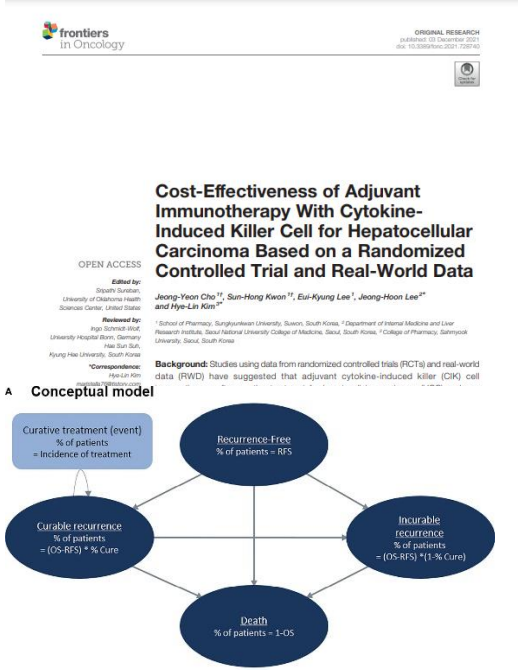



Intervention group




Comparator group

# Partitioned Survival Model


frontiers in Oncology

ORIGINAL RESEARCH

**Cost-Effectiveness of Adjuvant Immunotherapy With Cytokine-Induced Killer Cell for Hepatocellular Carcinoma Based on a Randomized Controlled Trial and Real-World Data**

OPEN ACCESS

Jeong-Yeon Cho[†], Sun-Hong Kwon[†], Eui-Kyung Lee, Jeong-Hoon Lee* and Hye-Lin Kim*

**Background:** Studies using data from randomized controlled trials (RCTs) and real-world data (RWD) have suggested that adjuvant cytokine-induced killer (CIK) cell

A **Conceptual model**

Curative treatment (event)
% of patients
= Incidence of treatment

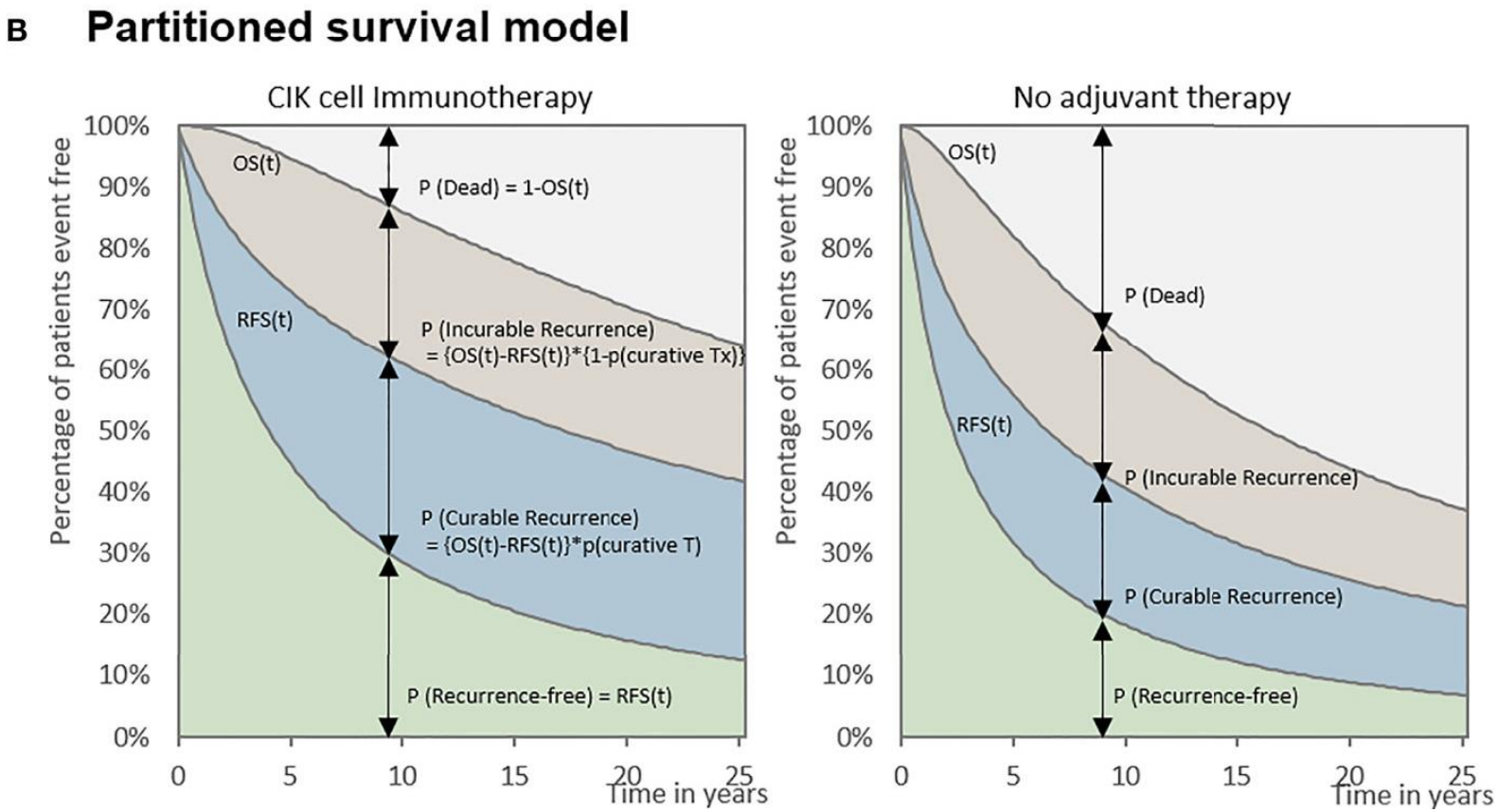
Recurrence-Free
% of patients = RFS

Curable recurrence
% of patients
= (OS-RFS) * % Cure

Incurable recurrence
% of patients
= (OS-RFS) *(1-% Cure)

Death
% of patients = 1-OS

https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2021.728740/full



# 3-4. Cost-effectiveness Analysis: Base-Case Analysis

Case 2

- **Incremental cost effectiveness ratio (ICER)**

  The cost per unit of the health outcome/effect.

Function: $$\mathrm{ICER} = \frac{C_2 - C_1}{E_2 - E_1} = \frac{\Delta C}{\Delta E}$$

- **Net monetary benefit (NMB)**

Function: $$\mathrm{NMB} = \lambda \times \Delta E - \Delta C$$

$C_1$ : the cost under the comparator.
$C_2$ : the cost under the intervention of interest.
$E_1$ : the effectiveness under the comparator.
$E_2$ : the effectiveness under the intervention of interest.
$\lambda$ : threshold, willingness to pay (WTP)

✓ **Decision criteria**

- ICER < $\lambda$
- NMB > 0

$\lambda$ = 3 times of GDP per capita in Taiwan (2021)

(Edlin et al., 2015; Gray et al., 2010)

# 4-2. Base Case Analysis

Case 2

## Base-case: Cost-effectiveness outcomes in 5 years

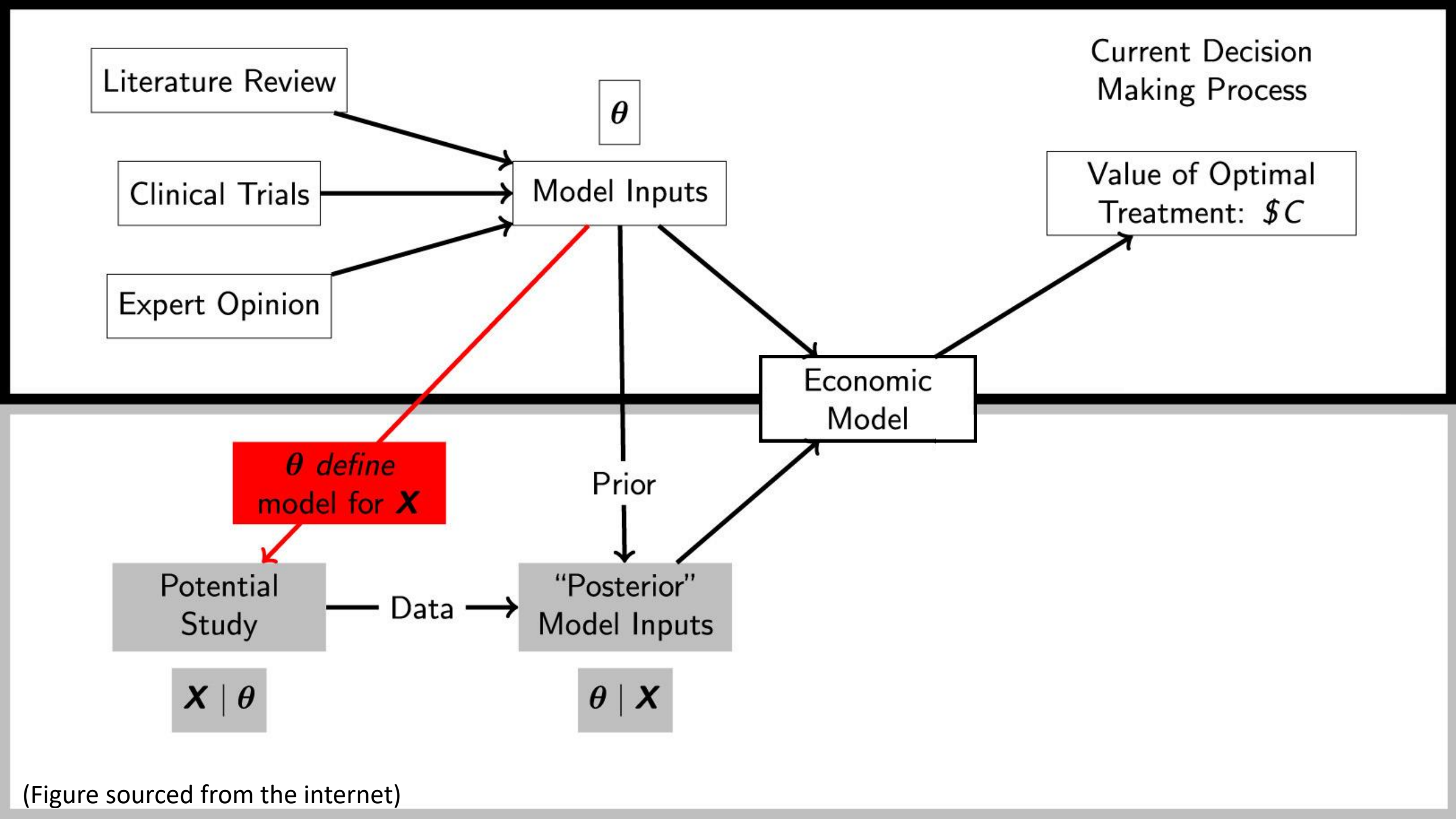
| | Current regimen (5FU) | New regimen (mFOLFOX/pemigatinib) | Incremental change |
|---|---|---|---|
| Cost | 524,472 | 984,168 | 459,697 |
| Total cost of PF state | 369,229 | 795,614 | |
| • Genetic test cost | 0 | 30,000 | |
| • Medication costs (PF) | 63,430 | 387,176 | |
| • Non-medication cost (PF) | 305,799 | 378,437 | |
| Total cost of PD state | 155,243 | 188,555 | |
| Life years | | | |
| Progression-free | 0.36 | 0.48 | 0.12 |
| Overall | 0.67 | 0.86 | 0.19 |
| Quality-adjusted life years | | | |
| Progression-free | 0.26 | 0.35 | 0.09 |
| Overall | 0.47 | 0.61 | 0.13 |
| Incremental cost per QALY (ICER) | | WTP (λ) = 3 times GDP (NT$2,889,684) | 3,411,098 |
| NMB | | | -70,269 |

LYs: life years, QALYs: quality-adjusted life years, ICER: incremental cost-effectiveness ratio, NMB: net monetary benefit

**Findings:**

- ICER (NT$ 3,411,098) > WTP (NT$2,889,684)
- NMB (NT$ -70,269) < 0

**NOT cost-effectiveness in base-case analysis!**




(Figure sourced from the internet)

# Q1: When we make decisions based on point estimates in cost-effectiveness analysis, what potential issues or concerns are there?

- ***Why*** and ***what*** do we (have to) be worried or concerned about the "evidence-based" decision?

  ☐ ***Why?***

  ☐ ***What?***

  Not sure about the evidence (point estimates of CEA and NMB/NHB):

# What is uncertain about cost-effectiveness analysis?

The repercussions of a wrong decision, founded on inadequate evidence.

- Decisions should not be based on little or poor quality evidence
- Always a chance that the wrong adoption decision is made, resulting in health benefit and resources forgone

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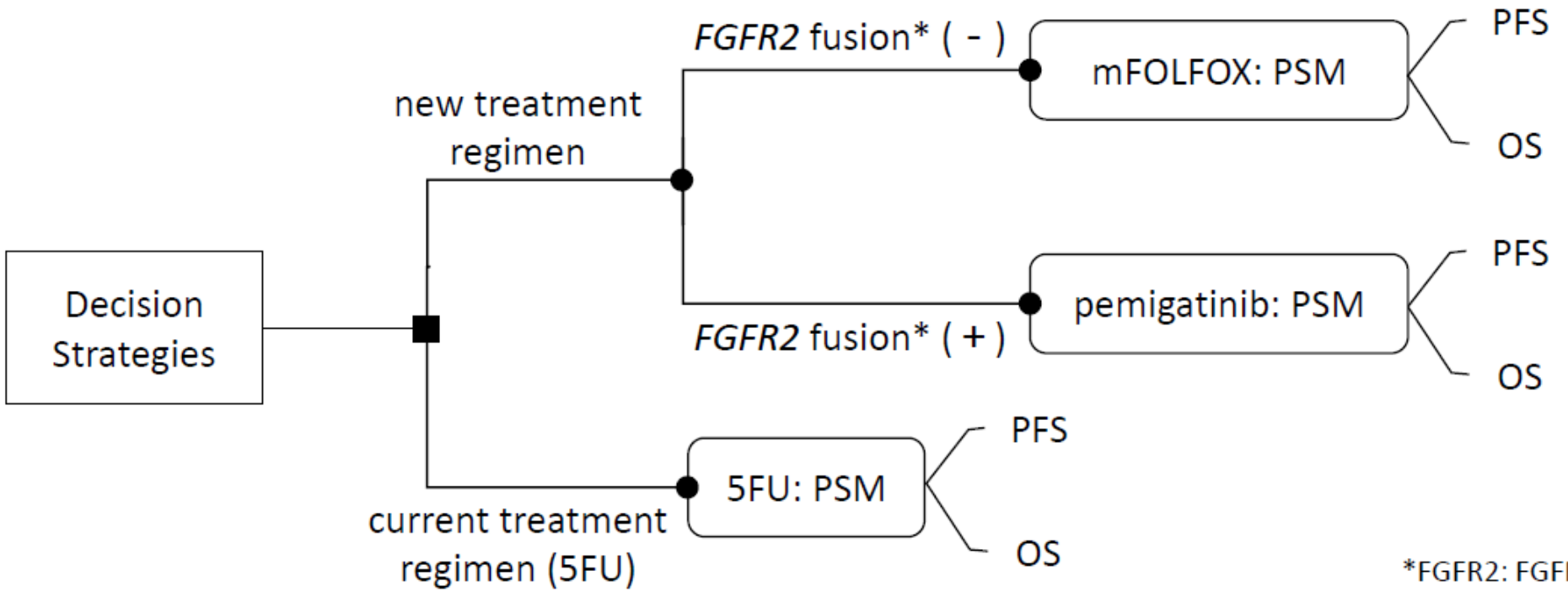


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# 3-2. Building the Decision Analytical Model

Case 2

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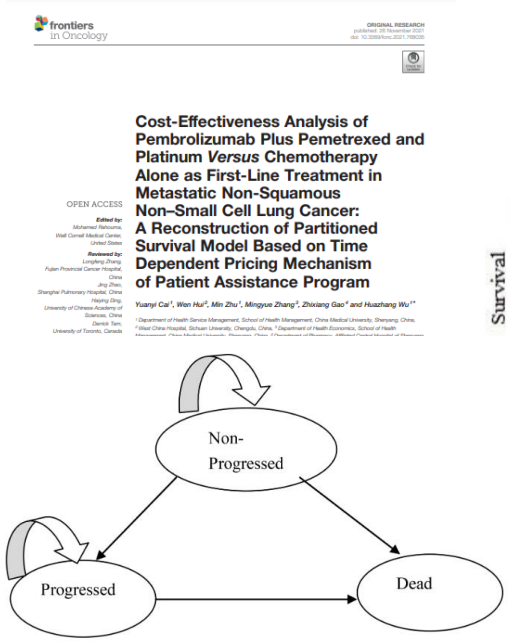
Case 2

# Partitioned Survival Model

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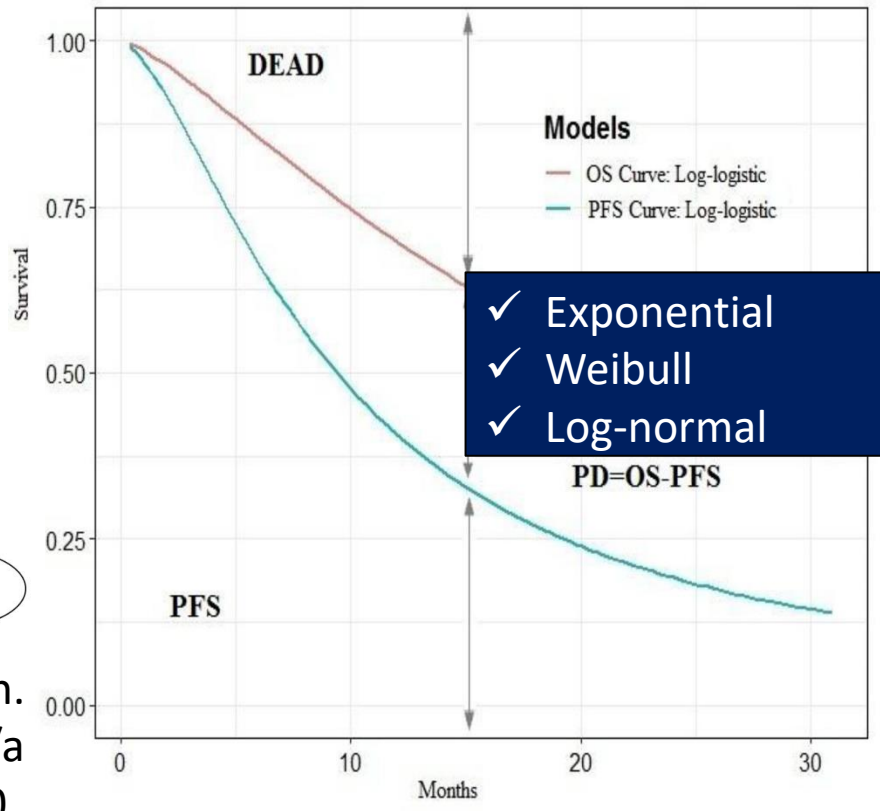
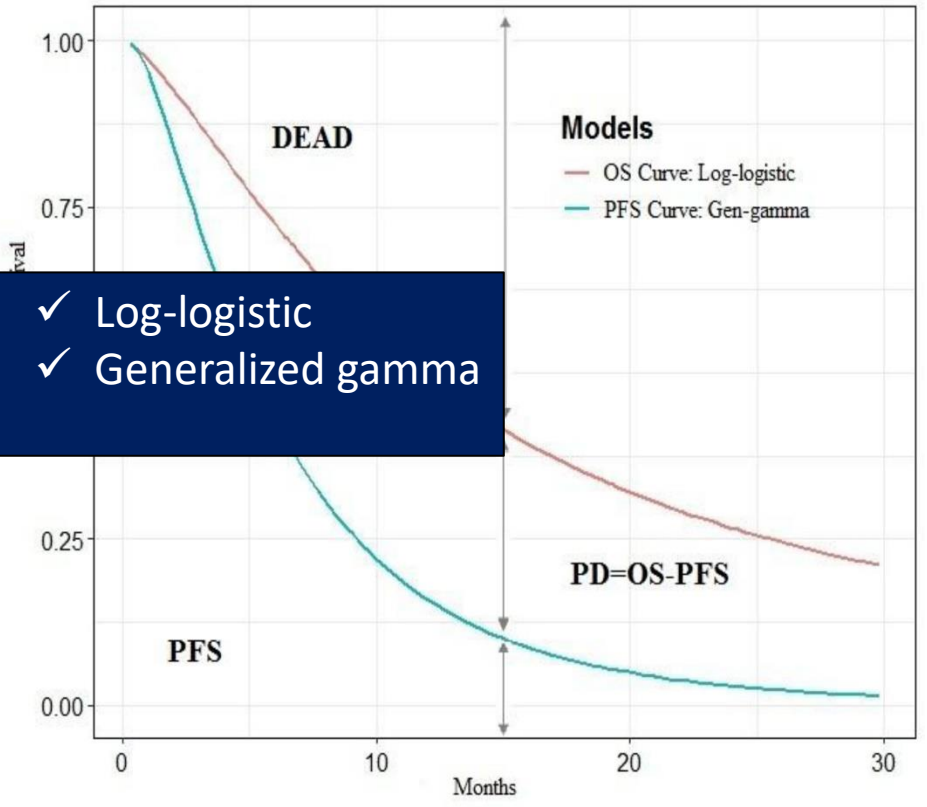


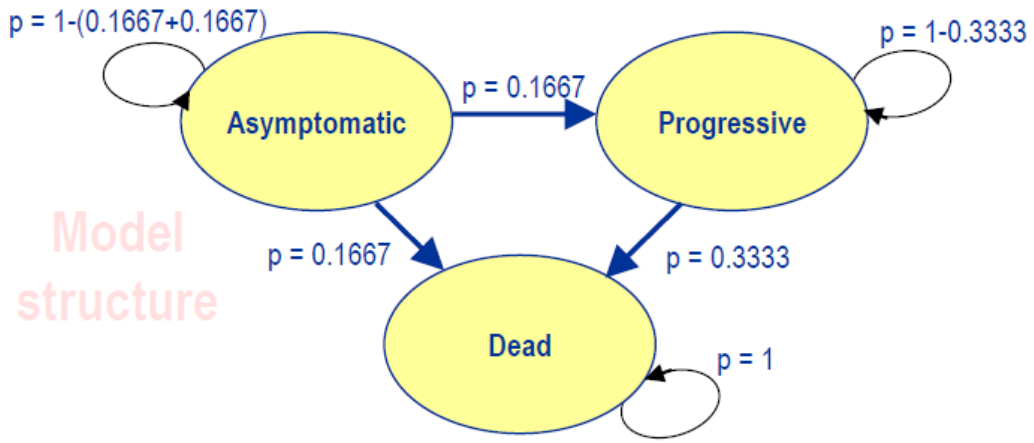

Intervention group

- ✓ Exponential
- ✓ Weibull
- ✓ Log-normal
- ✓ Log-logistic
- ✓ Generalized gamma




Comparator group

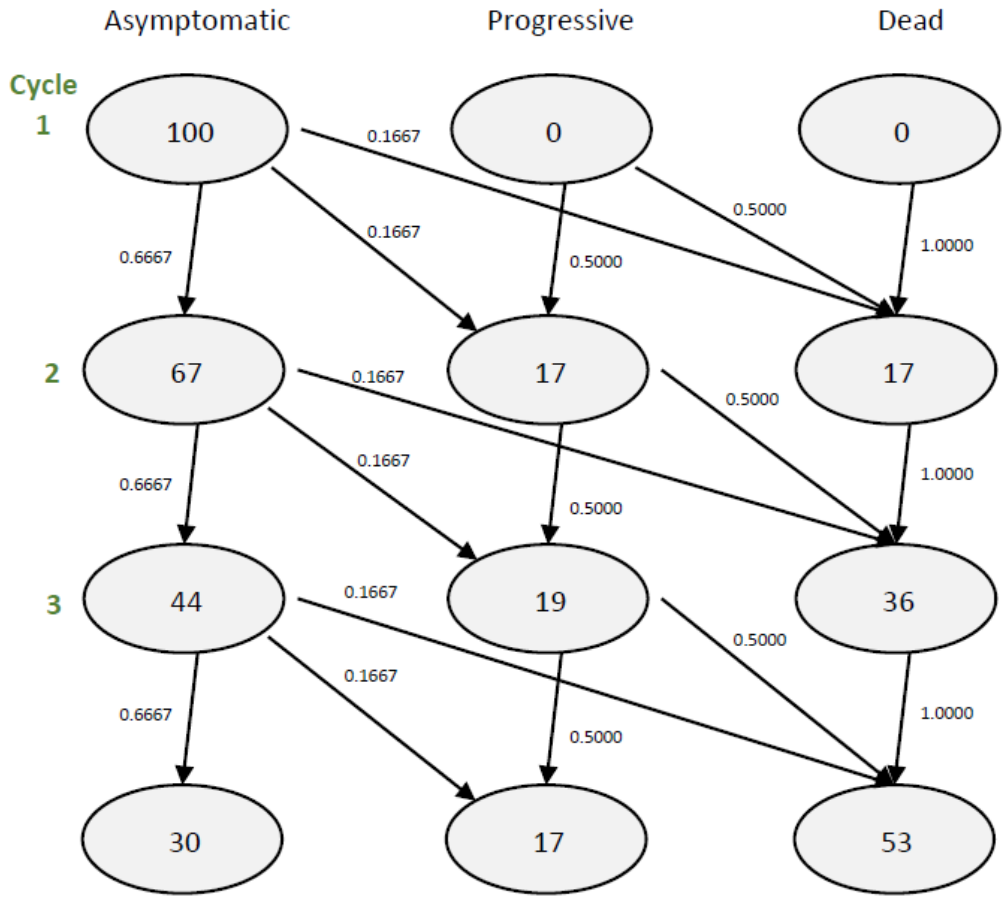
# Outline of a simple Markov model




Model structure

| Current treatment | Asymptomatic | Progressive | Dead | Cost | QALY |
|---|---|---|---|---|---|
| Asymptomatic | 0.6667 | 0.1667 | 0.1667 | £150 | 0.9 |
| Progressive | | 0.5000 | 0.5000 | £325 | 0.78 |
| Dead | | | 1.0000 | | |

Parameter values



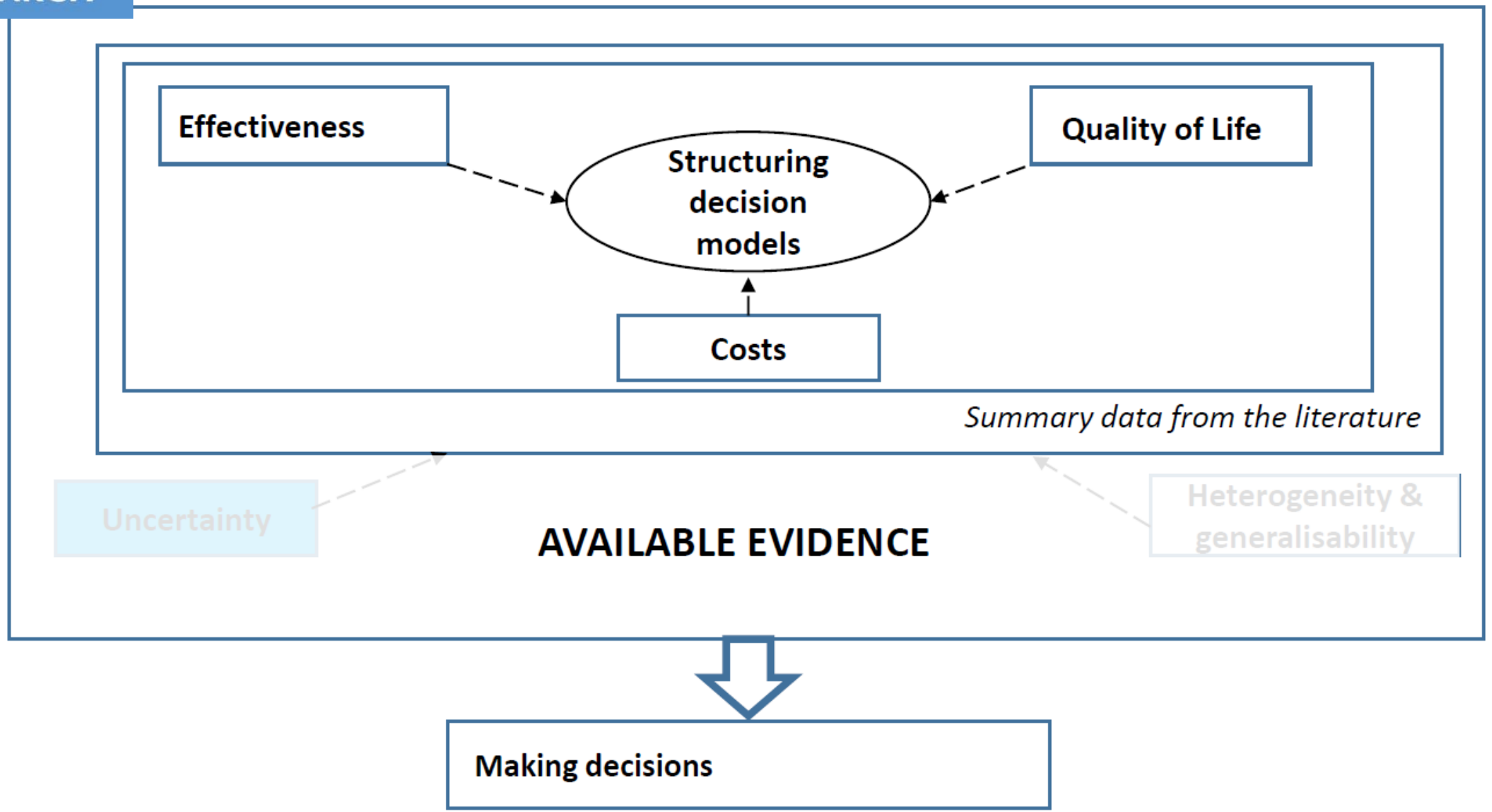

Cohort simulation

# What is uncertain about cost-effectiveness analysis?

The repercussions of a wrong decision, founded on inadequate evidence.

- Decisions should not be based on little or poor quality evidence
- Always a chance that the wrong adoption decision is made, resulting in health benefit and resources forgone
- Different possible values for the parameters
  - Lack of knowledge about the parameter values
  - Different outcomes in different populations
- Structural uncertainty
  - Choice of health states, choice of modelling approach
- Distinguish between
  - Uncertainty, variability, heterogeneity and policy choices

# Course structure – where are we up to?



# Q2. What are bias, variability, heterogeneity, uncertainty?

- (Briggs: **Box 2.1.; page 80-82)**

# Box 2.1. Key concept in understanding uncertainty and heterogeneity in decision models for cost-effectiveness analysis

# First and second order uncertainty

## 1st order

- Distribution of outcomes in population

≈ Sample variance

- Standard deviation in a mean value
  - Range of outcomes in sample

- Incorporate in CEA by simulating and recording pathway of individual patients through a model
- Large number of patients required to estimate mean and standard deviation
- Must repeatedly sample large numbers of patients to estimate uncertainty in mean and standard error

## 2nd order

- Distribution of sample mean outcome

≈ Variance of sample mean

- Standard error of mean
  - Range of population mean values supported by the sample outcomes

- Incorporate in CEA by simulating and recording pathway of cohort through a model
- One cohort provides estimate of mean but no information on standard deviation
- Large number of cohorts entered into models to estimate uncertainty in mean and standard error

# 1st order uncertainty – screen share example

- Simulate individual patients progress through model
- Random numbers to determine occurrence of chance events
- Markov trace generated for multiple individuals to get mean costs and QALYs

| TRANSITION MATRIX *From* | *To* Asymptomatic | Progressive | Dead |
|---|---|---|---|
| Asymptomatic | 0.6667 | 0.1667 | 0.1667 |
| Progressive | | 0.6666 | 0.3333 |
| Dead | | | 1.0000 |

| | Asymptomatic | Progressive | Dead |
|---|---|---|---|
| Asymptomatic | 1, 2, 3, 4 | 5 | 6 |
| Progressive | | 1, 2, 3, 4 | 5, 6 |
| Dead | | | 1, 2, 3, 4, 5, 6 |

# Uncertain decisions

- 1st order uncertainty and variation within groups of patients not the focus of CEA
  - Decision must be made for group as a whole
  - Variability cannot be reduced
  - Computationally time consuming when combined with 2nd order uncertainty
- 2nd order uncertainty is the focus of CEA
  - Informs questions about likelihood of making wrong decision, and likelihood of new information changing the optimal decision
- Structural uncertainty
  - Lack of knowledge about most appropriate model structure
  - Different modelling approaches provide different estimates of mean costs and QALYs
    - Contributes to uncertainty in mean outcomes

# Heterogeneity – multiple decisions

- 'Baseline' characteristics 'explain' a proportion of overall variability between patients (e.g. age, sex)
- Can condition decision on these characteristics, and recommend different options in different groups
- To incorporate in CEA, generate mean parameter values per sub-group population
  - Variability within sub-group will remain
  - Need to present results by sub-group (defined by patient characteristics)

# Policy choices and value judgements

- The authority taking the decision may set some parameter values
  - For example, the discount rate applied to costs and health outcomes
- The values are relevant for particular decision
  - E.g. NICE specifies 3.5% for costs and health outcomes
  - Sensitivity analysis of 1.5% per annum
- Different decision makers may have different values
  - Heterogeneity in value of parameter between decision makers
  - Choice taken by an individual decision maker is not uncertain

'5.1.2 There is considerable debate about the most **appropriate methods** to use for some aspects of health technology assessment. This **uncertainty relates to choices that are essentially value judgements**; for example, whose preferences to use for valuation of health outcomes.... The reference case specifies the methods considered by the Institute to be the most appropriate for the Appraisal Committee's purpose and consistent with an NHS objective of maximising health gain from limited resources.'

*NICE Guide to the methods of technology appraisal 2013*

# An analogy with regression(Briggs, page 83)

$$\mathrm{Y} = \alpha \ + \sum_{j=1}^{p} \beta_j X_j + \varepsilon$$

# Q3: what should we focus on in CEA analysis?

- Parameter uncertainty
- Heterogeneity
- Structural
- Variability
- Policy choice

# Types of uncertainty - Summary

| Need to address | Not main focus of CEA |
| --- | --- |
| | |
| | |
| | |

# Q4: how to handle heterogeneity?

| **Data** | **Probabilities from binomial data** | **Probabilities from time-to-event data** | **Continuous variable like cost and utility** |
|---|---|---|---|
| Model | | | |
| E[Y] | | | |
| Var(Y) | | | |
| Distribution | | | |
| Notes | | | |