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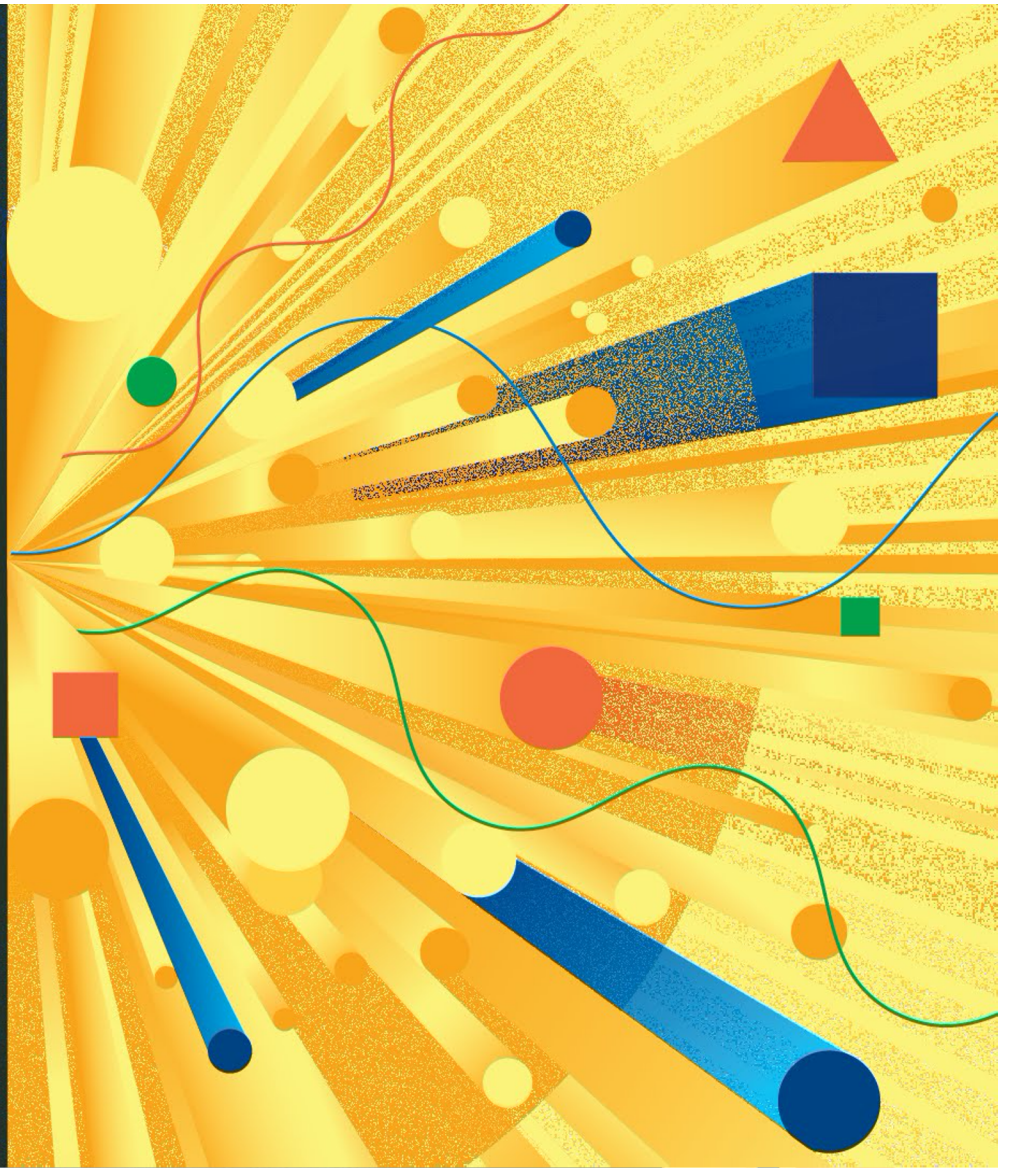
REIMAGINING THE THERAPEUTIC LANDSCAPE



Opportunities at the Intersection of Pharmacometrics and Health Economics for Insightful Drug Development Decision Making:

A Problem Based Learning Session with Interactive Scenario Evaluations

Moderators:

Marc R. Gastonguay, PhD - Metrum Research Group

Jing Liu, PhD - Pfizer

Overview

Session Introduction

Marc R. Gastonguay, PhD – Metrum Research Group

Introduction to Health Economics Concepts and Economic Models

Jean Lachaine, PhD – PeriPharm Inc.

Linking PMX and HE Models

Anna (Georgieva) Kondic, PhD, MBA – Nektar Therapeutics

Interactive Simulation Based on an Integrated Pharmacoeconomic-Pharmacometric Model

Daniel G. Polhamus, PhD – Metrum Research Group

Live Q&A

ISPOR 2020 Top 10 Trends in Health Economics

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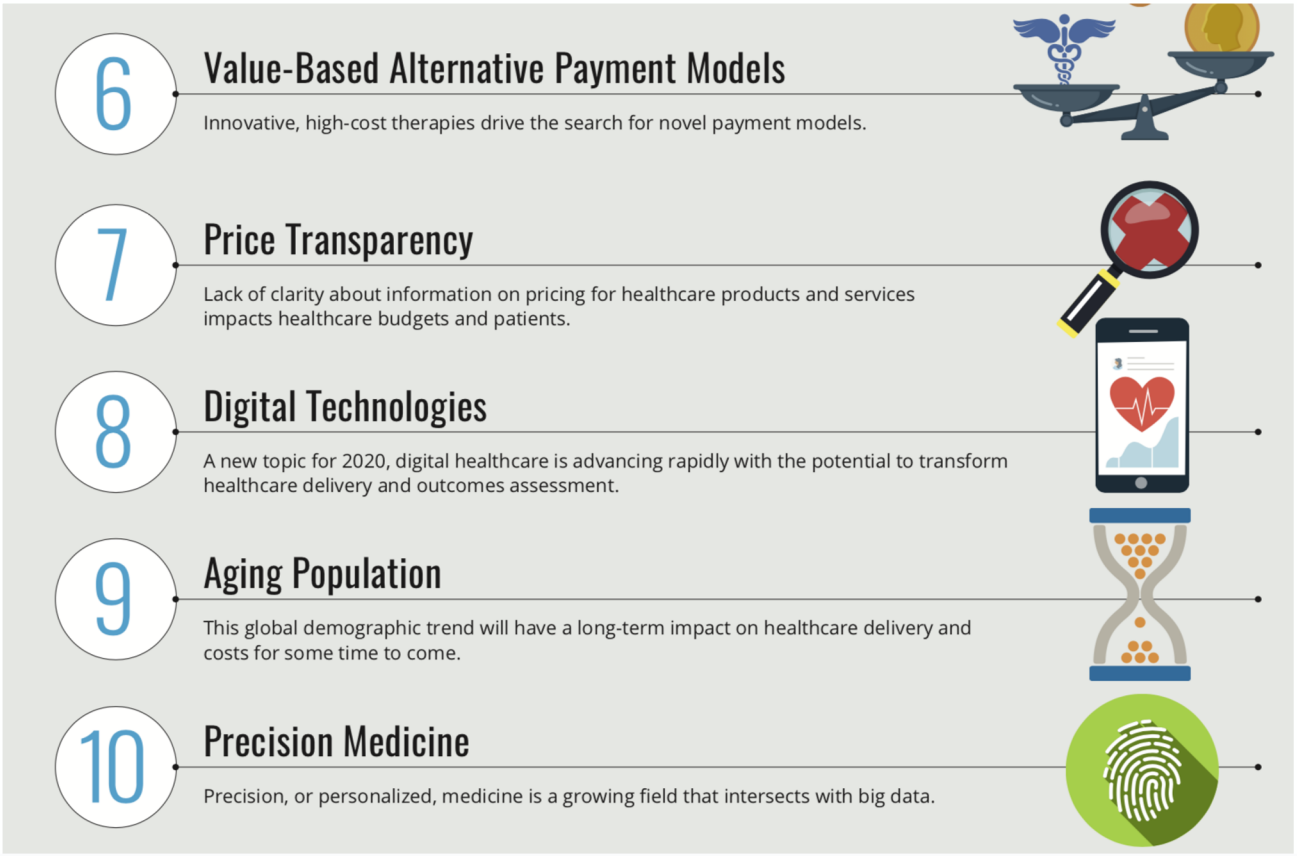
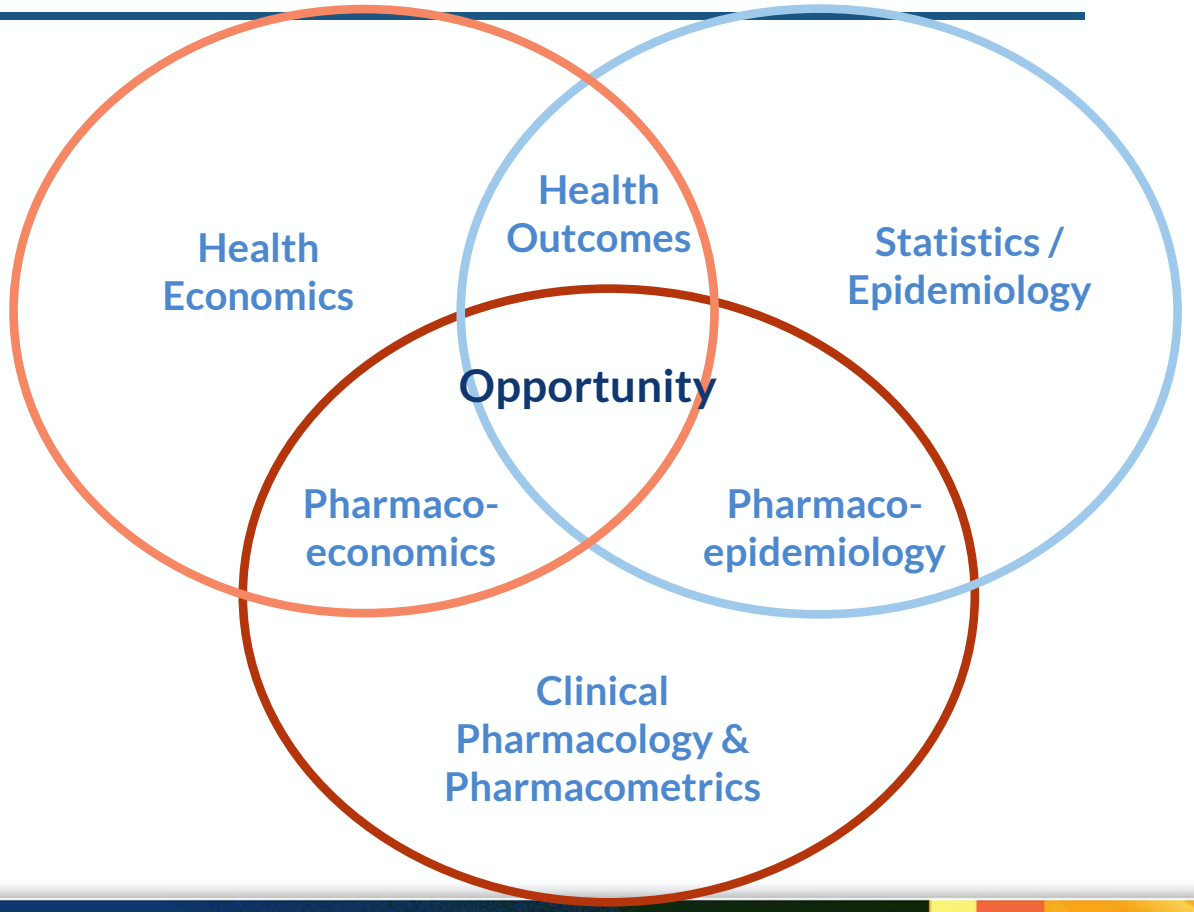


Opportunity at the Intersection

- Shared Learning, Resources, Science, Technology
- Better Inform Drug Development Decisions
- Better Inform Health Economic Decisions



Jean Lachaine Ph.D.
PeriPharm Inc

Intoduction to Health Economics Concepts and Economic Models

Role of The Economic Evaluation in Health Care

Health care resources are limited

Choices need to be made for an optimal allocation of resources

Economic evaluations can support the decision making process

Economic Evaluations in Health Care

- Compare different interventions on the basis of their costs and their outcomes.

- The objective of the economic evaluation is not to identify the less costly alternative, but the most efficient alternative.

Key Drivers of Drug Reimbursement Decisions

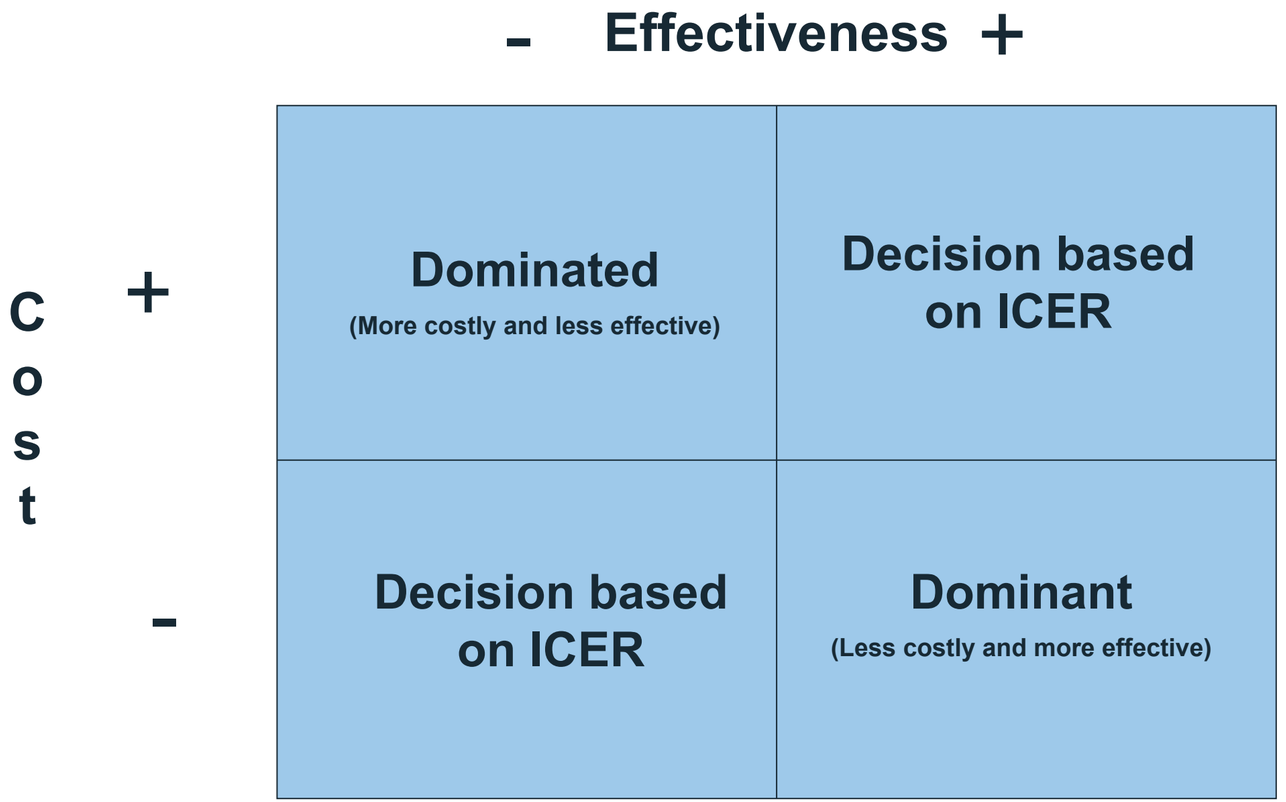
- Therapeutic value
  - According to the available clinical evidence
- Cost-effectiveness
  - Depends on the cost-effectiveness or cost-utility ratio (cost per QALY)
  - Closely linked to the magnitude of the clinical effect as well as the drug costs
- Budget impact
  - Supplemental costs (or savings) encountered following the addition of the new drug

Economic Evaluation of New Medications

- The most common type of economic evaluation is the « Cost-utility » analysis
- Results are estimated in terms of cost per QALY (Quality adjusted life year)
- Number of QALYs = Duration x Utility
- Incremental cost-effectiveness ratio (ICER):

$$\frac{\text{Costs of new drug} - \text{Cost of comparator}}{\text{QALYs with new drug} - \text{QALYs with comparator}}$$

Cost-Effectiveness Analysis (Decision Rules)



Calculation of Incremental Cost-Utility Ratio (Example)

- Standard of care =
  - Cost = $20,000
  - Survival = 1.2 years / Utility = 0.7 □ 0.84 QALY

- New drug =
  - Cost = $40,000
  - Survival = 1.4 years / Utility = 0.8 □1.12 QALY

$$\text{ICER} = \frac{\$40{,}000 - \$20{,}000}{1.12\ \text{QALY} - 0.84\ \text{QALY}} = \frac{\$20{,}000}{0.28\ \text{QALY}} = \$71{,}429 / \text{QALY}$$

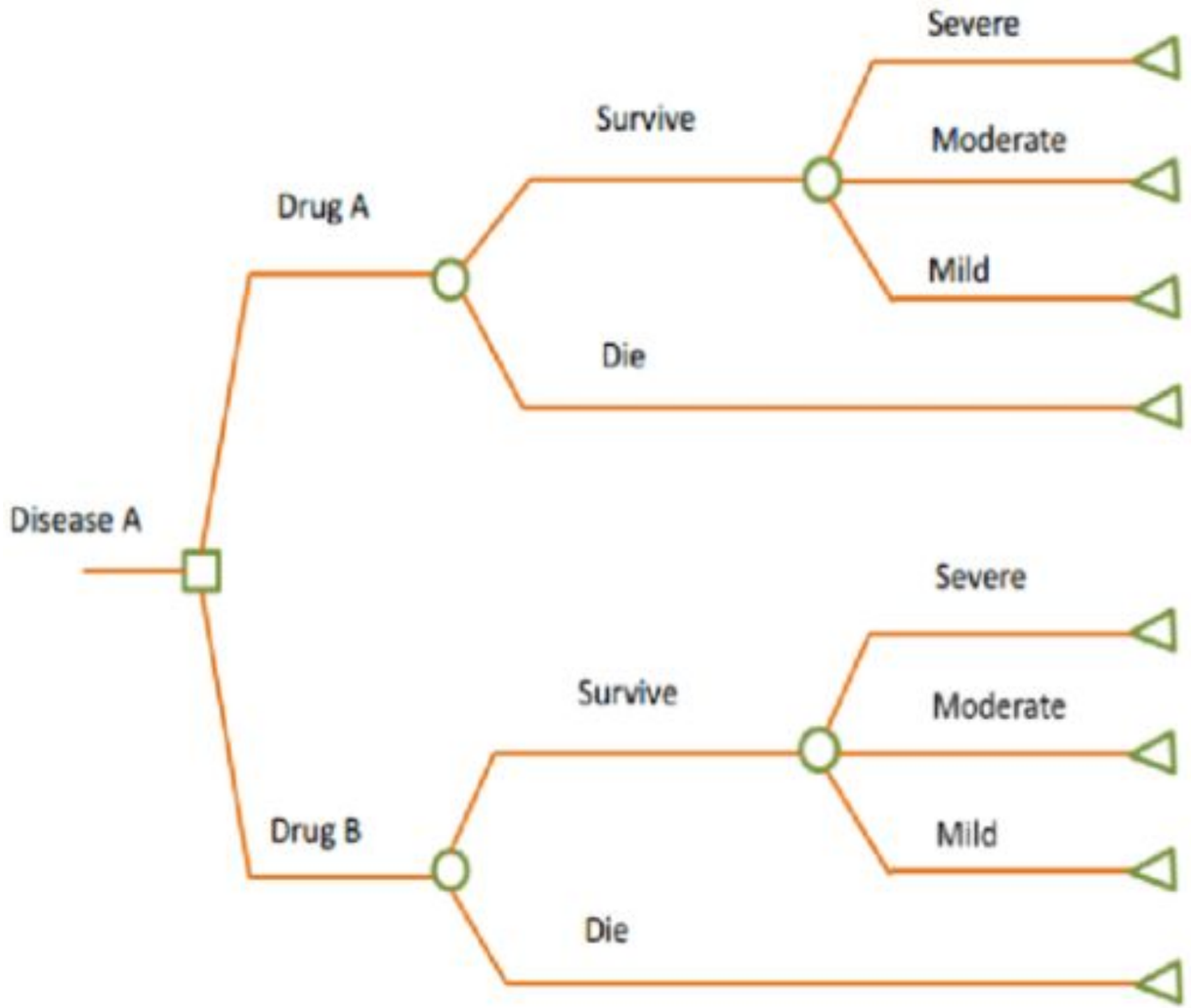
Cost-Utility Analysis

Intervention	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness	Average Cost-Effectiveness ratio	ICER
SoC	$20,000		0.84		$2,500	
New drug	$40,000	$20,000	1.12	0.28	$4,000	$71,429 / QALY

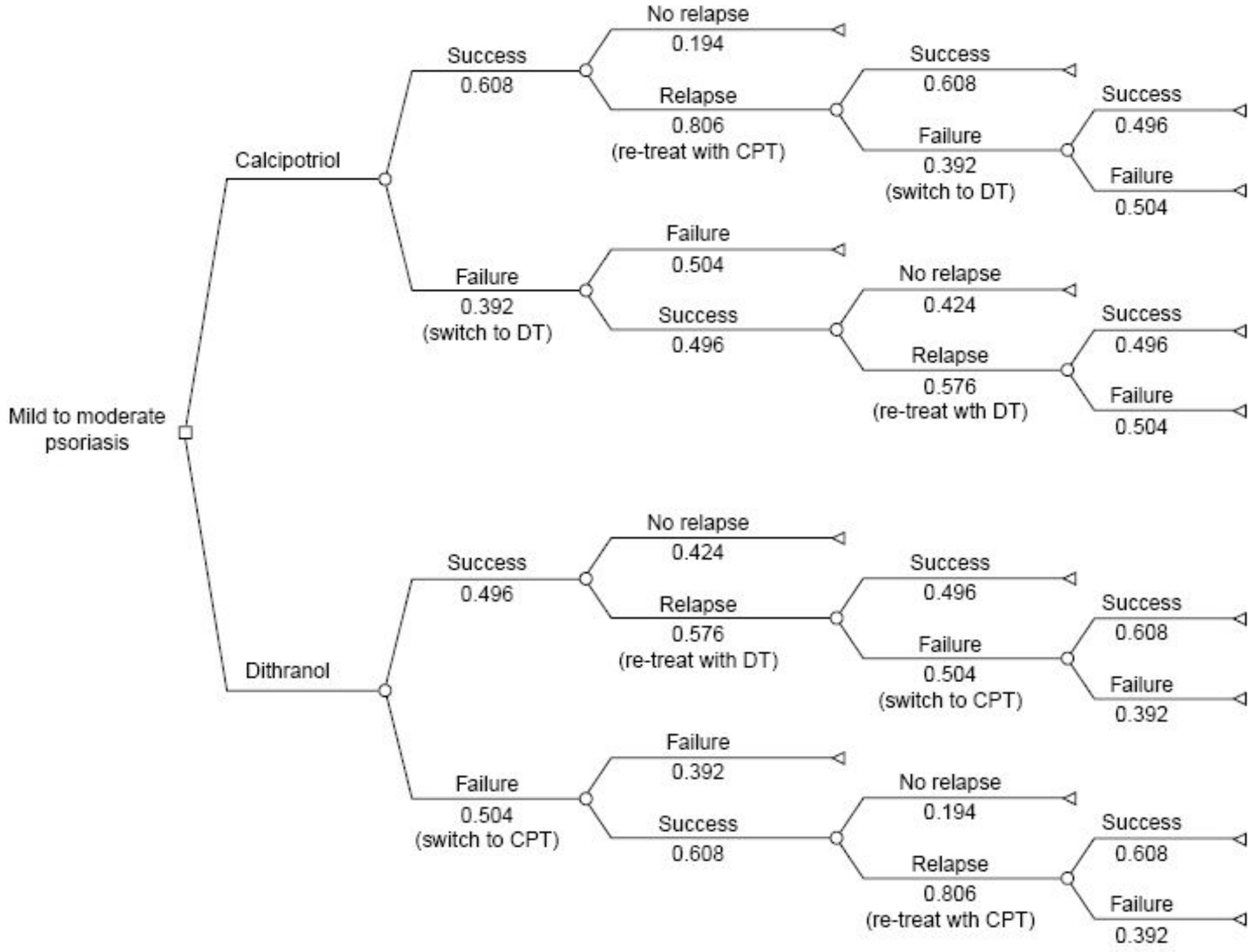
Health Economic Models

- Decision trees
- Markov Models
- Partitioned Survival Models
- Discrete event simulations

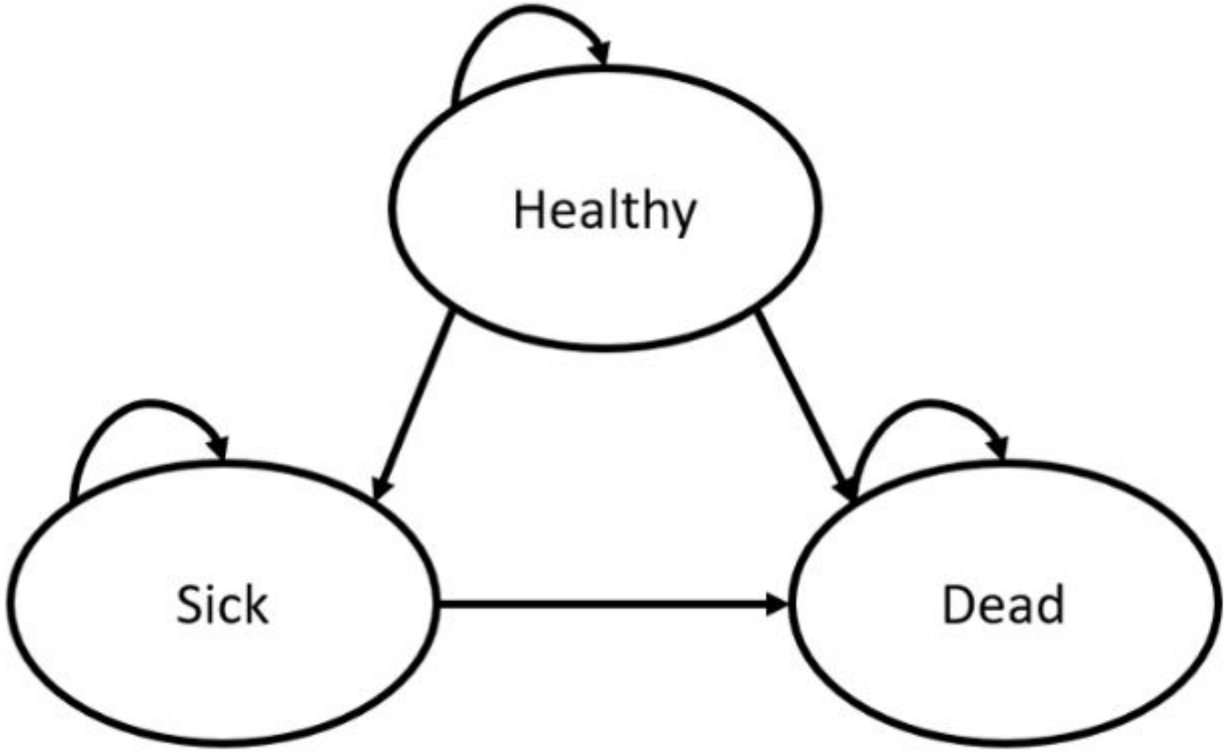
Health Economic Modelling: Decision Tree



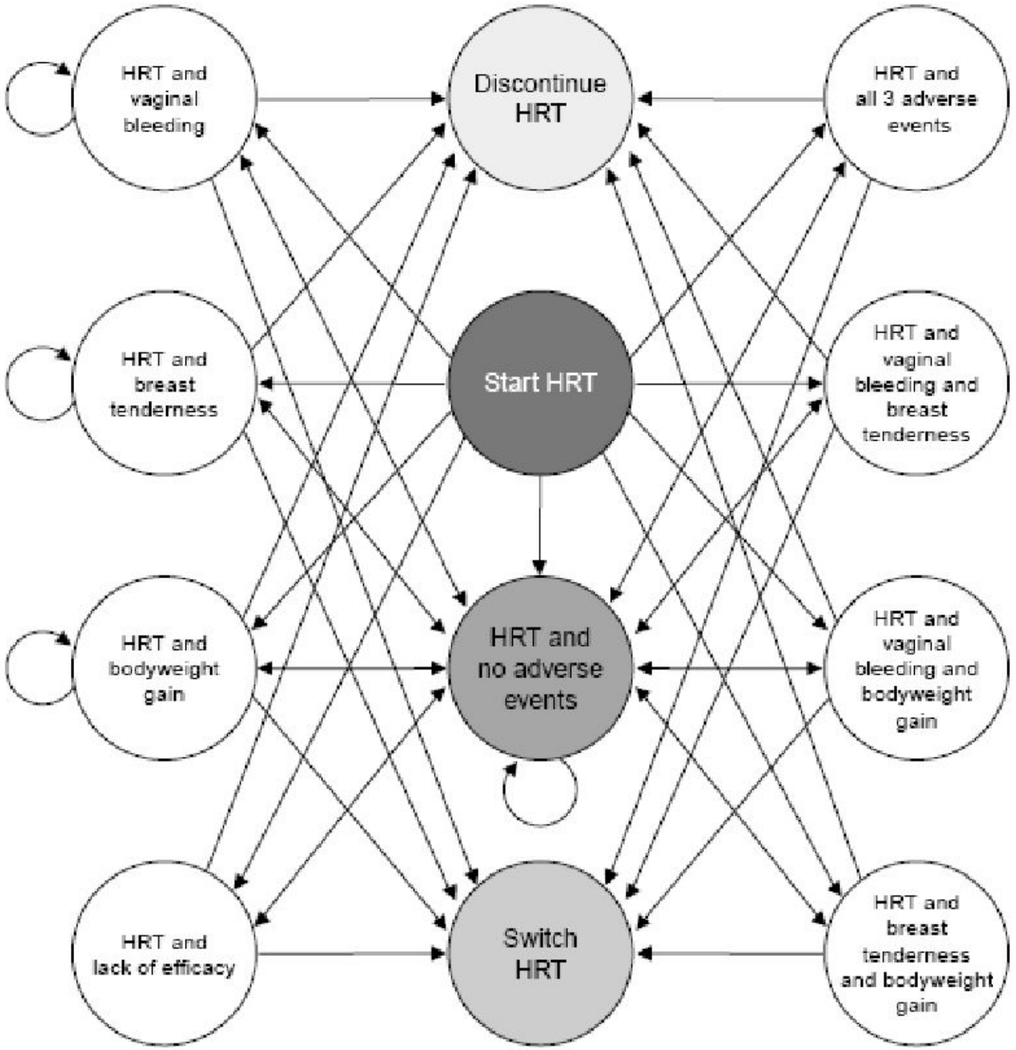
Health Economic Modelling: Decision Trees



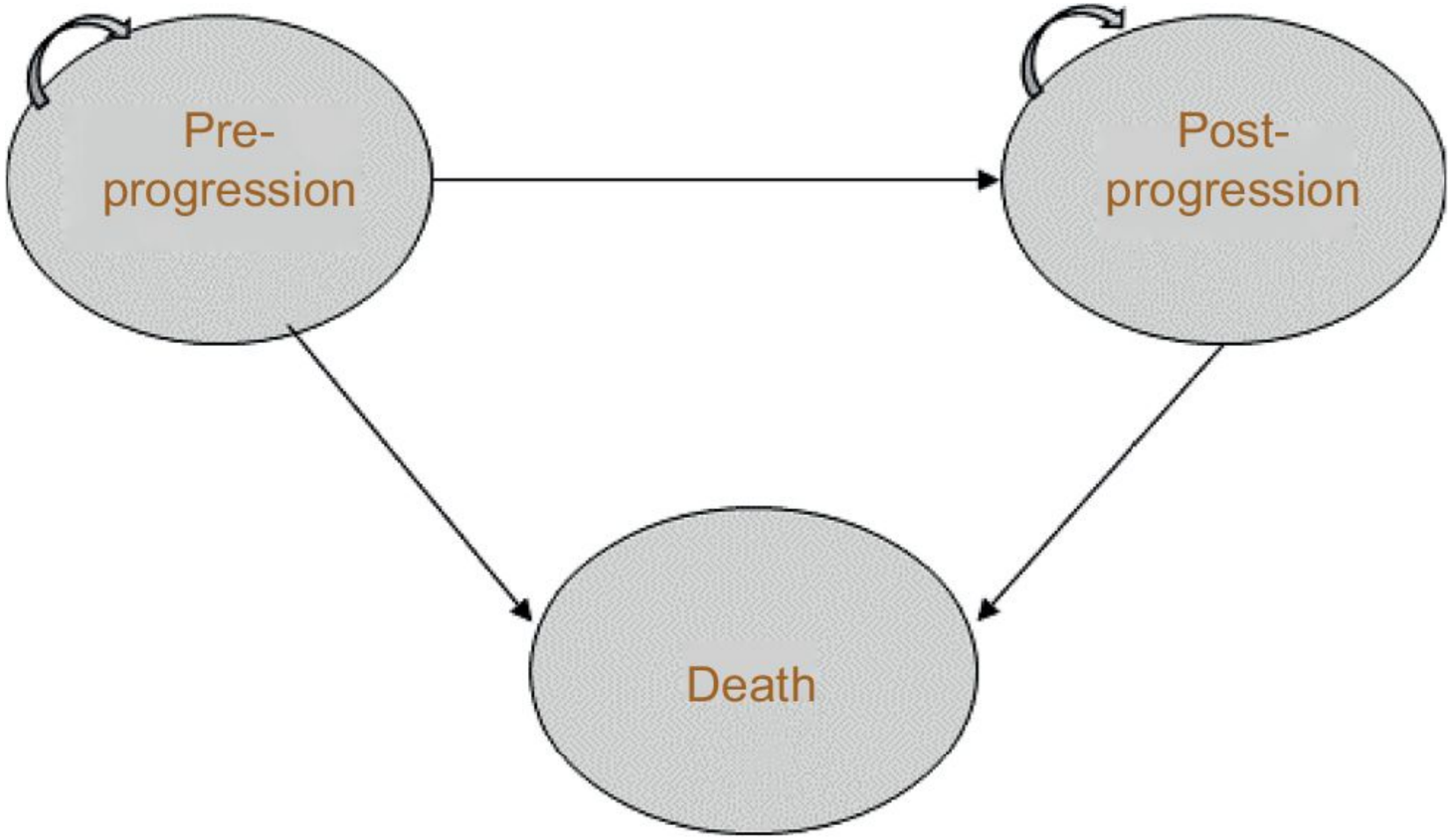
Health Economic Modelling: Markov Models



Health Economic Modelling: Markov Models

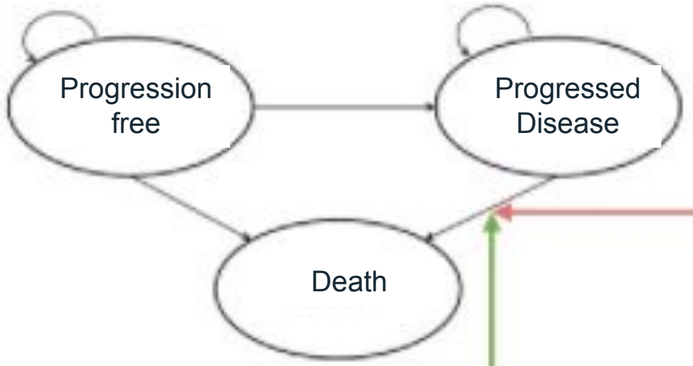


Health Economic Modelling: Markov Models



Health Economic Modelling: Partitioned Survival Models

Conventional Markov Models



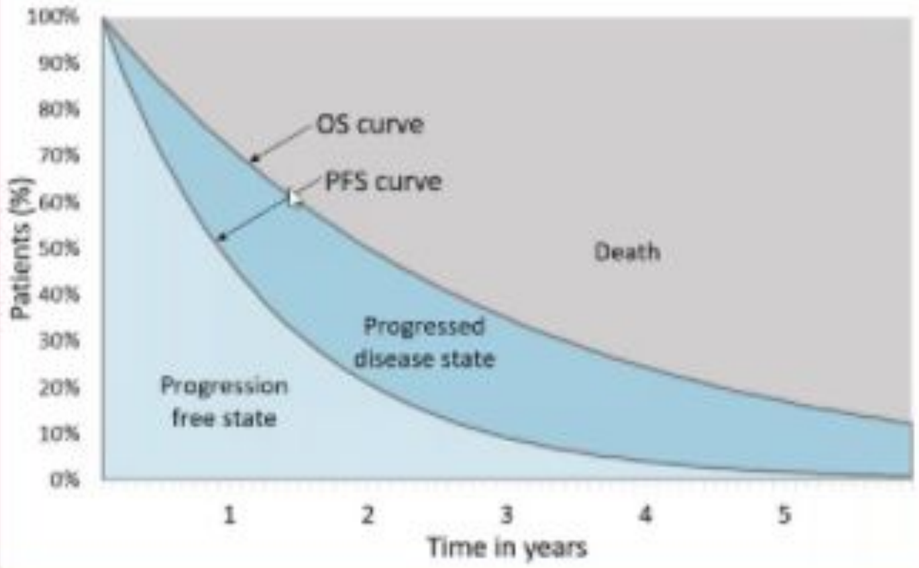
Transition probabilities

State membership determined using matrices of transition probabilities which determine the probability that an individual will transition in a given time period.

Partitioned Survival Models

Survival curves

State membership derived from non-mutually exclusive survival curves. Overall survival (OS) is portioned to estimate the proportion of patients in the progression-free and progressed disease health states.



Health Economic Modelling: Discrete Event simulations

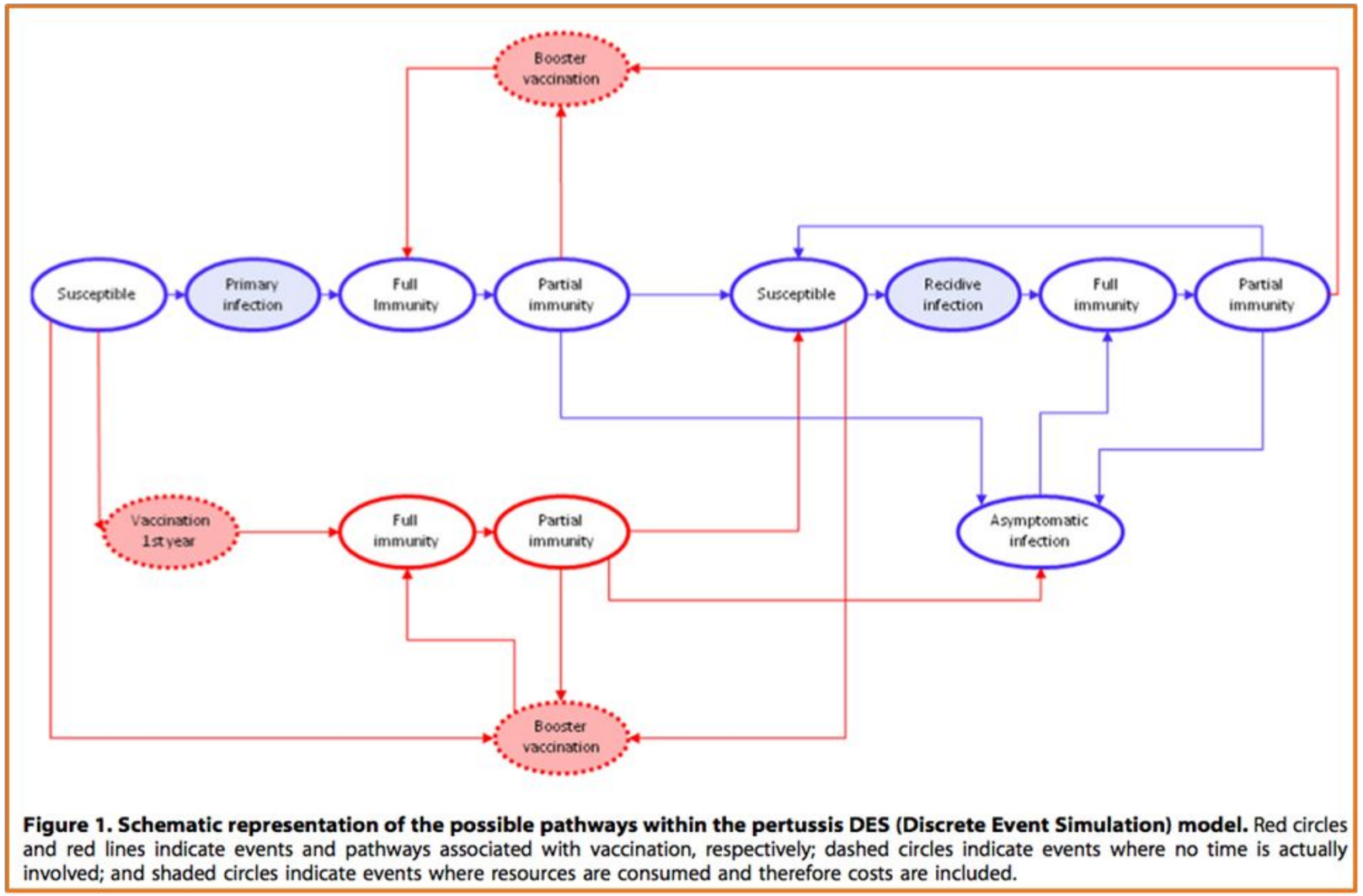


Figure 1. Schematic representation of the possible pathways within the pertussis DES (Discrete Event Simulation) model. Red circles and red lines indicate events and pathways associated with vaccination, respectively; dashed circles indicate events where no time is actually involved; and shaded circles indicate events where resources are consumed and therefore costs are included.

The economic evaluation in healthcare, is now a key criterion in decision making

*Even if good **health has no price**, we cannot deny that diseases have a cost…*

Anna Georgieva Kondic, PhD, MBA

Linking Pharmacometrics and Health Economics: A Personal Perspective

Outline

- General concepts
- Challenges and opportunities
- Case studies
- Conclusions

Framing the opportunity: value proposition of a new therapy

- Traditional paradigm
  - Cost-effectiveness and budget impact
  - Separate regulatory process for approval and reimbursement with different tools
- Evolving paradigm: driving towards precision and personalized medicine
  - Matching the patient with the right treatment
  - Value based reimbursement
  - Number of joint regulatory-HTA advice meetings is increasing; new tools are emerging

Conceptual Framework of PMx-PE interaction (Srinivasan et al)

- Drug model
- Disease model
- Trial model

How to strengthen the value proposition?

A word (or two) of caution

- Goal is to decrease the uncertainty and guesswork in the decision making
- Fit for purpose models
- Internal vs external decisions
- Must-haves vs nice-to-have
    - Focus on cases studies where joint approach provides further clarity
- Speed and ease of use are of utmost importance

Early (prior to P2) economic evaluation

Questions/focus

- Given an assumed efficacy, what may be a good price?
- What is a needed efficacy in order to meet a prescribed threshold?
- Is there a need for enrichment of a particular sub-populations to facilitate registration?
- How important are quality of life and routes of administration?
- Include QoL and other tools (e.g. ease of use) as secondary endpoints in a clinical trial (if a key parameter)?
- Benchmark single arm studies

What does success look like

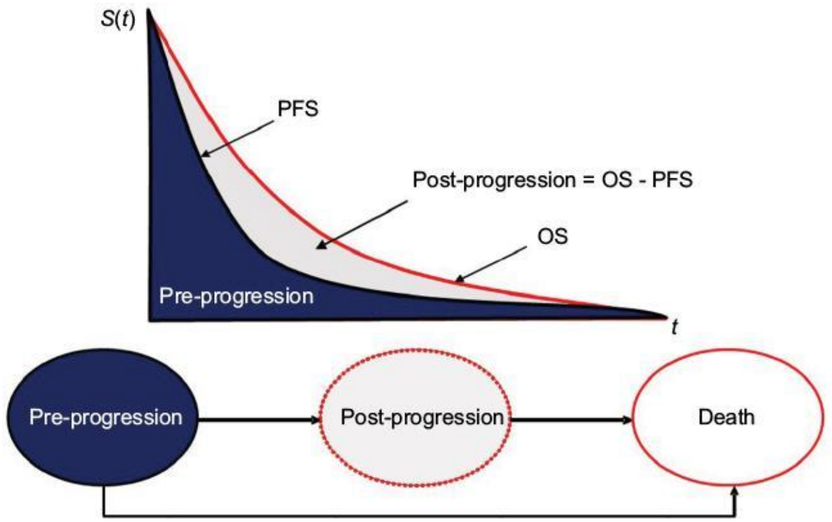
- General requirements:
  - Commercial and clinical interest in go/no go decisions
  - Multi-disciplinary team efforts, alignment needed on multiple levels

- Tool requirements
  - Visual in order to answer questions on the spot (GUI)
  - Be able to incorporate uncertainty and variability
  - Fast and powerful computational capabilities
  - Ability to incorporate new and dynamically changing information (e.g. competitive landscape) in a seamless fashion

- Ongoing and iterative process: knowledge database, rather than a tool
  - New data integration, including drugs, biomarkers and patient populations
  - Quality control

Application 1: Combinations in Oncology

- Evaluate a proposed design for a late phase clinical study of the combination in ovarian cancer
- Both drugs in combination approved and expensive
- The economic evaluation pointed out to a higher hurdle than expected for efficacy for both PFS and OS in order to achieve acceptable ICER
  - Identify responders and enrich patient population in clinical study
  - A conversation starter rather than a definitive Go-No go; value in cancer goes beyond cost-effectiveness



Application 2: Commercial potential of an asset

- Characterize commercial potential of a molecule in CV space using disease modeling and HE approaches
  - Price range
  - Sequential clinical approach evaluation
- Factors impacting project
  - Published models for several diseases
  - Multitude of patients with different responses
  - Clear reimbursement guidance determining the hurdle
  - Ability to integrate team point of view and assumptions in a single framework

Aspiring to understand the real world

Focus

- Problem statement: bridging efficacy-to-effectiveness gap
  - Characterize the impact of the differences between RCT and RW
  - Prepare for address in order to maximize “value” (including value-based reimbursement)
- Why?
  - Different patient populations
  - Different adherence and behavioral patterns
  - Country-specific pathways
- Multiple tools are being considered

Case study 3: Hodgkins Lymphoma

- Innovative Medicines Initiative (IMI) initiative
- HL was ne of the case studies for different methodologies
  - Clear discrepancy between performance of approved treatments in RW as compared to RCT
  - Simplest scenario:
    - Age
    - Tolerability
    - Mixture of the two
- Conduct simulations for novel therapies to inform on clinical drug design and optimize on value

Conclusions

- Pharmacometrics and pharmacoeconomics are well-established quantitative disciplines
- Joint efforts can strengthen the quality of decision making and impact bottom line
- Several promising efforts exist yet this is an area of enormous growth potential

Thank you!

Daniel Polhamus, PhD
Metrum Research Group

Interactive Simulation Based on an Integrated Pharmacoeconomic-Pharmacometric Model

Pharmacoeconomic (PE) Model: Dupilumab in Atopic Dermatitis

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Economic Evaluation of Dupilumab for Moderate-to-Severe Atopic Dermatitis: A Cost-Utility Analysis

Marita Zimmermann MPH PhD,[a] David Rind MD MSc,[b] Rick Chapman PhD, MS,[b]
Varun Kumar MBBS MPH MSc,[b] Sonya Kahn MPH,[b] Josh Carlson PhD MPH[a]

6.3% yearly discontinuation used in article, but RWE suggests substantially higher rates (~83% persistence at 1 year)

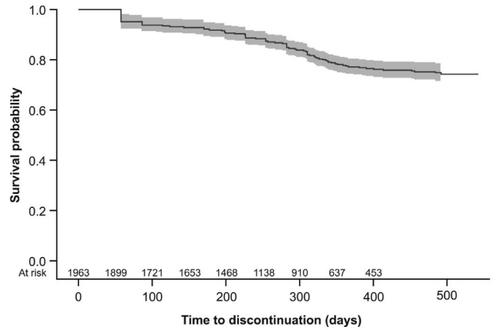
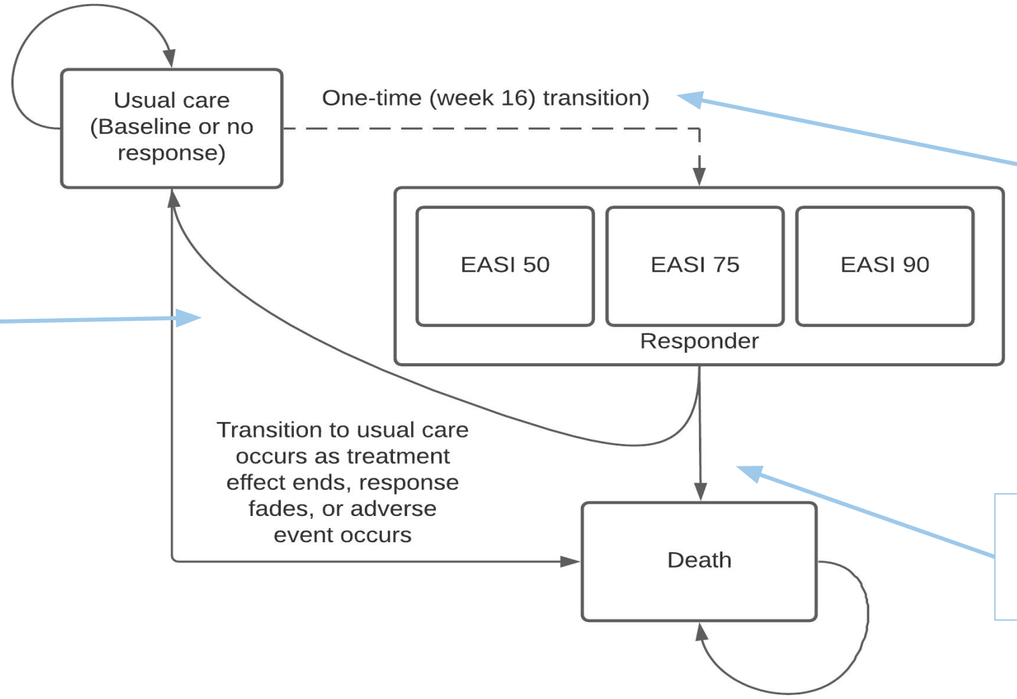


Figure 2. Persistence with dupilumab treatment allowing a 30-day grace period. Kaplan-Meier survival analysis was used to estimate persistence with dupilumab therapy. Blue shading represents the Hall-Wellner 95% confidence band.

Silverberg, et al 2021



In combined PD-PE model, this is determined by week 16 response rate from longitudinal model

WHO gender and age based mortality

Pharmacometric (PM) Model: Dupilumab Effects on EASI

Longitudinal EASI score is a fractional decrease of baseline EASI score (E0). For patient *i*'s *j*th observation at time *t* :

$$\mathrm{EASI}(t_{ij}|\mathrm{drug}_i) = \frac{\mathrm{E0}_i}{1 + g_{\mathrm{Pbo}}(t_{ij}) + g_{\mathrm{TCS}}(t_{ij}) + g_{\mathrm{Drug}}(t_{ij})}$$

Drug effects are hyperbolic Emax models:

$$g_{\mathrm{Pbo}}(t_i) = \frac{\mathrm{Emax}_{\mathrm{Pbo}} \times t_i}{\mathrm{ET50}_{\mathrm{Pbo}} + t_i}$$

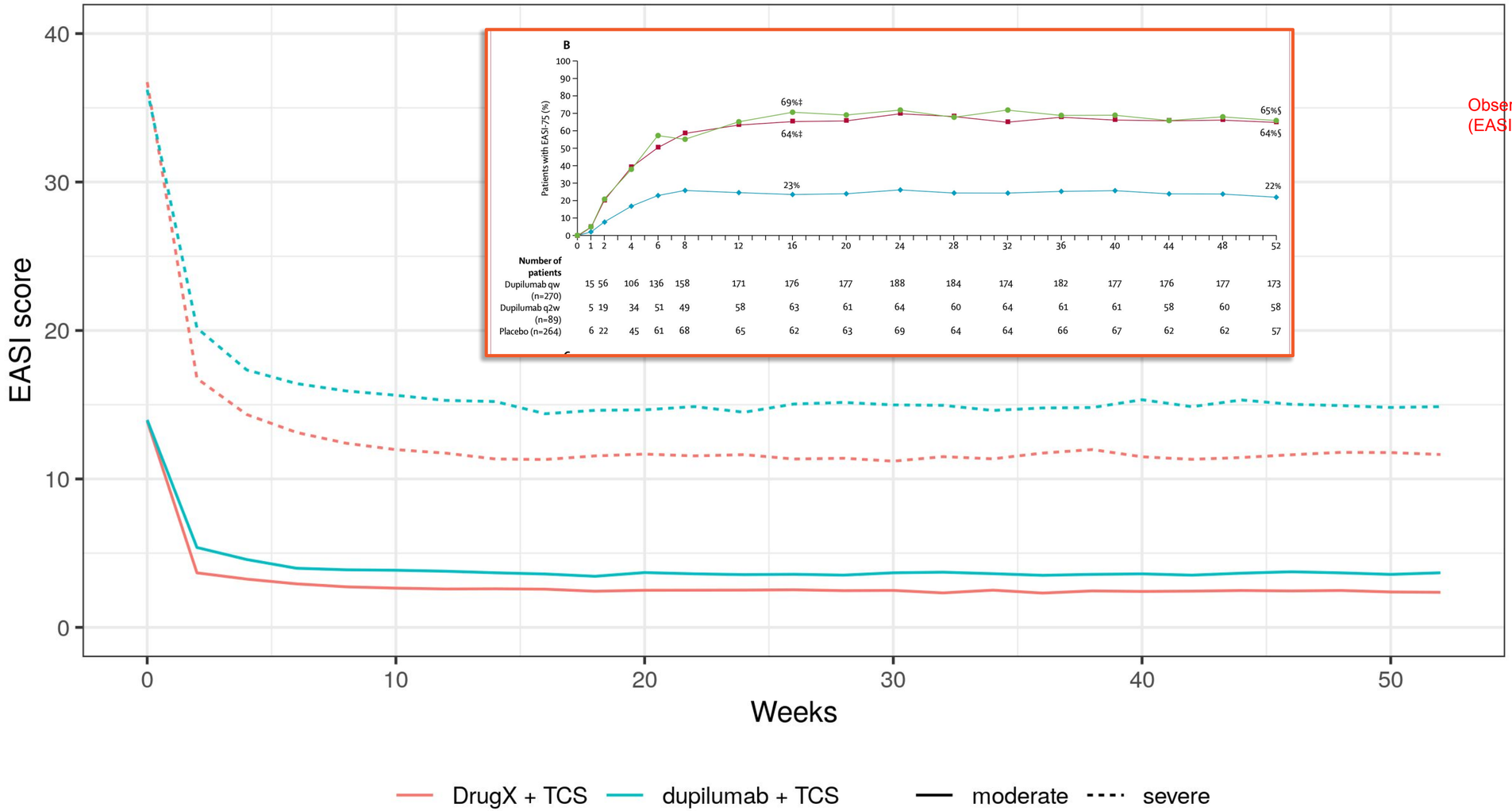
$$g_{\mathrm{TCS}}(t_i) = \frac{\mathrm{Emax}_{\mathrm{TCSi},i} \times t_i}{\mathrm{ET50}_{\mathrm{TCS}} + t_i} \times e^{-k_{\mathrm{off,TCS}} \quad (t_i - \mu_{\mathrm{TCS}})^+}$$

$$g_{\mathrm{Drug}}(t_i) = \frac{\mathrm{Emax}_{\mathrm{Drug},i} \times t_i}{\mathrm{ET50}_{\mathrm{Drug}} + t_i}$$

Primary data sources:

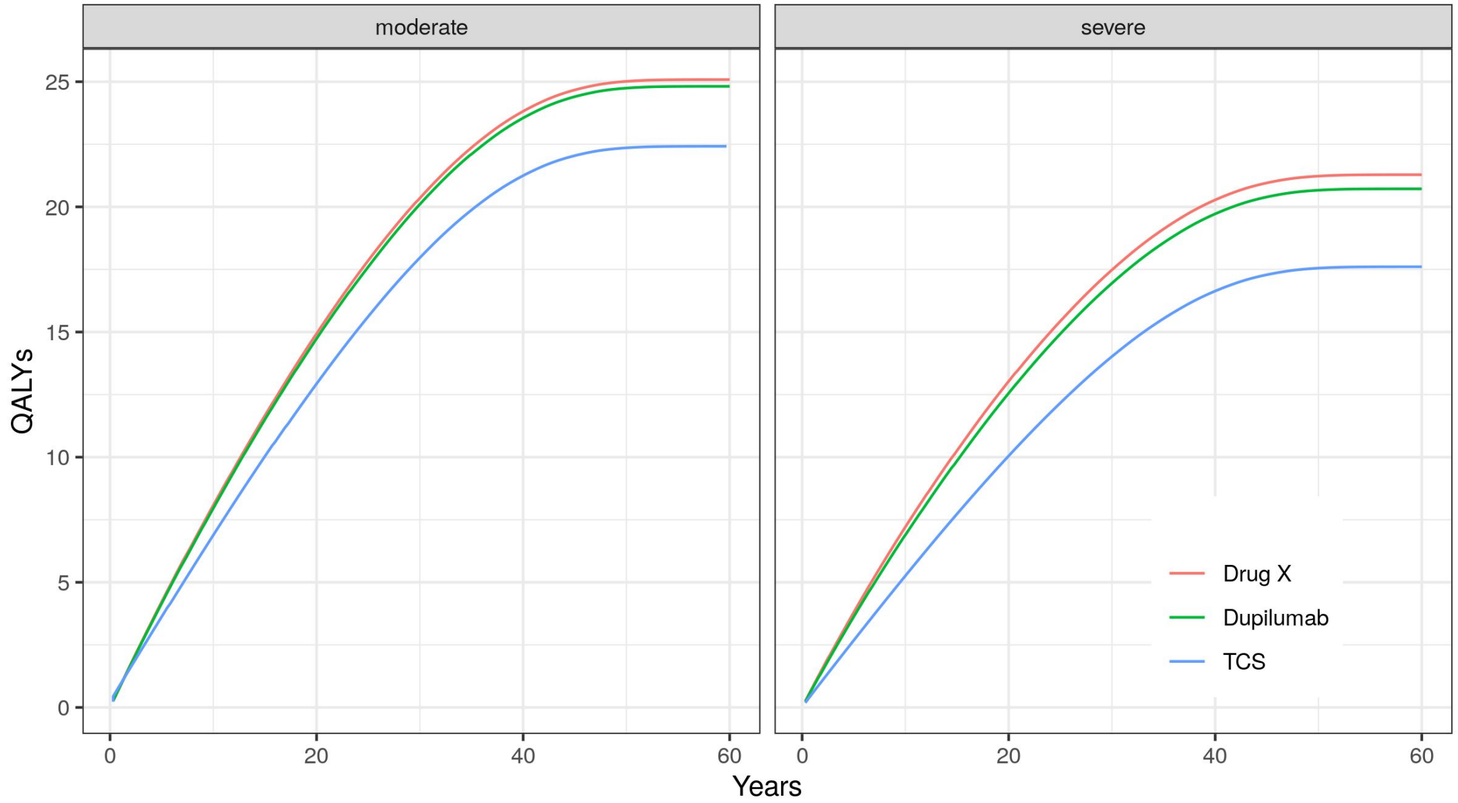
- SOLO 1&2
  - 16 weeks, placebo controlled in moderate-to-severe AD where TCS provided inadequate control or was medically inadvisable. TCS as rescue.
- LIBERTY AD-CHRONOS
  - Long-term (1 yr) management of moderate-to-severe AD with concomitant TCS
- Abrocitinib dose ranging
  - Used to specify proportional residual error

Efficacy Benchmarking via PMPE Model



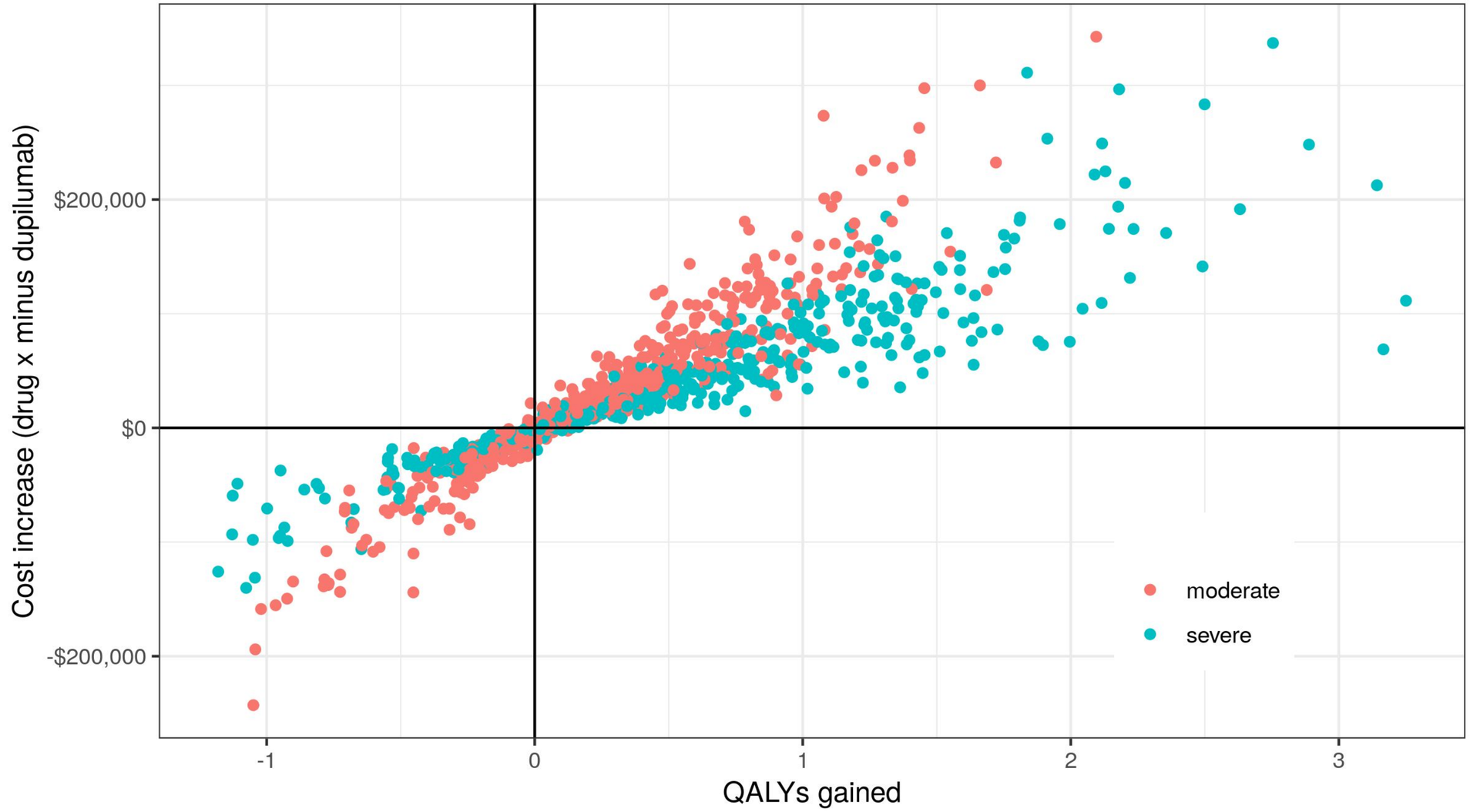
Observed dupilumab 52 week efficacy (EASI-75) – Blauvelt et al, 2017

Projected Quality Adjusted Life Years (QALYs)

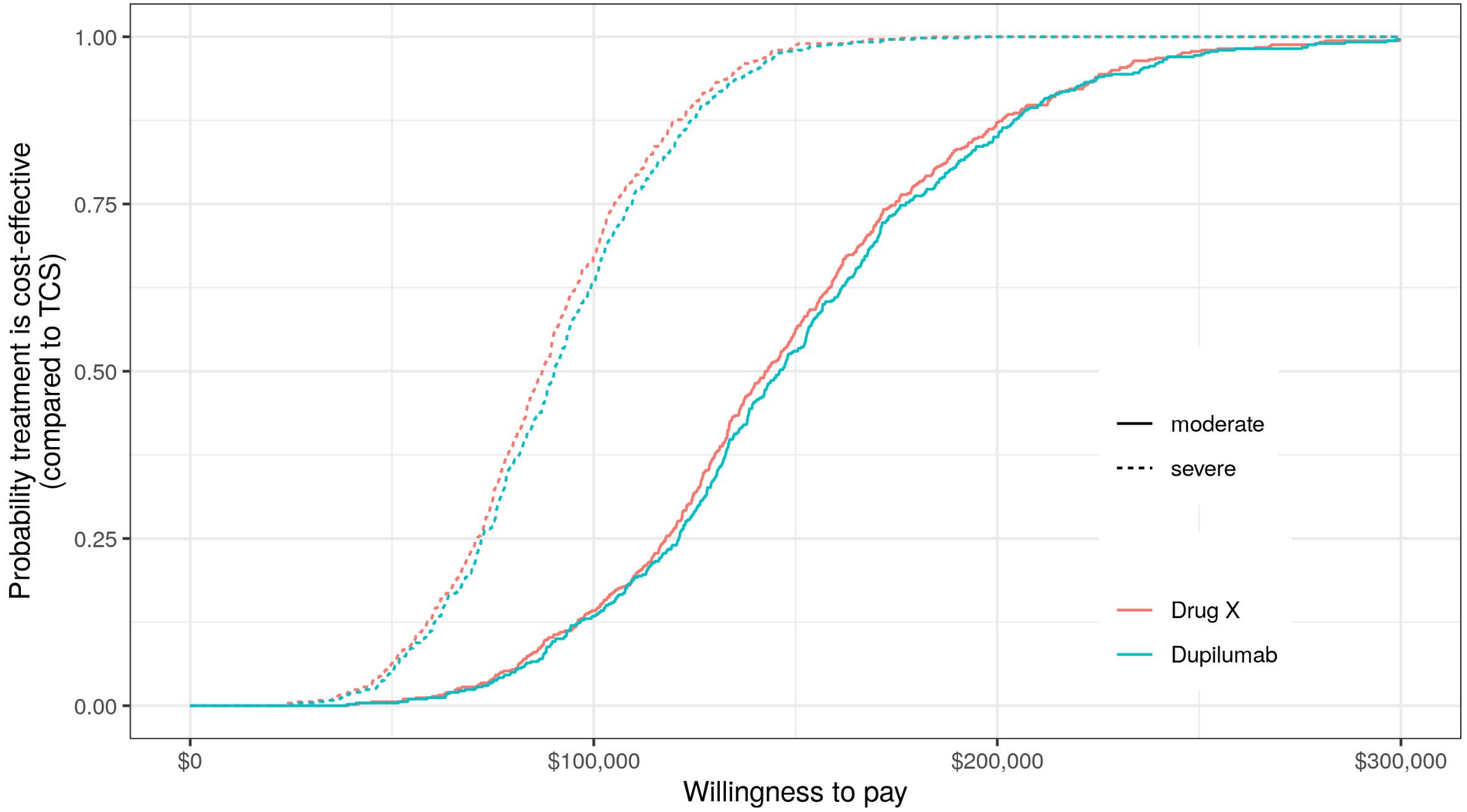


- Superior clinical efficacy translates into marginal differences in QALYs

Incremental Cost-Effectiveness Ratio (ICER)



Cost-Utility Analysis



Access to the Interactive Simulator

If you would like to explore the prototypical PMPE simulation app demonstrated in this session, please indicate **PMPE App** in the subject line and send your **name** and **email address** to:

training@metrumrg.com