American Conference on Pharmacometrics (ACoP11), the Annual Scientific Meeting of the International Society of Pharmacometrics (ISoP)
November 9-13, 2020

Markov Models at the Intersection of Pharmacometrics and Health Economics

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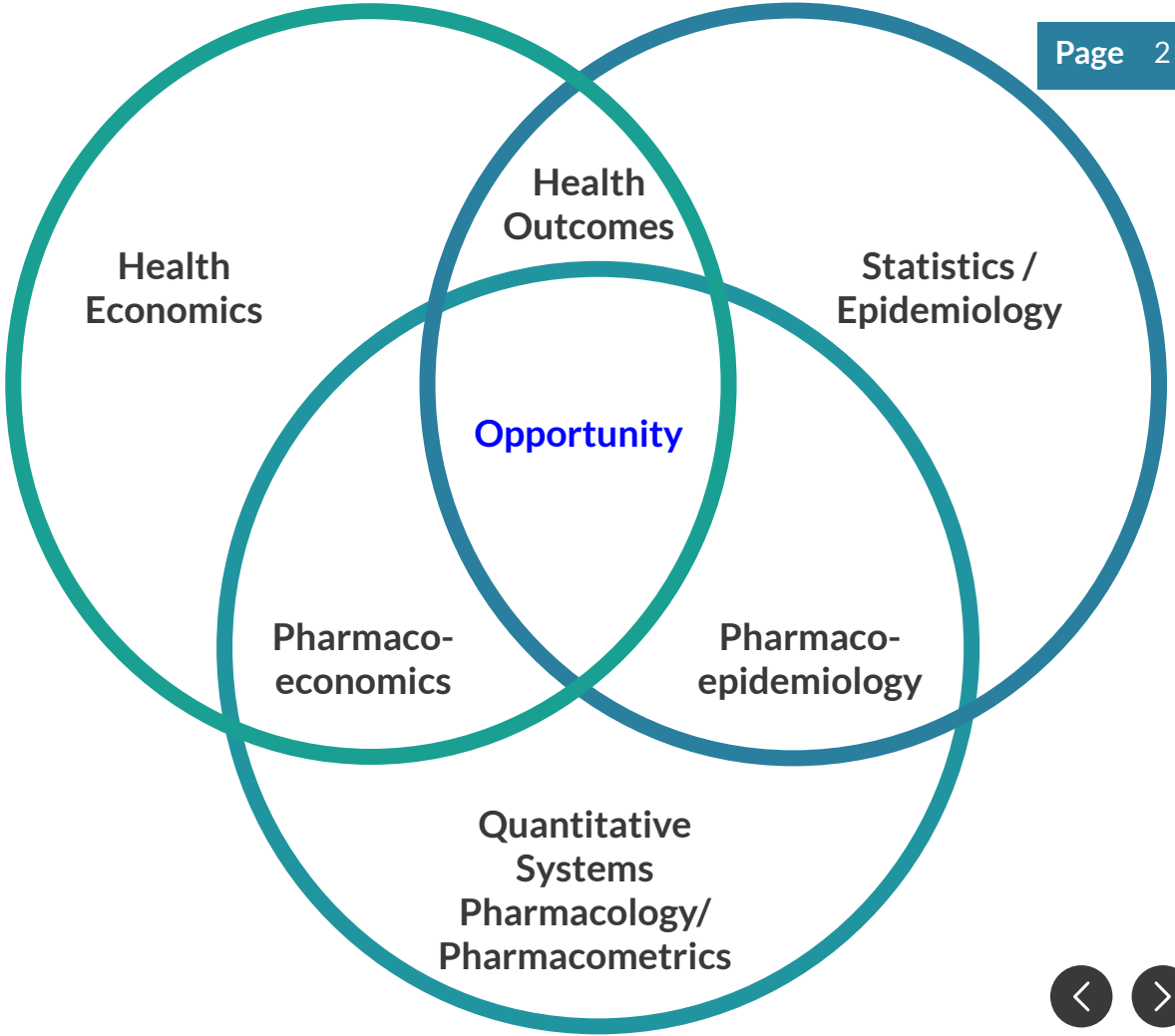
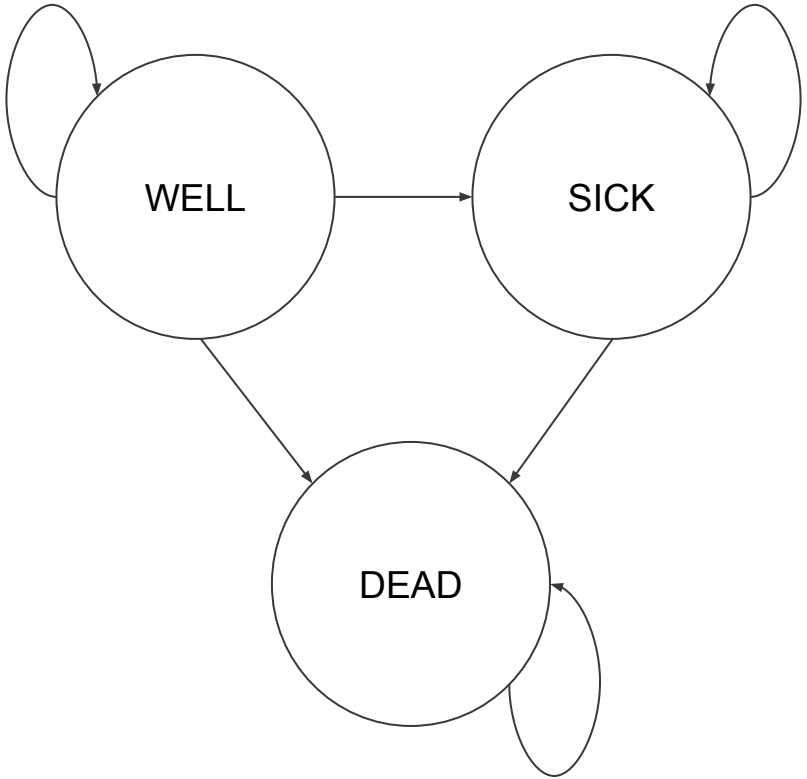
Chief Executive Officer
Metrum Research Group

Opportunity
at the Intersection

- Better Inform Drug Development Decisions
- Better Inform Economic and Outcome Decisions



Markov Models (MM) in Health Economics Analyses



QALY[a]: measure of benefit, dependent on **number of individuals** and/or **duration** in any state

ICER[b]: cost per QALY

Static Markov Models in HE Analyses: Approach based on discrete-time and proportion of individuals

Proportion of individuals in the population move across the states according to a set of transition probabilities only once per time interval (*sometimes lengthy* "Markov cycle")

Time-dependent covariates possible

[a] *Quality-Adjusted Life Years,* [b] *Incremental Cost-Effectiveness Ratio*

Denosumab Pharmacoeconomic Analysis

JOURNAL OF MEDICAL ECONOMICS, 2018
VOL. 21, NO. 5, 525–536
https://doi.org/10.1080/13696998.2018.1445634
Article 0212-FT.R1/1445634

Taylor & Francis
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ORIGINAL RESEARCH

A cost-effectiveness analysis of denosumab for the prevention of skeletal-related events in patients with multiple myeloma in the United States of America

Noopur Raje[a], Garson David Roodman[b], Wolfgang Willenbacher[c], Kazuyuki Shimizu[d], Ramón García-Sanz[e], Evangelos Terpos[f], Lisa Kennedy[g], Lorenzo Sabatelli[h], Michele Intorcia[h] and Guy Hechmati[i]

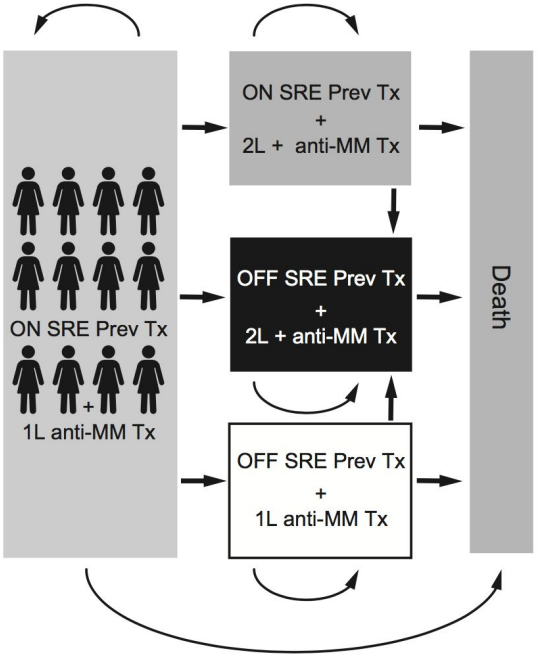


Figure 1. Depiction of model health states. 1L, first line; 2L+, second line or later; Abbreviations. MM, multiple myeloma; OFF SRE Prev Tx, patients not receiving treatment to prevent SREs; ON SRE Prev Tx, patients receiving treatment to prevent SREs; SRE, skeletal-related event; Tx, treatment.

Static Markov Model

Deterministic Sensitivity Analysis

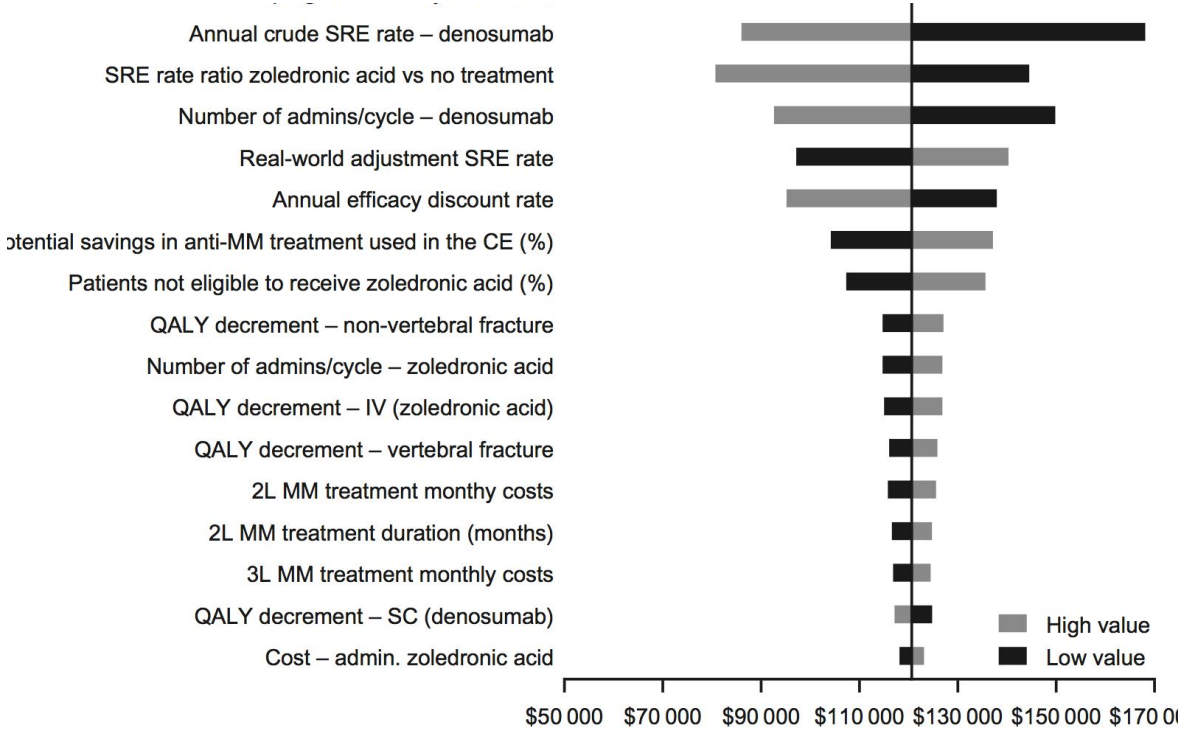


Figure 4. One-way deterministic sensitivity analyses of key variables from (a) the societal perspective and (b) the payer perspective. Ranges for para were as follows: annual efficacy discount rate = 0.00–0.05; percentage of patients not eligible to receive zoledronic acid = 0.05–0.15; annual crude denosumab = 0.55–0.64; annual crude SRE rate of zoledronic acid = 0.58–0.67; real world adjustment SRE rate = 2.01–4.01; SRE rate ratio for zoledron treatment = 0.42–0.82; zoledronic acid cost of administration = 189–231; denosumab number of cycles = 0.79–0.97; zoledronic acid number of cycles post-progression utility decrement = 0.57–0.72; QALY decrement SC = 0.0009–0.0014; QALY decrement IV = 0.0017–0.0025; QALY decrement verte =0.05–0.15; QALY decrement non-vertebral fracture = 0.05–0.15; MM second-line treatment duration = 7.66–9.36; percentage of potential savings in a ment used in the cost-effectiveness analysis = 0.40–0.60; second-line MM treatment monthly costs = 16,430–20,081; third-line MM treatment m s = 16,530–20,204. Abbreviations. 2L, second line; 3L, third line; CE, cost-effectiveness analysis; IV, intravenous; MM, multiple myeloma; RR, ri subcutaneous injection; SRE, skeletal-related event; QALY, quality-adjusted life-year.

Dynamic Markov Models: Infectious Disease

Haeussler *et al. BMC Medical Research Methodology* (2018) 18:82
https://doi.org/10.1186/s12874-018-0541-7

BMC Medical Research Methodology

https://doi.org/10.1186/s12874-018-0541-7

RESEARCH ARTICLE Open Access

A dynamic Bayesian Markov model for health economic evaluations of interventions in infectious disease

Katrin Haeussler[1,2*], Ardo van den Hout[1] and Gianluca Baio[1]

Infectious Disease Health States

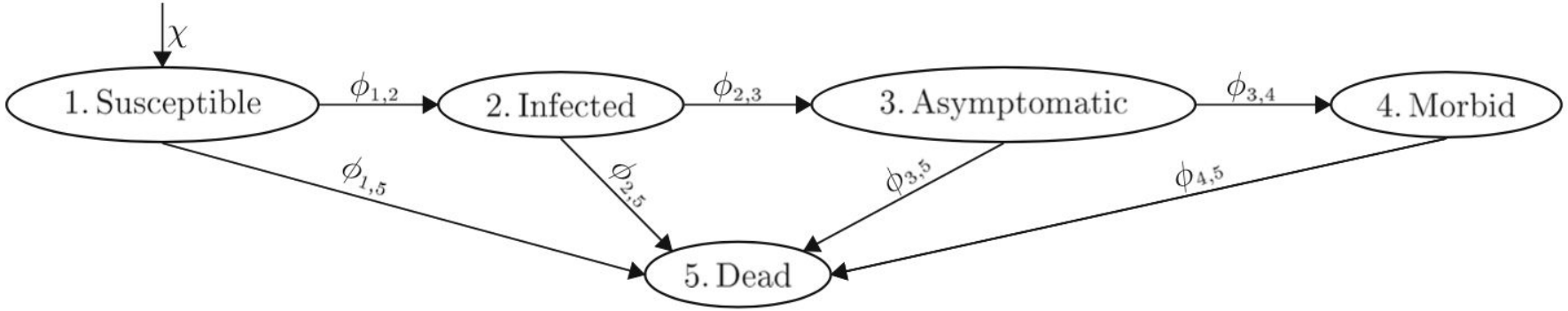
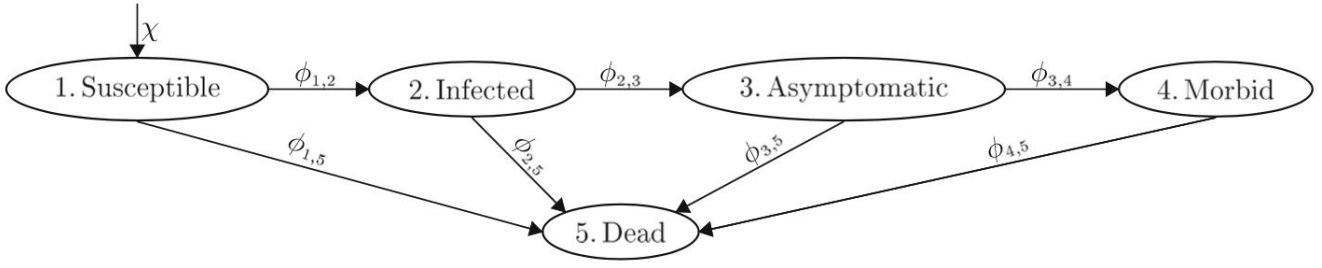


Fig. 1 Model structure of a hypothetical chronic sexually transmitted infection. The arrows represent the possible transitions. These are governed by the parameters $\phi_{r,s}$ with indices $r, s \in \mathcal{S}$ representing origin and target states, respectively. The replenishment of the pool of susceptibles by newborns proceeds at a rate χ

Infectious Disease Health States: Static MM



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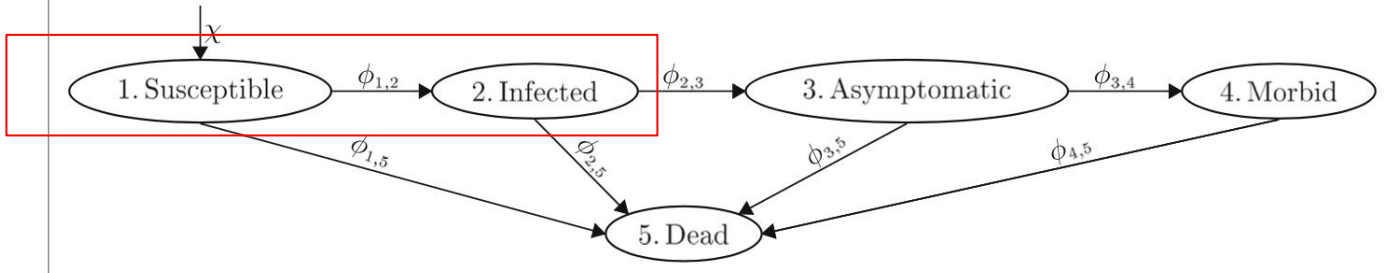
$$\mathbf{\Pi} = \begin{pmatrix} \pi_{1,1} & \pi_{1,2} & 0 & 0 & \pi_{1,5} \\ 0 & \pi_{2,2} & \pi_{2,3} & 0 & \pi_{2,5} \\ 0 & 0 & \pi_{3,3} & \pi_{3,4} & \pi_{3,5} \\ 0 & 0 & 0 & \pi_{4,4} & \pi_{4,5} \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

Infectious Disease Health States: Dynamic MM



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$$
\begin{aligned}
\frac{dn_1(t)}{dt} &= \chi\,[n_1(t) + n_2(t) + n_3(t) + n_4(t)] - \rho_{1,2}(t)n_1(t) \\
&\quad - \rho_{1,5}n_1(t) \\
\frac{dn_2(t)}{dt} &= \rho_{1,2}(t)n_1(t) - \rho_{2,3}n_2(t) - \rho_{2,5}n_2(t) \\
\frac{dn_3(t)}{dt} &= \rho_{2,3}n_2(t) - \rho_{3,4}n_3(t) - \rho_{3,5}n_3(t) \qquad (1) \\
\frac{dn_4(t)}{dt} &= \rho_{3,4}n_3(t) - \rho_{4,5}n_4(t) \\
\frac{dn_5(t)}{dt} &= \rho_{1,5}n_1(t) + \rho_{2,5}n_2(t) + \rho_{3,5}n_3(t) + \rho_{4,5}n_4(t).
\end{aligned}
$$

Bayesian Posterior Predictive Distribution

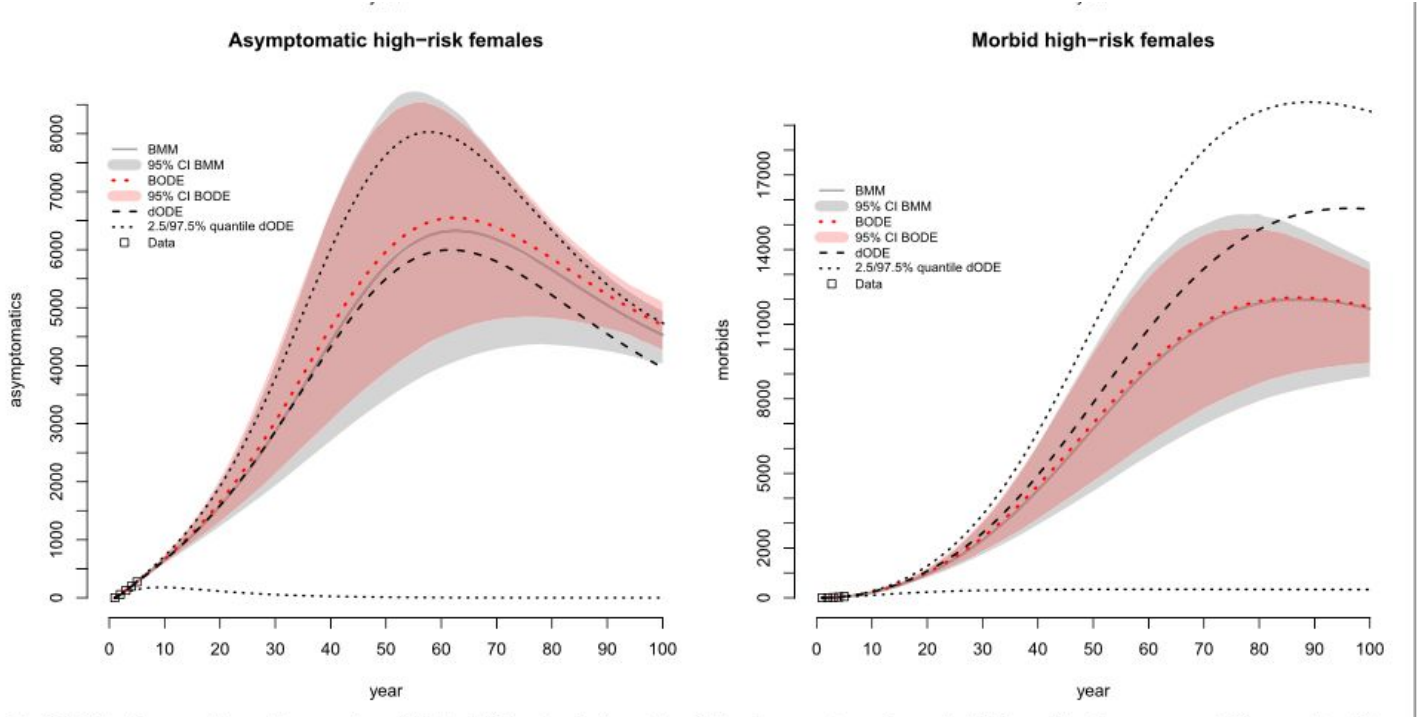
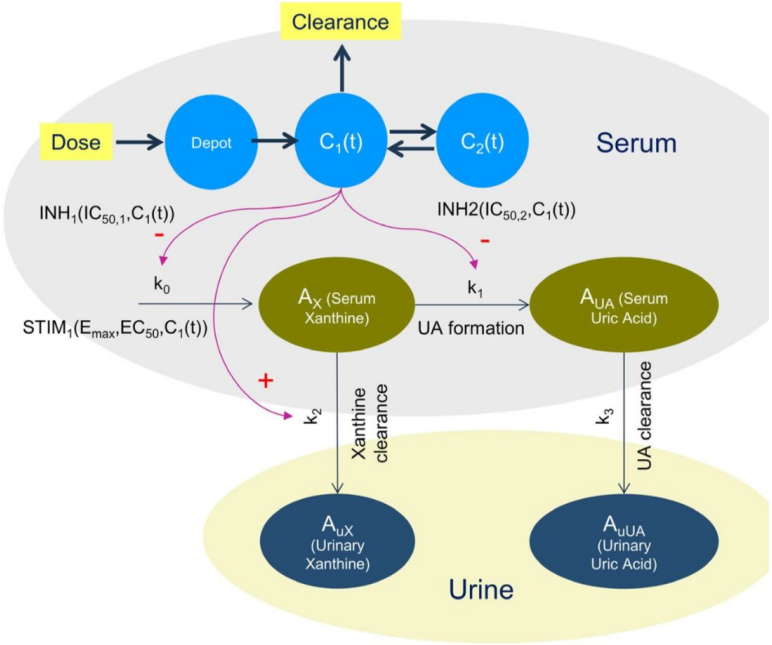
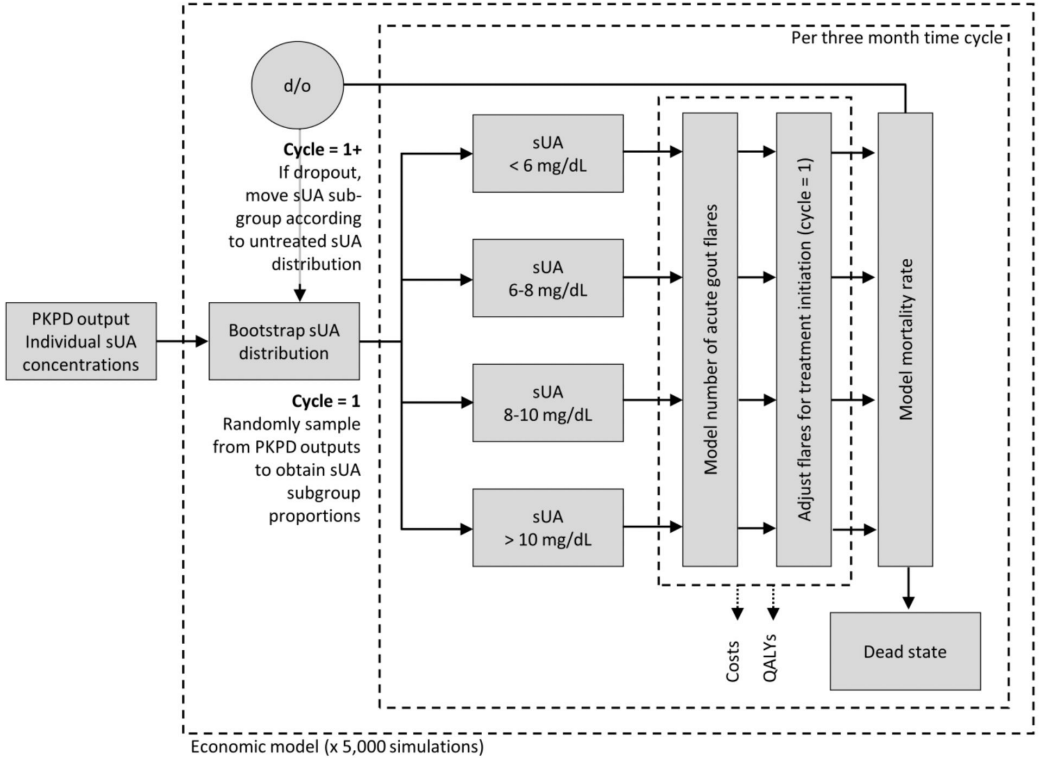


Fig. 2 Calibration results on the number of high-risk females in the states following a systematic probabilistic calibration approach. The results of the Bayesian models are similar, with a slightly higher number of high-risk females in the states *Infected* and *Asymptomatic* estimated by the Bayesian ODE-based model. In contrast, the deterministic ODE-based model results in a lower estimate on the number of high-risk females in the states *Infected* and *Asymptomatic*; however, the outcome on the state *Morbid* is reversed

Linking PMX and PE: Xanthine Oxidase Inh. & Gout

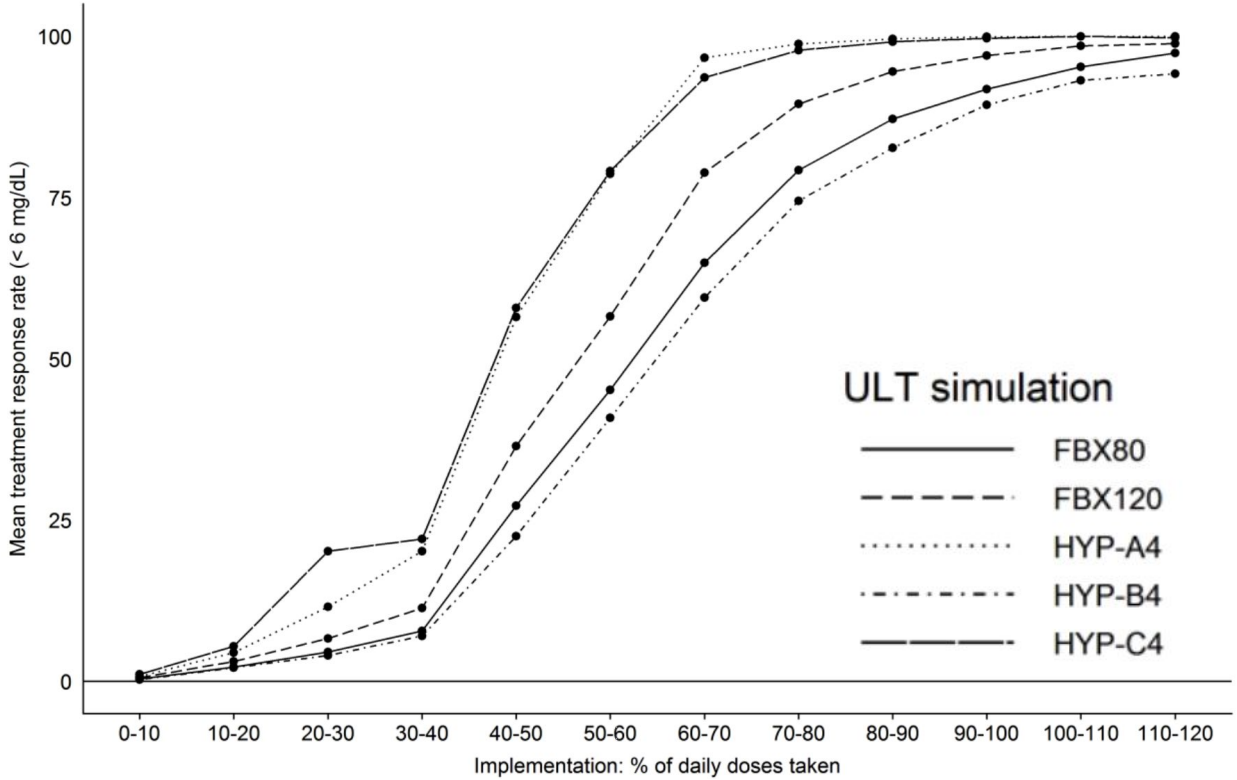
Individual-Level PKPD Modeling and Simulation





Integration of Pharmacometrics and Pharmacoeconomics to Quantify the Value of Improved Forgiveness to Nonadherence: A Case Study of Novel Xanthine Oxidase Inhibitors for Gout. Daniel Hill-McManus;Scott Marshall;Elena Soto;Dyfrig A Hughes ISSN: 0009-9236 , 1532-6535; DOI: 10.1002/cpt.1454. Clinical pharmacology & therapeutics : CPT. , 2019, Vol.106(3), p.652-660

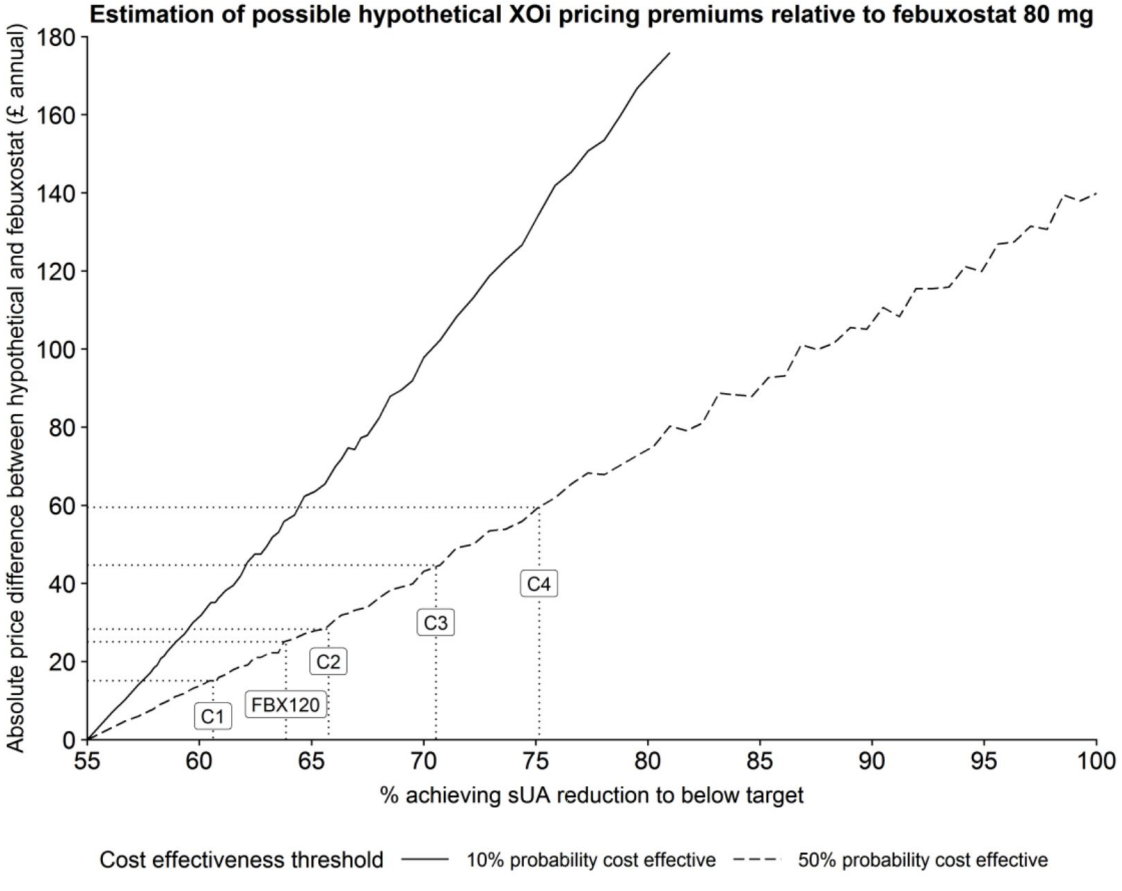
Simulation: Response vs. Adherence



- Simulation-based comparison of febuxostat and hypothetical analogues
- Varied clearance, potency, for analogues
- Informed by adherence RWE

Integration of Pharmacometrics and Pharmacoeconomics to Quantify the Value of Improved Forgiveness to Nonadherence: A Case Study of Novel Xanthine Oxidase Inhibitors for Gout. Daniel Hill-McManus;Scott Marshall;Elena Soto;Dyfrig A Hughes ISSN: 0009-9236 , 1532-6535; DOI: 10.1002/cpt.1454. Clinical pharmacology & therapeutics : CPT. , 2019, Vol.106(3), p.652-660

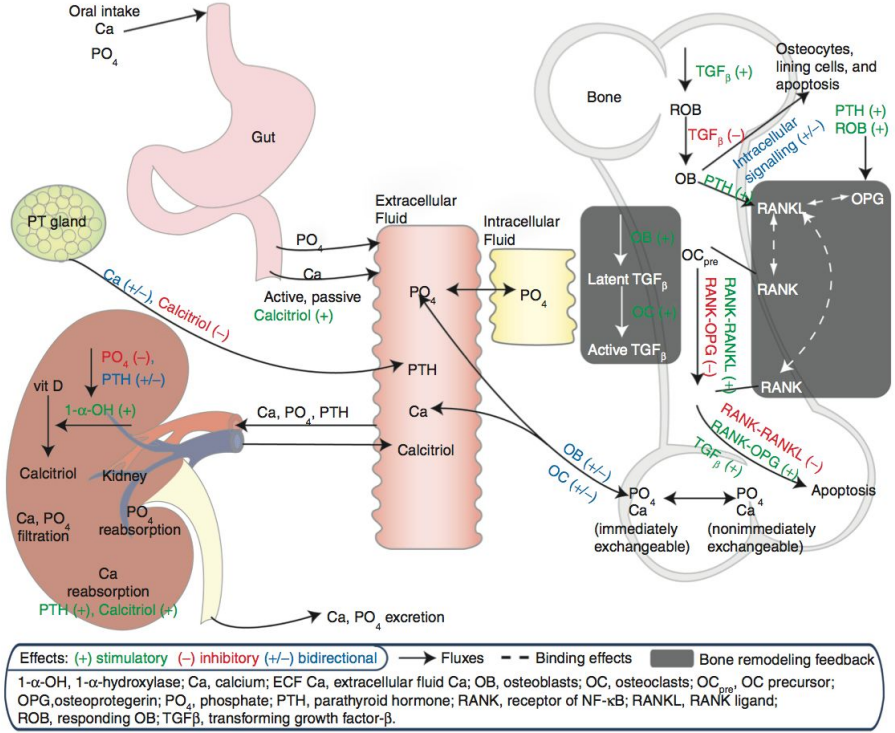
Simulation: Pricing vs Response



Curve of estimated pricing to achieve cost effectiveness versus febuxostat 80 mg with probability of 50% and 10% at a willingness to pay threshold of £20,000 per QALY

Integration of Pharmacometrics and Pharmacoeconomics to Quantify the Value of Improved Forgiveness to Nonadherence: A Case Study of Novel Xanthine Oxidase Inhibitors for Gout. Daniel Hill-McManus;Scott Marshall;Elena Soto;Dyfrig A Hughes ISSN: 0009-9236 , 1532-6535; DOI: 10.1002/cpt.1454. Clinical pharmacology & therapeutics : CPT. , 2019, Vol.106(3), p.652-660

Multi-Scale Systems Pharmacology Models



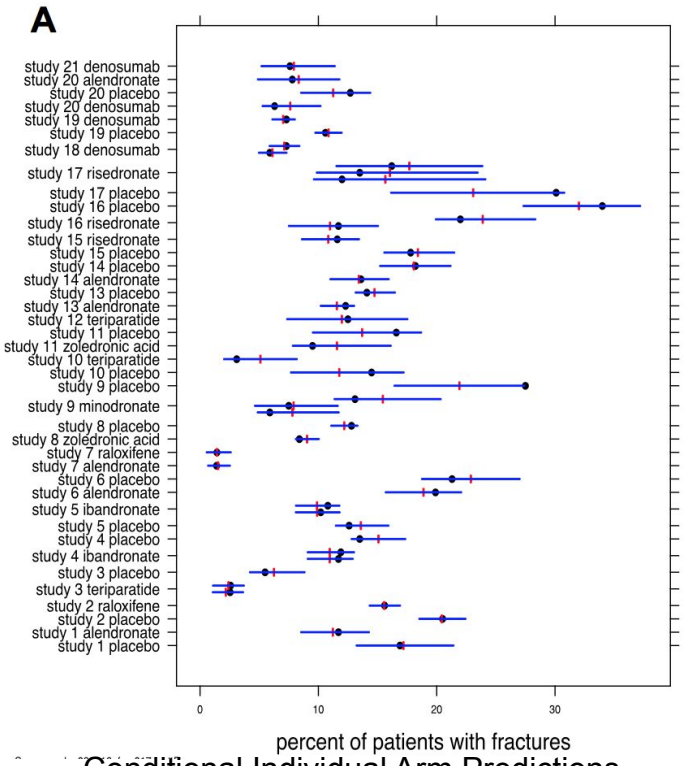
Peterson, MC and Riggs, MM. Predicting Nonlinear Changes in Bone Mineral Density Over Time Using a Multiscale Systems Pharmacology Model CPT: Pharmacomet. Syst. Pharmacol. November 2012

- Osteoporosis
- Primary Hyperparathyroidism
- Hyperparathyroidism Secondary to Chronic Kidney Disease

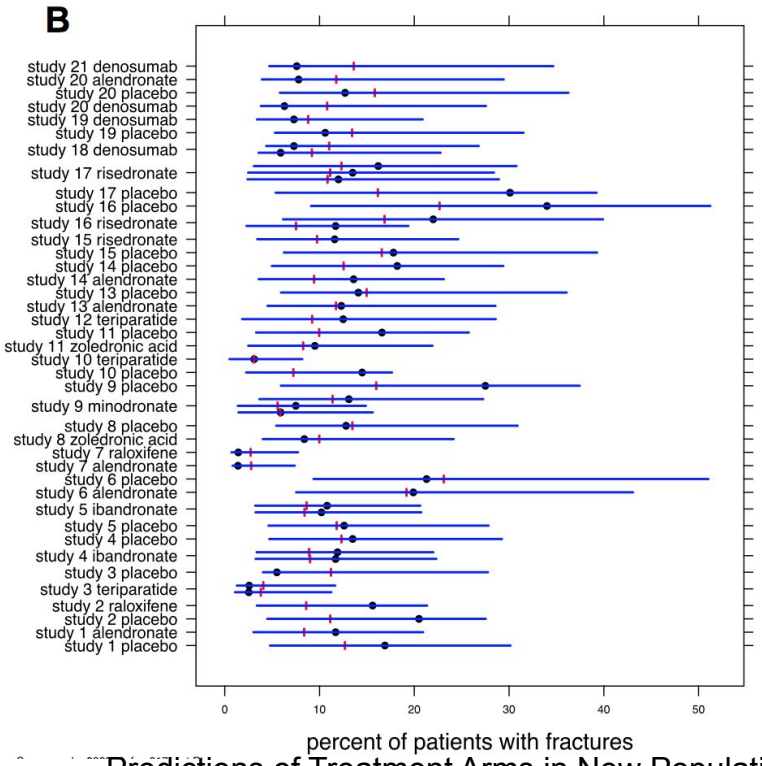
- Estrogen Modulators
- Bisphosphonates
- Parathyroid Hormone
- RANK-L pathway
- Wnt Signaling

- Bone Biomarkers
- Bone Mineral Density
- Fracture

Fracture Rate MSSP/Model-Based Meta Analysis



Conditional Individual Arm Predictions



Predictions of Treatment Arms in New Populations

RJ Eudy-Byrne, W Gillespie, MM Riggs, MR Gastonguay. A model of fracture risk used to examine the link between bone mineral density and the impact of different therapeutic mechanisms on fracture outcomes in patients with osteoporosis J Pharmacokinet Pharmacodyn (2017) 44:599–609

Fracture Hazard Ratio by Treatment

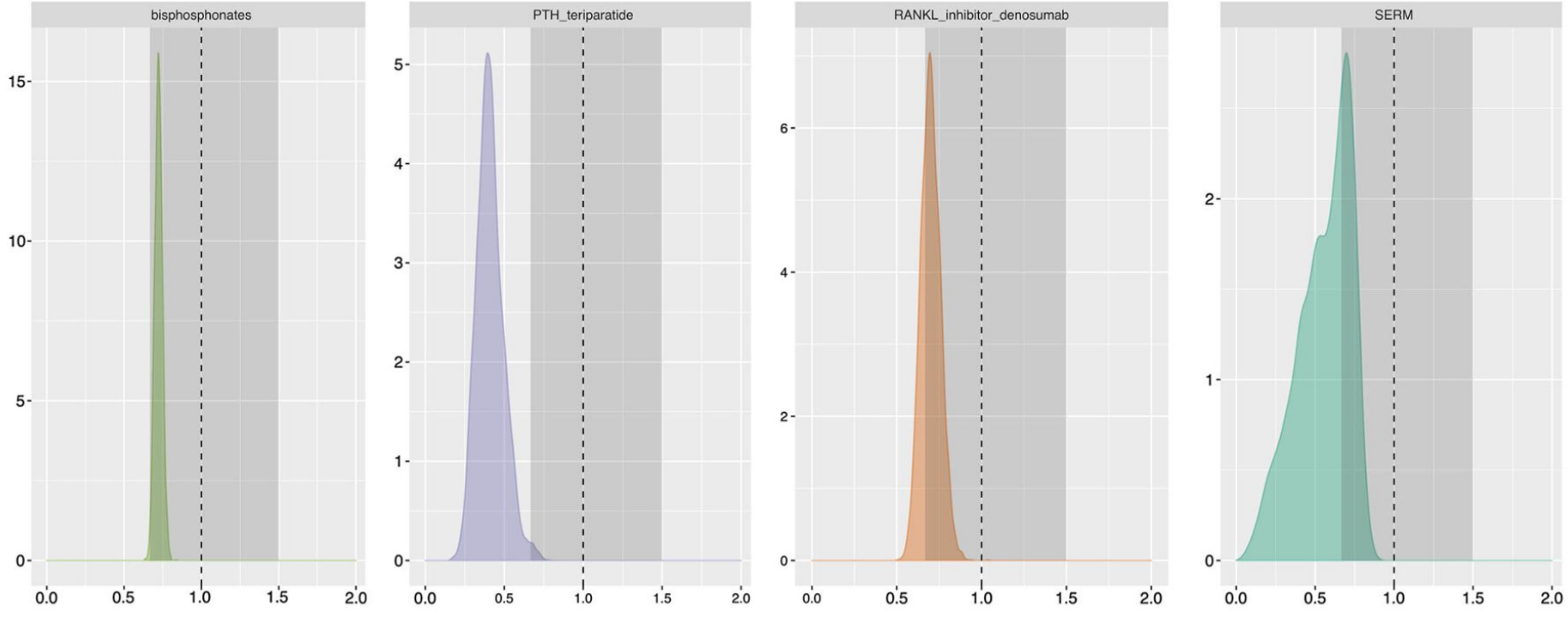
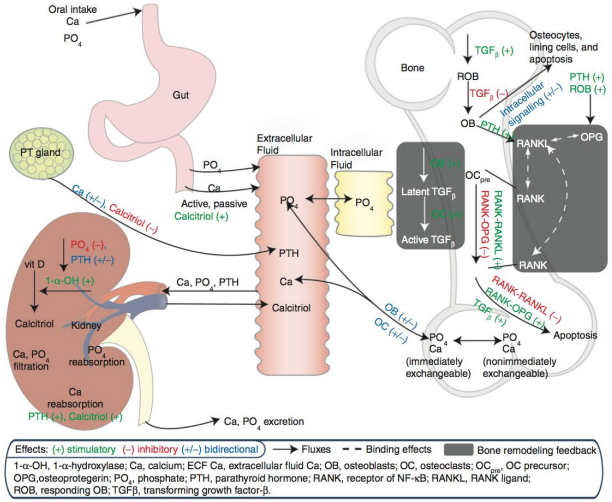
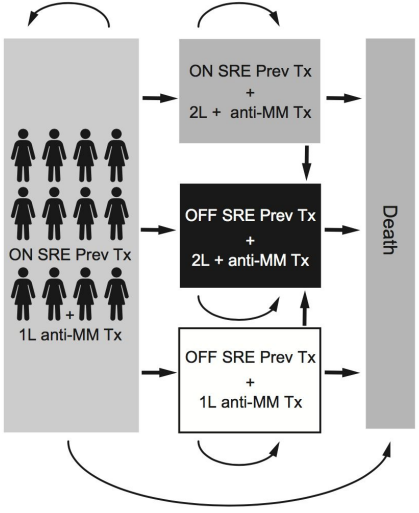


Fig. 3 Hazard ratios for each treatment relative to placebo calculated and density plots for this calculation over the posterior distribution of parameter estimates are represented, for the model with both drug–BMD interaction and additional drug effect

RJ Eudy-Byrne, W Gillespie, MM Riggs, MR Gastonguay. A model of fracture risk used to examine the link between bone mineral density and the impact of different therapeutic mechanisms on fracture outcomes in patients with osteoporosis J Pharmacokinet Pharmacodyn (2017) 44:599–609

Linking MSSP/Fracture Model & Pharmacoeconomics





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Early Development ICER ($/QALY) Predictions

- New drug, target
- New dose, regimen
- Combination therapies

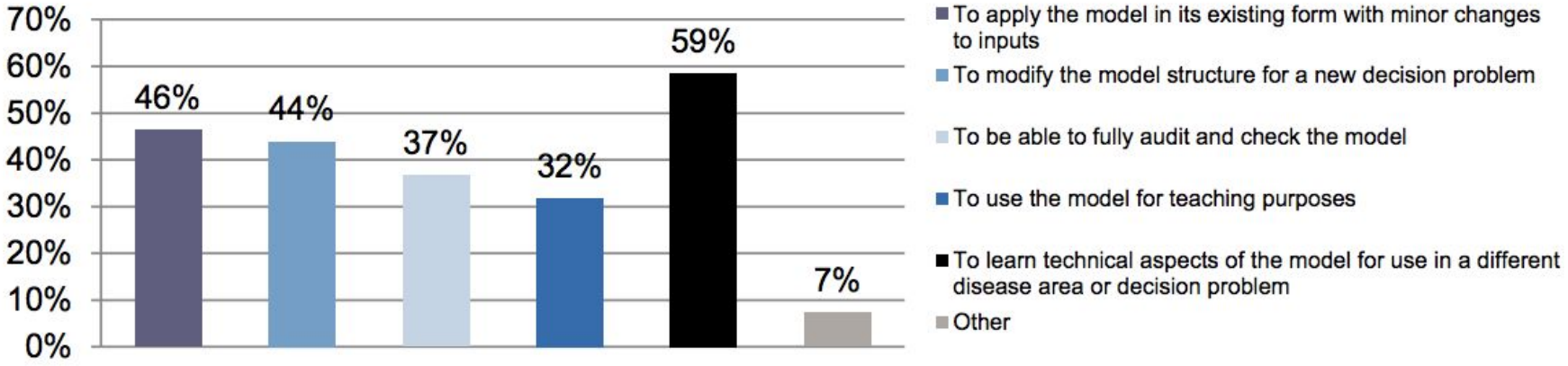
Open Source Models in Health Economics

PharmacoEconomics (2017) 35:125–128
DOI 10.1007/s40273-016-0479-8

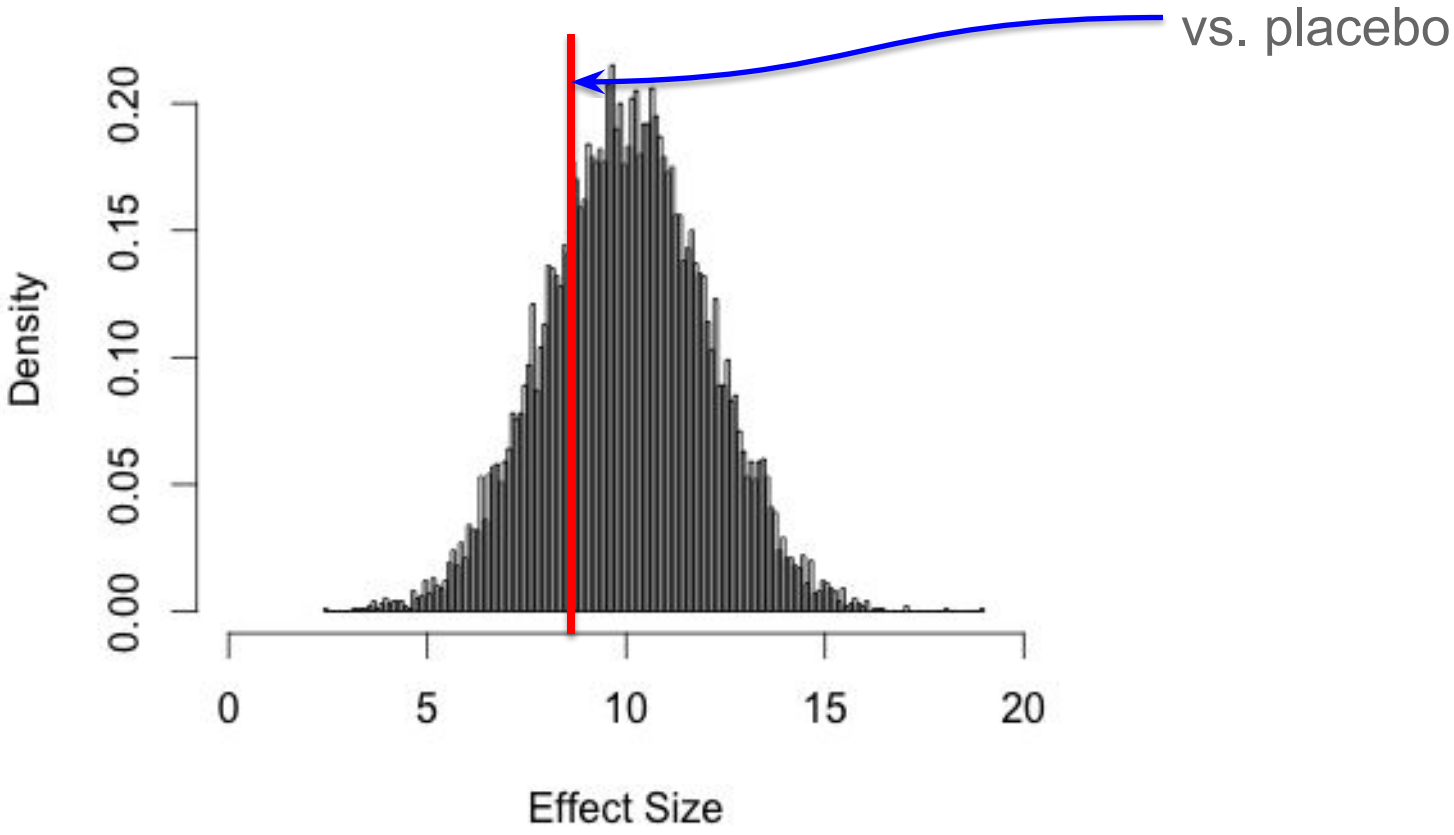
RESEARCH LETTER

Benefits, Challenges and Potential Strategies of Open Source Health Economic Models

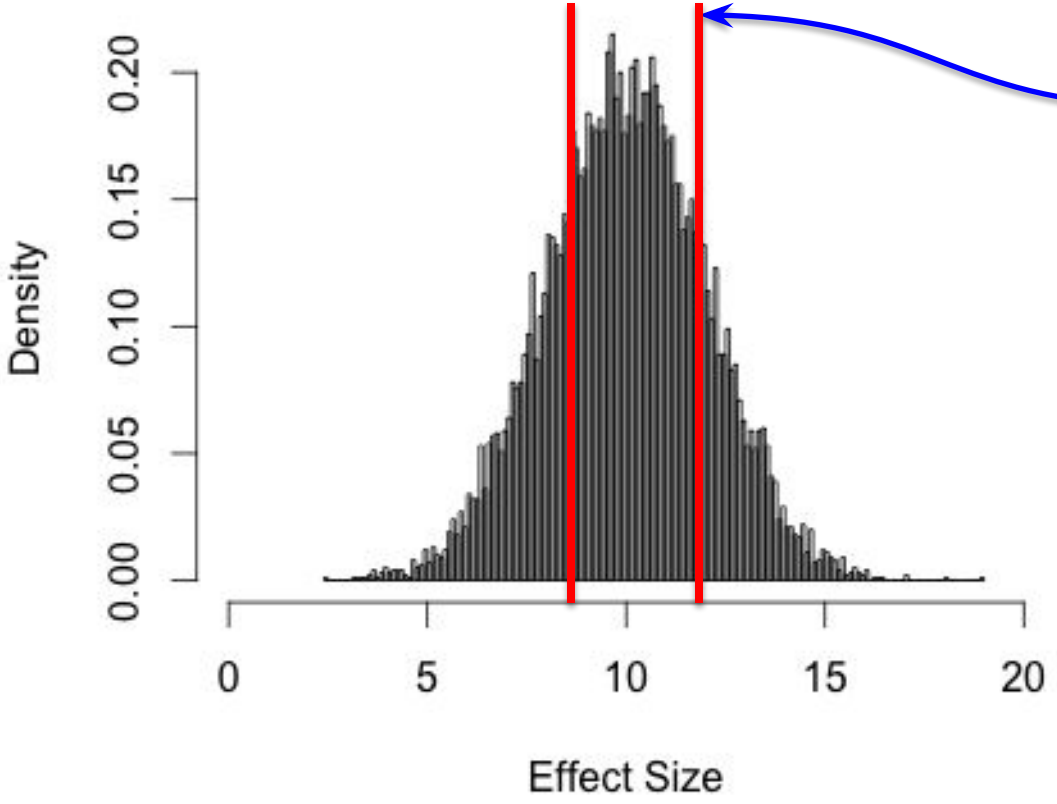
William C. N. Dunlop[1] · Nicola Mason[2] · James Kenworthy[1] · Ron L. Akehurst[2]



Probability of Success: Outdated Thinking

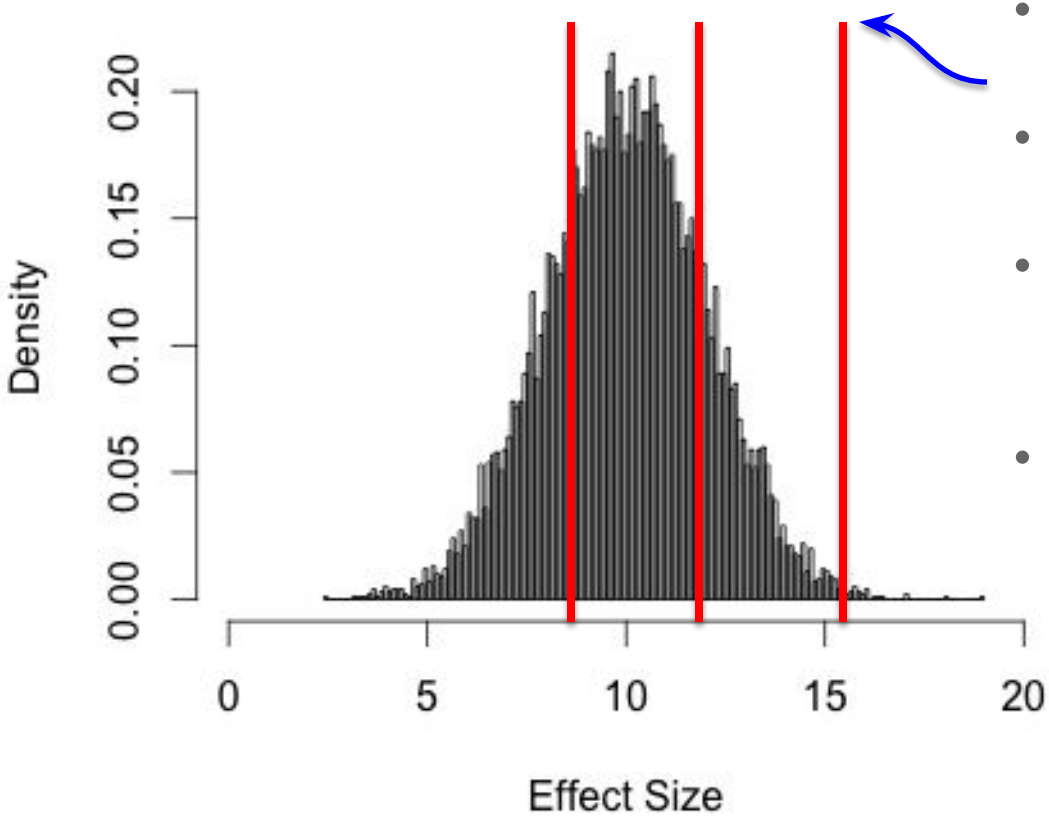


Probability of Success: Evolving Thinking



vs. active control

Probability of Success: New Opportunity



- vs. future competitor
- informed by predicted ICER
- in Real World treatment population
- Continuously updated and re-assessed as development programs and standard of care evolve

Summary

- Markov Models in Health Economics
- Utility of **static** vs **dynamic** Markov Models
- Value of open science in HE Analyses
- Opportunities at the intersection of Pharmacometrics and Health Economics

Thank You