A Novel Approach Using PMPE Model for Cost-effectiveness Analysis of Tacrolimus-Diltiazem Combination in Liver Transplant Patients: Evidence from Real-world Clinical Data

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Introduction of PMPE

Conventional Pharmacoeconomic Evaluation

Data Source

Real World Research

Early Clinical Trials

Phase III Trials

Real World Data

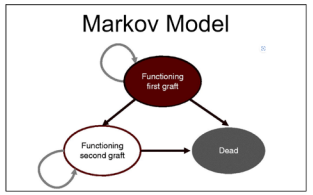
Relying on retrospective data

Difficult to predict and extrapolate

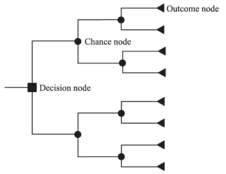
Pharmacoeconomic Evaluation

Pharmacoeconomic Model

Markov Model

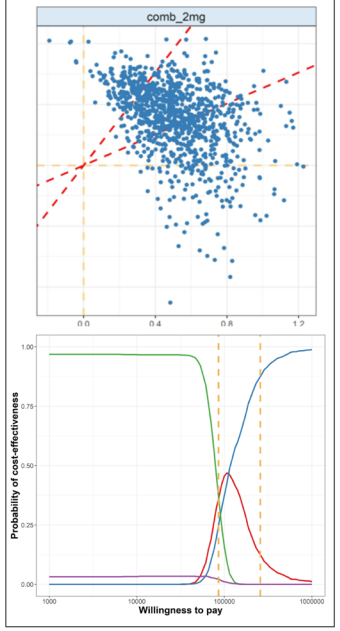


Decision Tree



Pharmacoeconomic Analysis

. Cost-effectiveness Analysis
. Cost-utility Analysis
. Cost-benefit Analysis



Conclude the comparative result

Introduction of PMPE

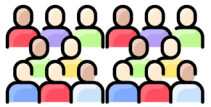
Pharmacometrics based Pharmacoeconomic Evaluation

Data Source

Real World Research

Early Clinical Trials

Phase III Trials



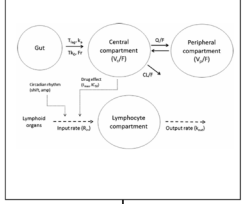
Real World Data

Vitual Clinical Trials

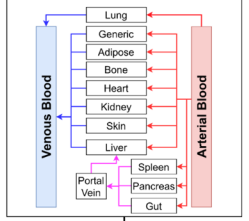
- Different Formulation
- Various Dosage Regimen
- Adherance and Non-adherence
- ...

Pharmacometrics Modeling

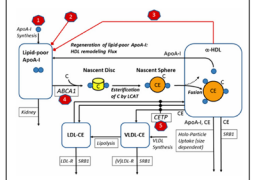
PK-PD Model



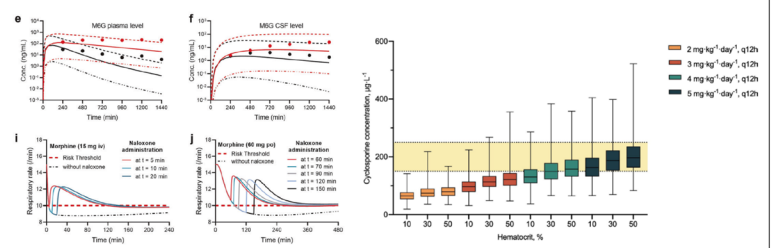
PBPK Model



Disease Model



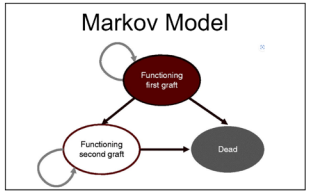
PK/PD Simulation



Pharmacoeconomic Evaluation

Pharmacoeconomic Model

Markov Model



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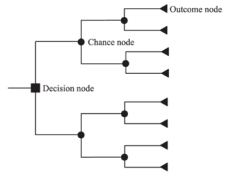

Pharmacoeconomic Analysis

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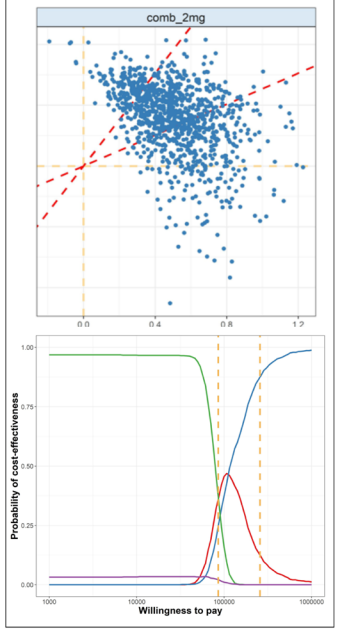
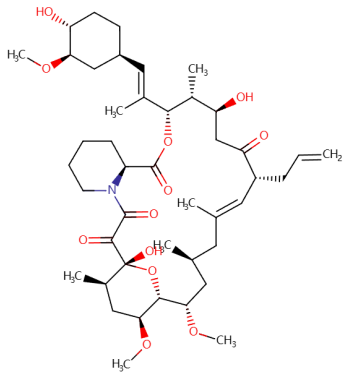


Optimize and select the optimal regimen

Why Tacrolimus?

Tacrolimus/TAC

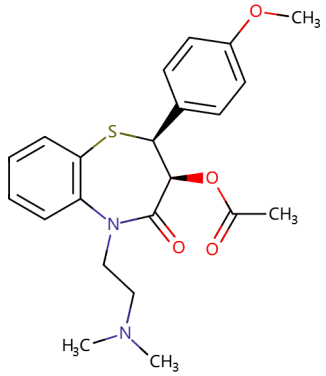
CYP3A4 substrate



+

Diltiazem/DTZ

CYP3A4 inhibitor



=

Exposure ↑

Price ↓

High Price

Dose	USA ($) Per tablet	CN ($) Per tablet
0.5 mg	3.88	1.87
1 mg	7.66	3.60

https://www.drugs.com/price-guide/prograf

No Study

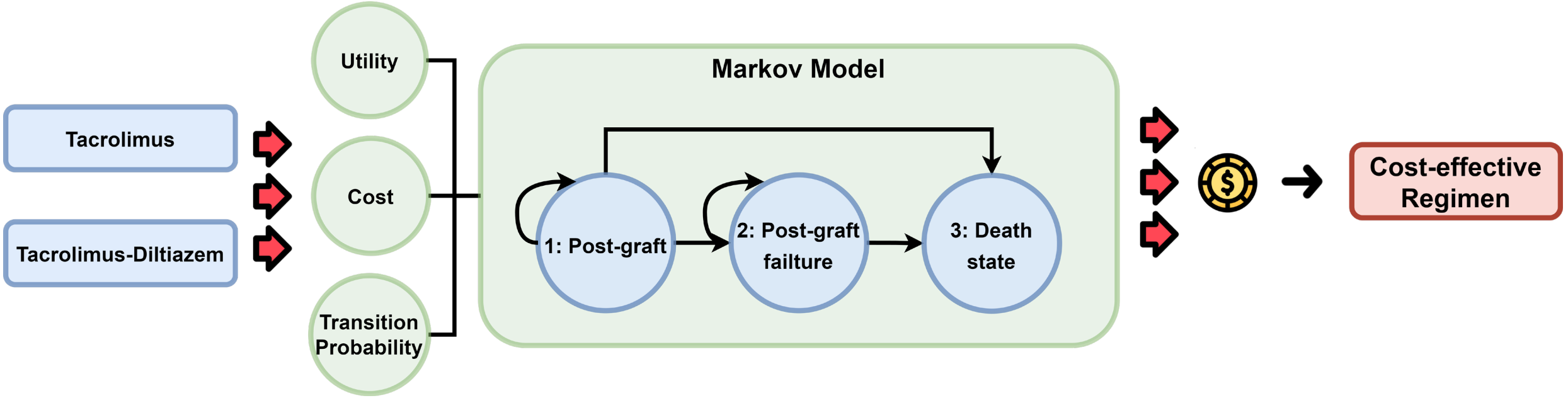
No cost-effective analysis of the combined use of tacrolimus-diltiazem

Real-world Data

- ✓ Total Patient (#) : 215
- ✓ Outcome (#):
  - Death: 40; Rejection: 19
- ✓ Transition (#):
  - Rejection → Death: 5
  - Post-graft → Death: 35

PE Model - Markov Model

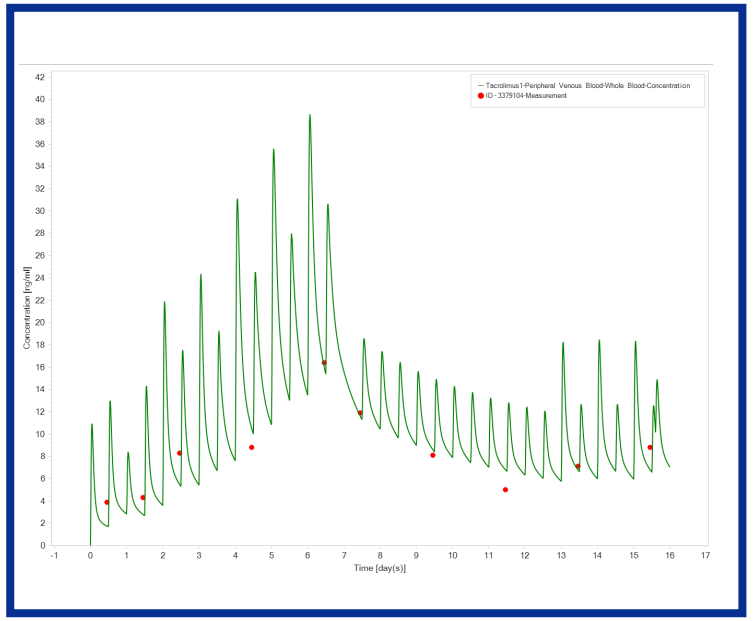
- General Flowchart for Conventional PE Evaluation

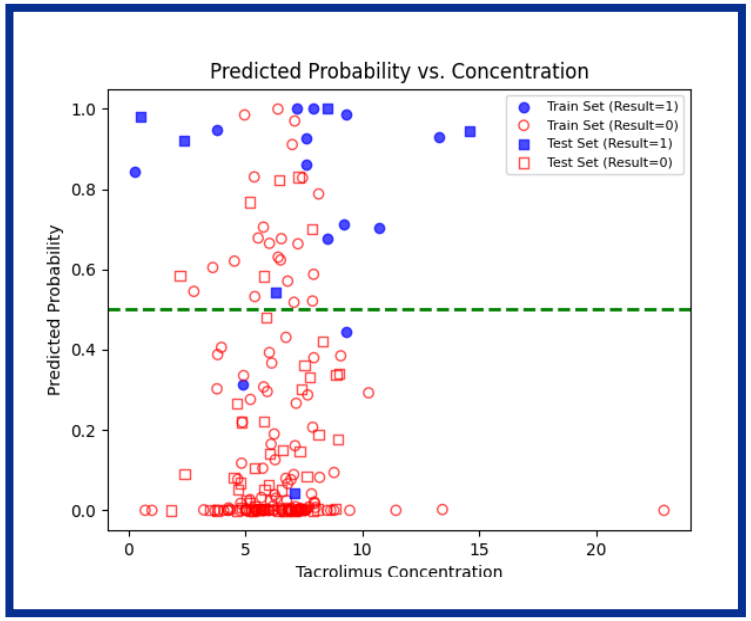


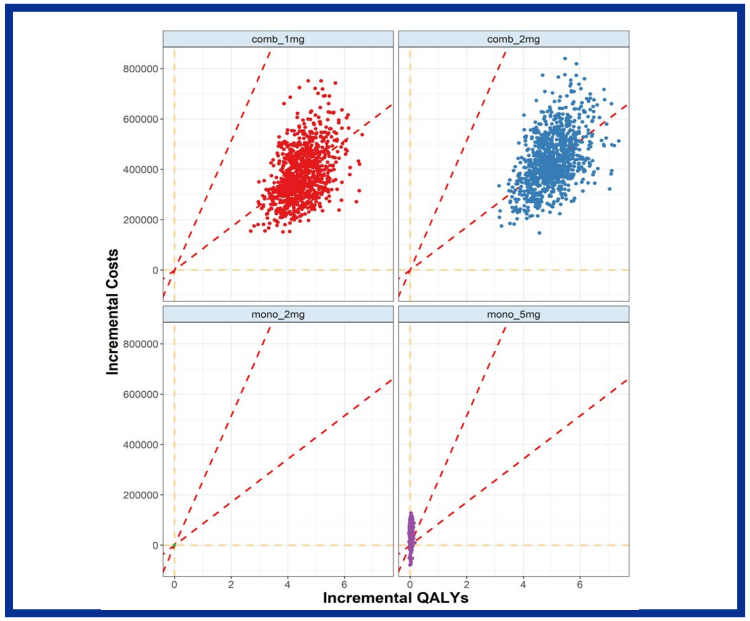
- How will Utility, Cost, Transition Probability, and Quality of Life change for untested regimens in clinical studies?
- Is there any unexplored but more cost-effective regimen?

Study Workflow

Dose → **PBPK model** → Conc → **PD model** → Graft failure ratio → **PE model** → Cost-effectiveness



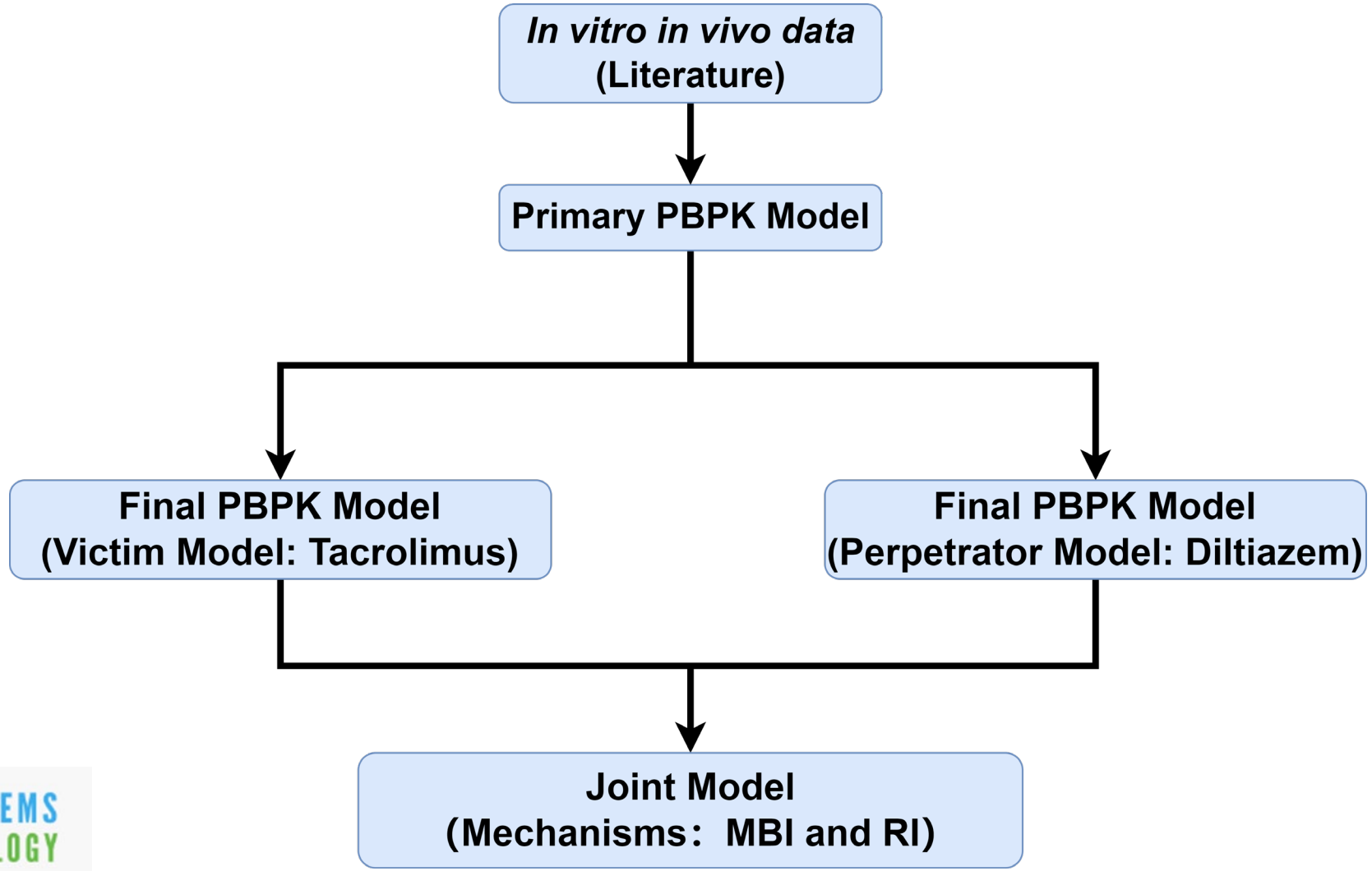




PBPK Simulation

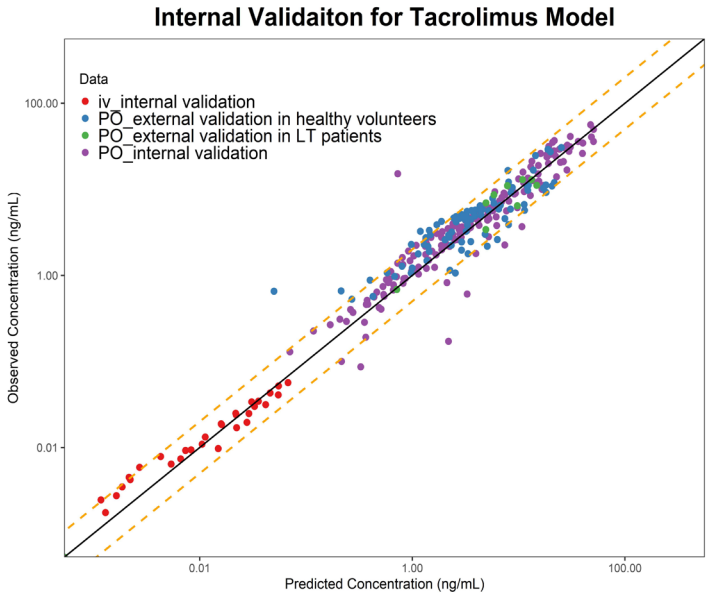
PD Simulation

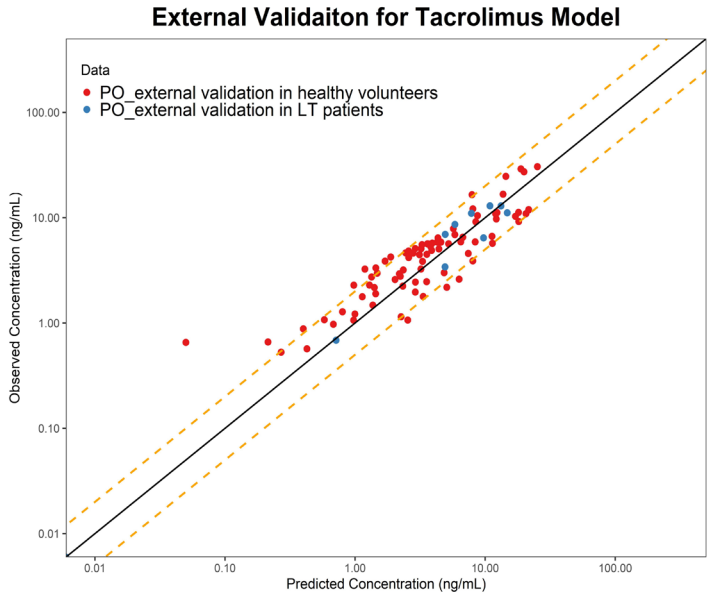
PBPK Model - Development

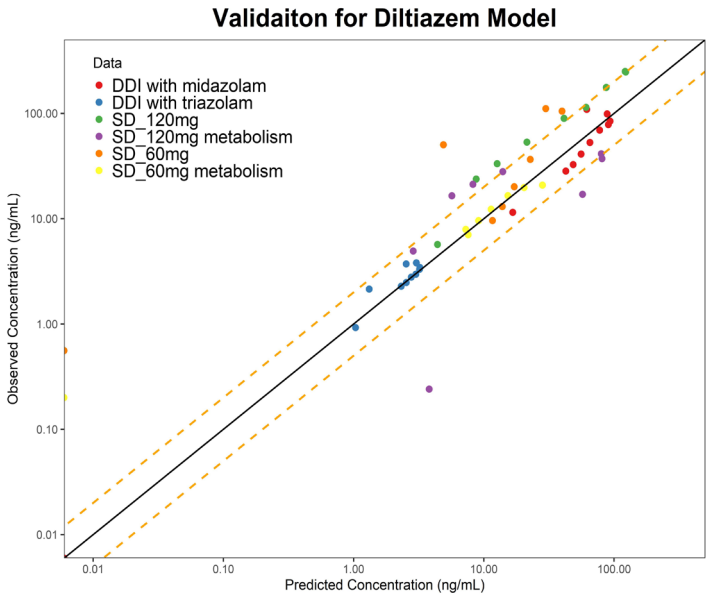


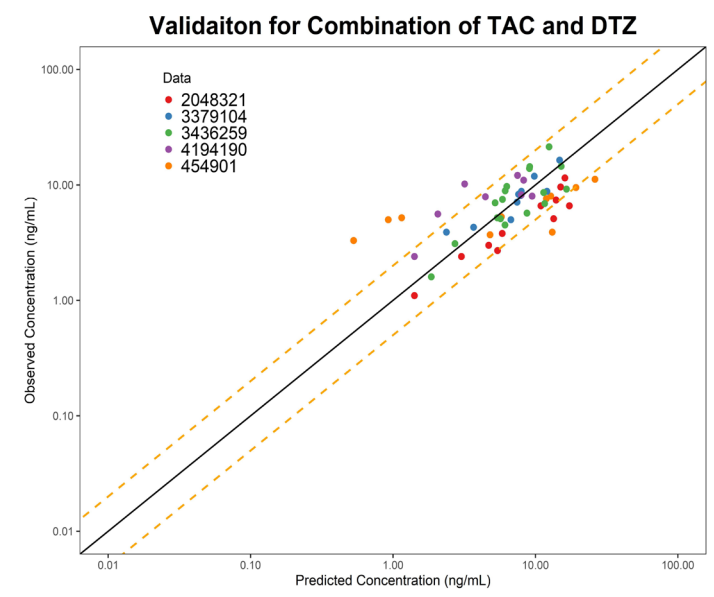
MBI: Mechanism-based Inhibition
RI: Reversible Inhibition

PBPK Model - Validation









PD Model - Development and Evaluation

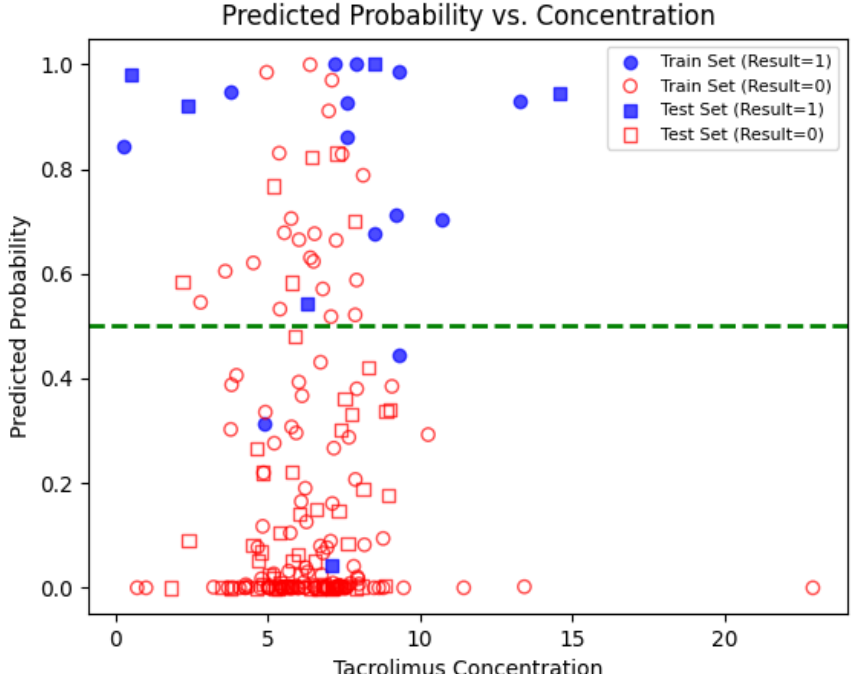
- PD outcome: Graft failure (**Binary**)
- PD analysis approach:

  Multivariate logistic regression
- WHY?
  - ✓ Handling multiple variables :

    Concentration, ALT, ALP, TBIL, GGT
  - ✓ Robust

- Average accuracy： 81.8%
- Confusion matrix:

	Negative	Positive	Accuracy
Negative	157	28	84.86%
Positive	3	16	84.21%



Visualization

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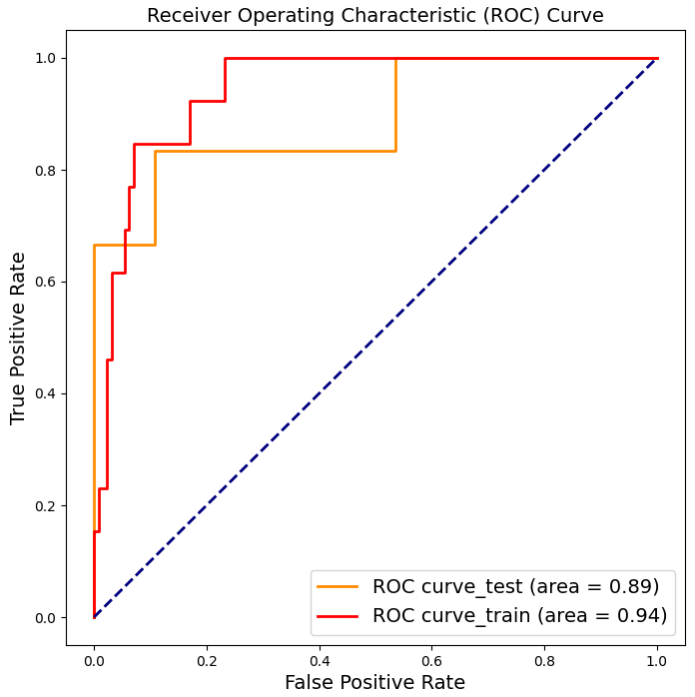


Visualization

PK-PD Model - Simulation

- Regimen 1-5： TAC Q12h 0.5,1, 2, 5, 7 mg
- Regimen 6-10： TAC Q12h 0.5, 1, 2, 5, 7 mg + DTZ Q12h 30 mg

Simulation outcome of different dosing regimens

	TAC		TAC - DTZ	
	PK simulation	PD simulation	PK simulation	PD simulation
Dose/mg	C_{trough} (ng/mL)	Graft failure ratio	C_{trough} (ng/mL)	Graft failure ratio
0.5	1.15	31%	2.50	26%
1	2.34	26%	5.15	15%
2	4.77	14%	10.89	8%
5	12.58	6%	31.03	3%
7	18.16	3%	46.43	2%

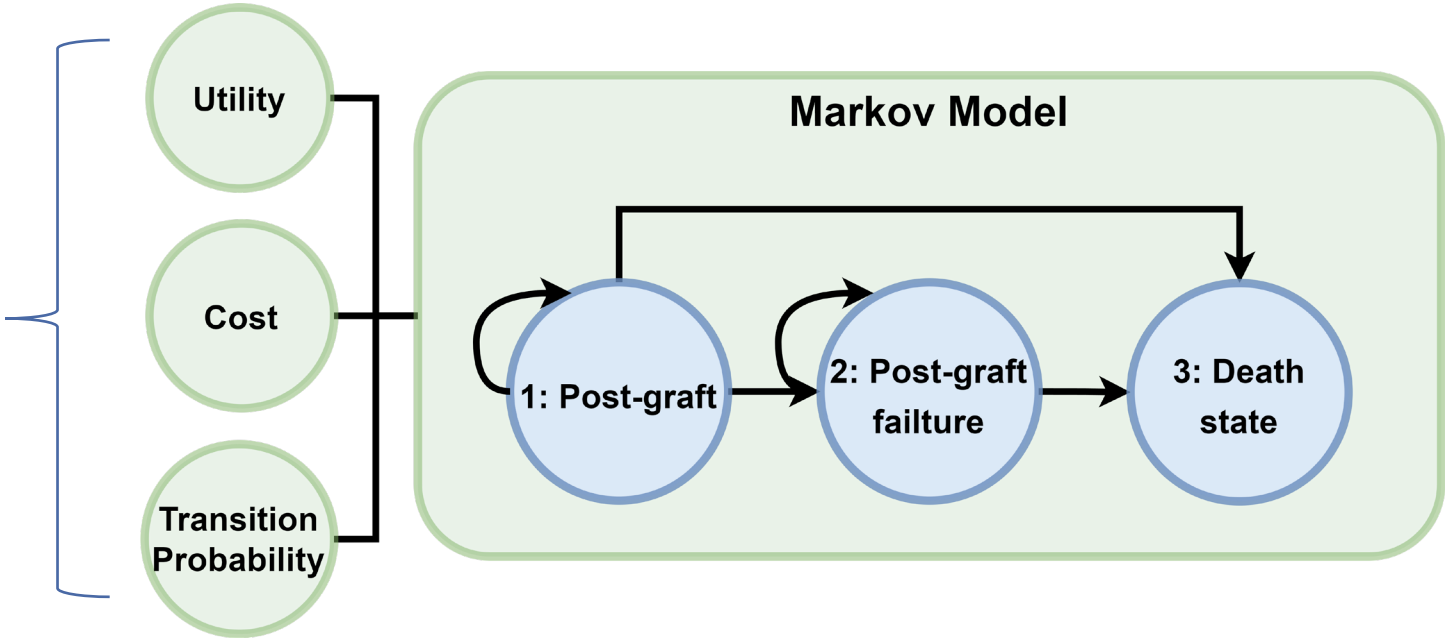
Selected Regimens

- Comb_1mg
- Mono_2mg
- Comb_2mg
- Mono_5mg

*Therapeutic range between 6-12 ng/mL, as recommended by clinical guideline *Diagnosis and treatment specification for immunosuppressive therapy and rejection of liver transplantation in China (2019 edition)*

Conceptual Framework - Markov Model

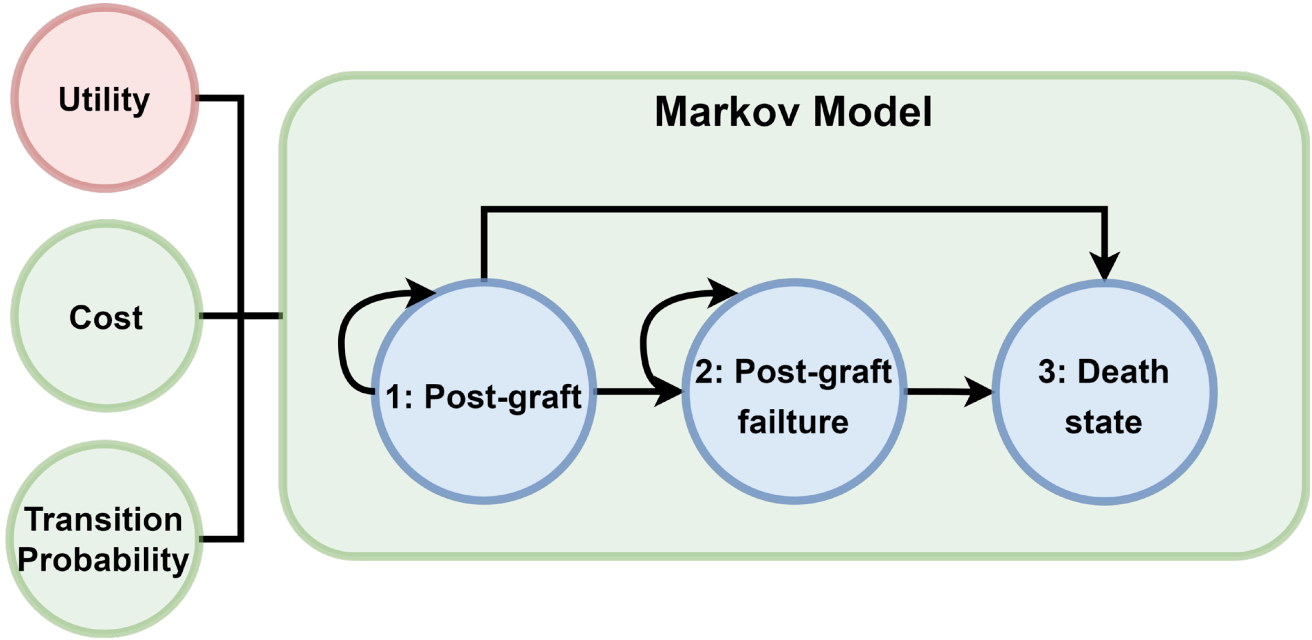
Key inputs for Markov Model



PE Model - Development

Utility

	Value
Post-graft(0-1 year)	0.7
Post-graft(1-10 years)	0.8
Post-graft failure(0-1 year)	0.6
Post-graft failure(1-10 years)	0.7

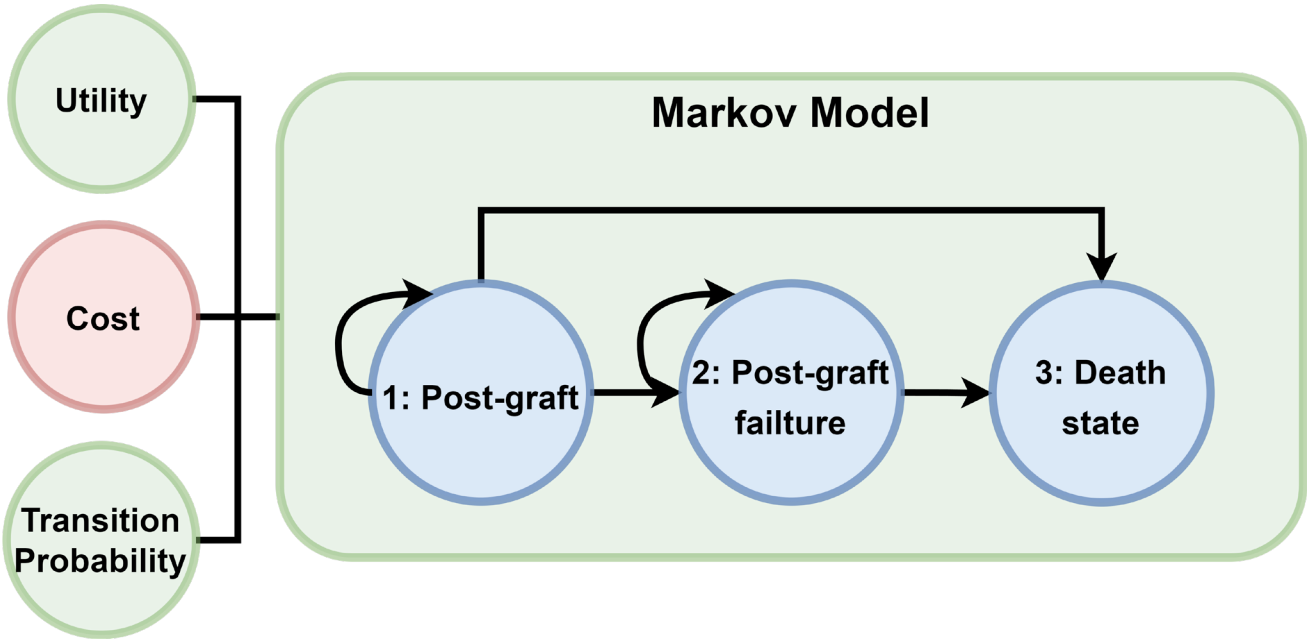


Tajima T. et al. *Hepatol Res*. 2024; 54(5): 465–78.

PE Model - Development

Cost

Cost		CN ($)
Drug	Tacrolimus (0.5 mg)	1.87 each pill
	Tacrolimus (1 mg)	3.60 each pill
	Diltiazem (30 mg)	0.05 each pill
Other	Liver transplantation (0-1 year)	37915.54
	After liver transplantation (1-10 years)	8896.91 per year
	Hospitalization of rejection	40087.52



Su S et al. Lancet Glob Health. 2022 Feb;10(2):e278-e287.

PE Model - Development

Transition Probability

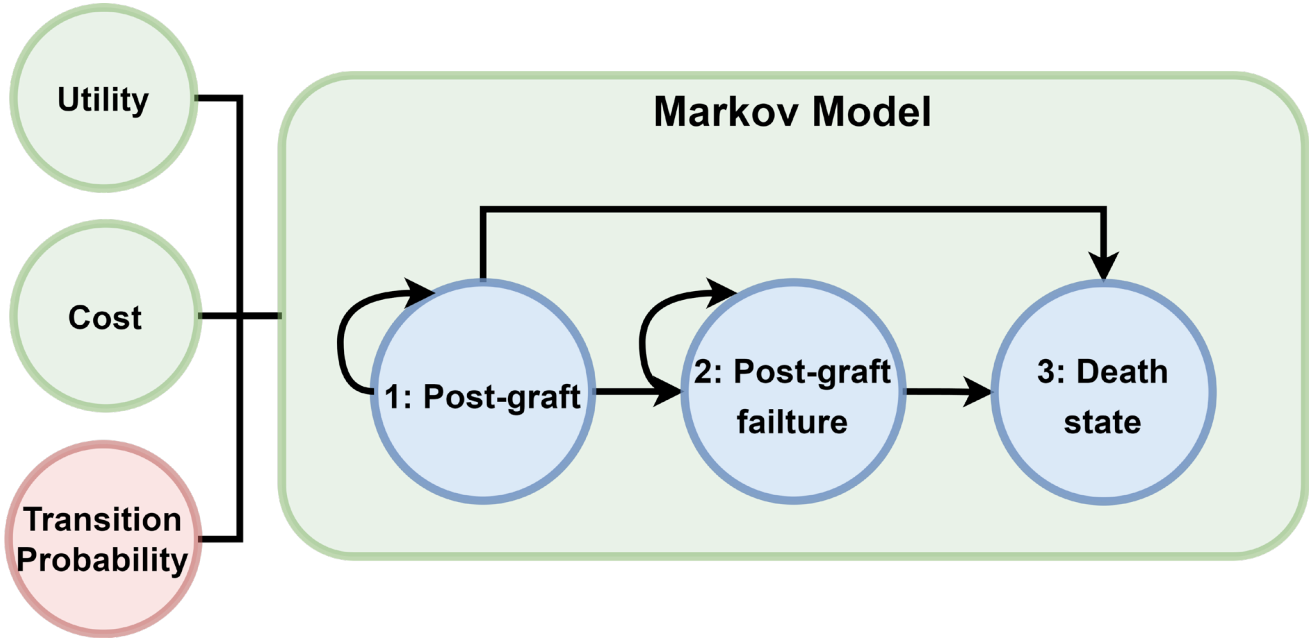
Tacrolimus

	Post-graft	Graft failure	Death
Post-graft	C*	PKPD Results	0.25
Graft failure	/	0.77	0.23
Death	/	/	1

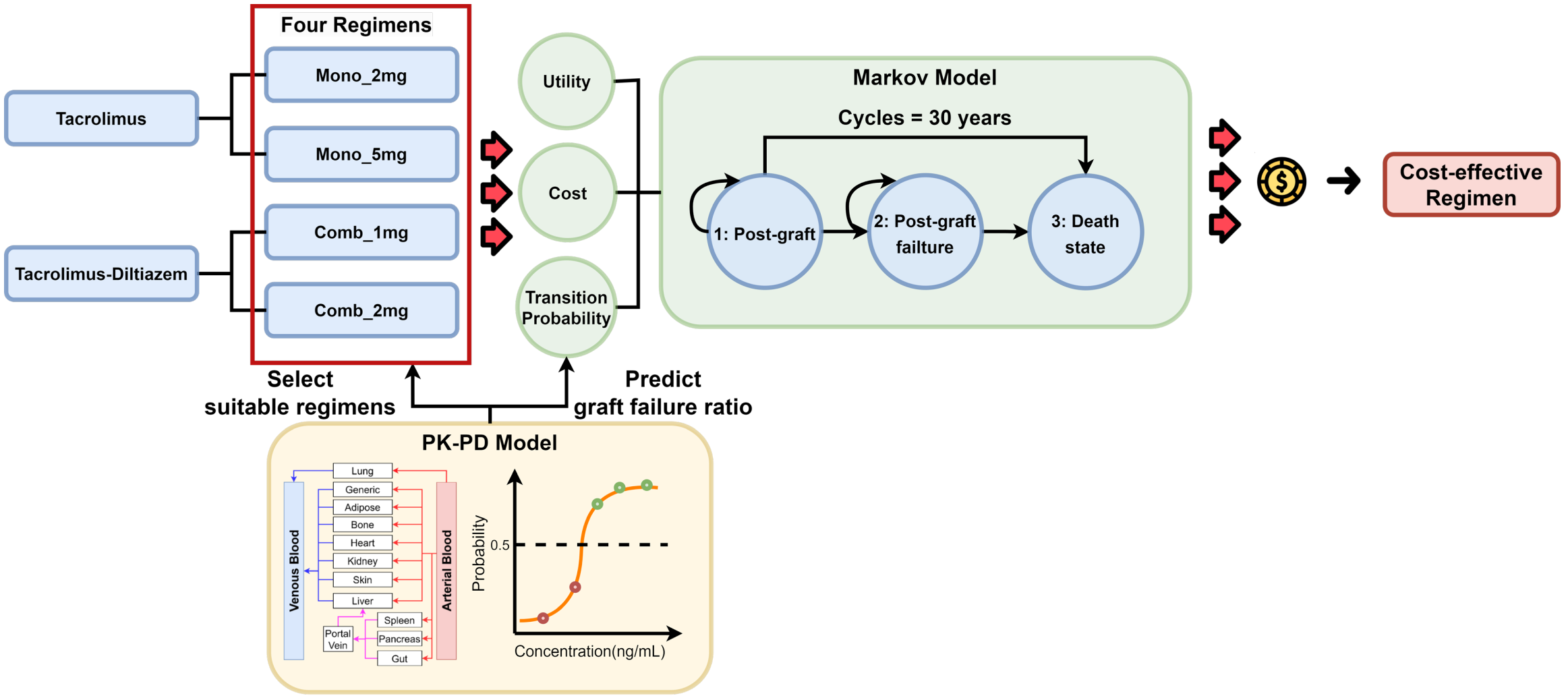
Tacrolimus -Diltiazem

	Post-graft	Graft failure	Death
Post-graft	C*	PKPD Results	0.07
Graft failure	/	0.78	0.22
Death	/	/	1

* C is an alias for the probability complement, 1 minus the sum of probabilities in a given row.



Integrating PM-PE Model - Simulation



PE Evaluation - Outcomes

- Comparison results of base and alternative regimens

Regimen compared	Ref	Δ Cost ($)	Δ LYs[c]	Δ Effect	ICER[d]	More cost-effective
Mono[a]_5mg vs Mono[a]_2mg	Mono_2mg	4,537.1	-0.07	0.02	191,406.9	Mono[a]_2mg
Comb[b]_1mg vs Mono[a]_2mg	Mono_2mg	52,468.8	3.54	2.7	19,729.7	Comb[a]_1mg
Comb[b]_2mg vs Comb[b]_1mg	Comb_1mg	3,367.16	0.98	1.0	3,334.34	Comb[b]_2mg

[a]: Administered alone
[b]: Combination
[c]: Life year
[d]: Incremental cost-effectiveness ratio

$$ICER = \frac{\Delta\, Cost}{\Delta\, Effect}$$

Monotherapy 5mg < Monotherapy 2mg < Combination 1mg* < Combination 2mg*

*dosage for tacrolimus. Diltiazem dose was fixed at 30mg

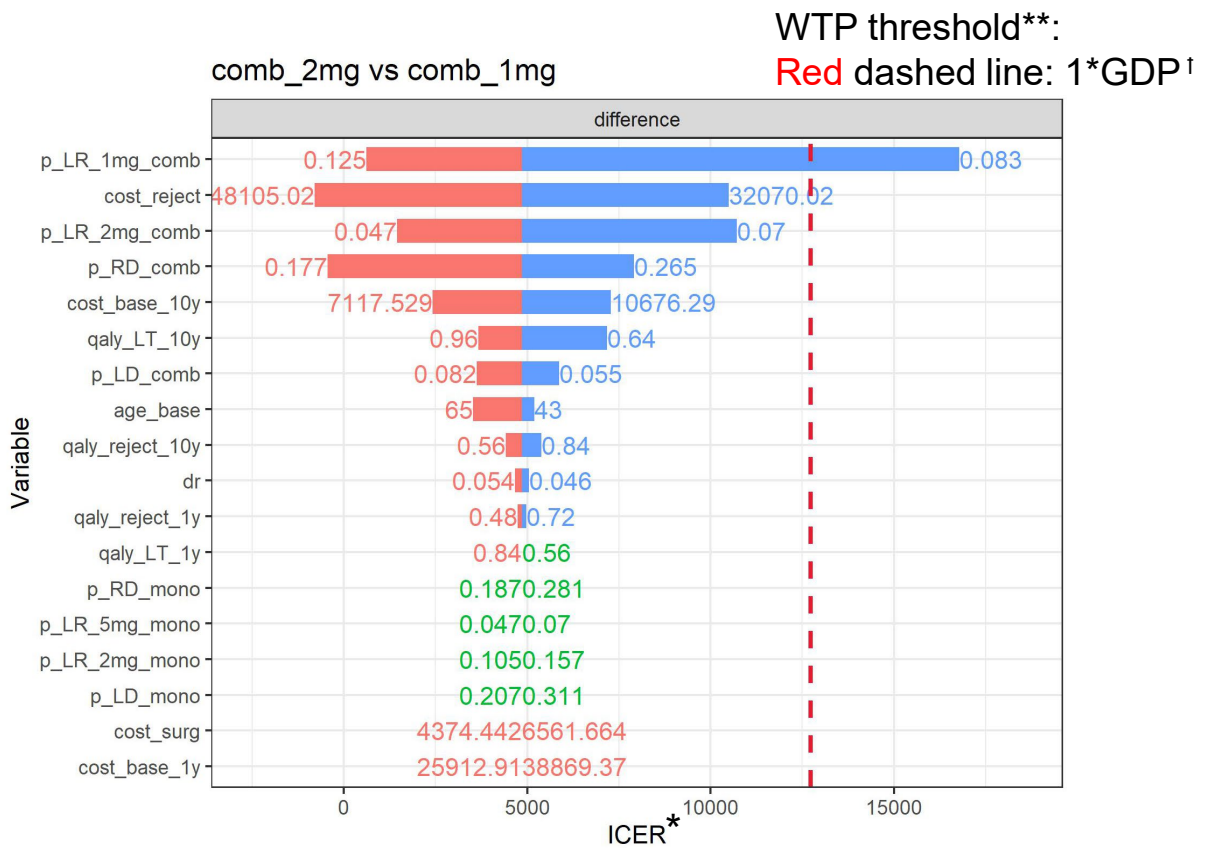
PE Evaluation - DSA

Deterministic Sensitivity Analysis, DSA

- Parameter values are changed one by one

Sensitivity Analysis Range of Parameters

- Cost, utility, and transition probability: - 20% ~ +20%
- Discount rate: 0 - 8%



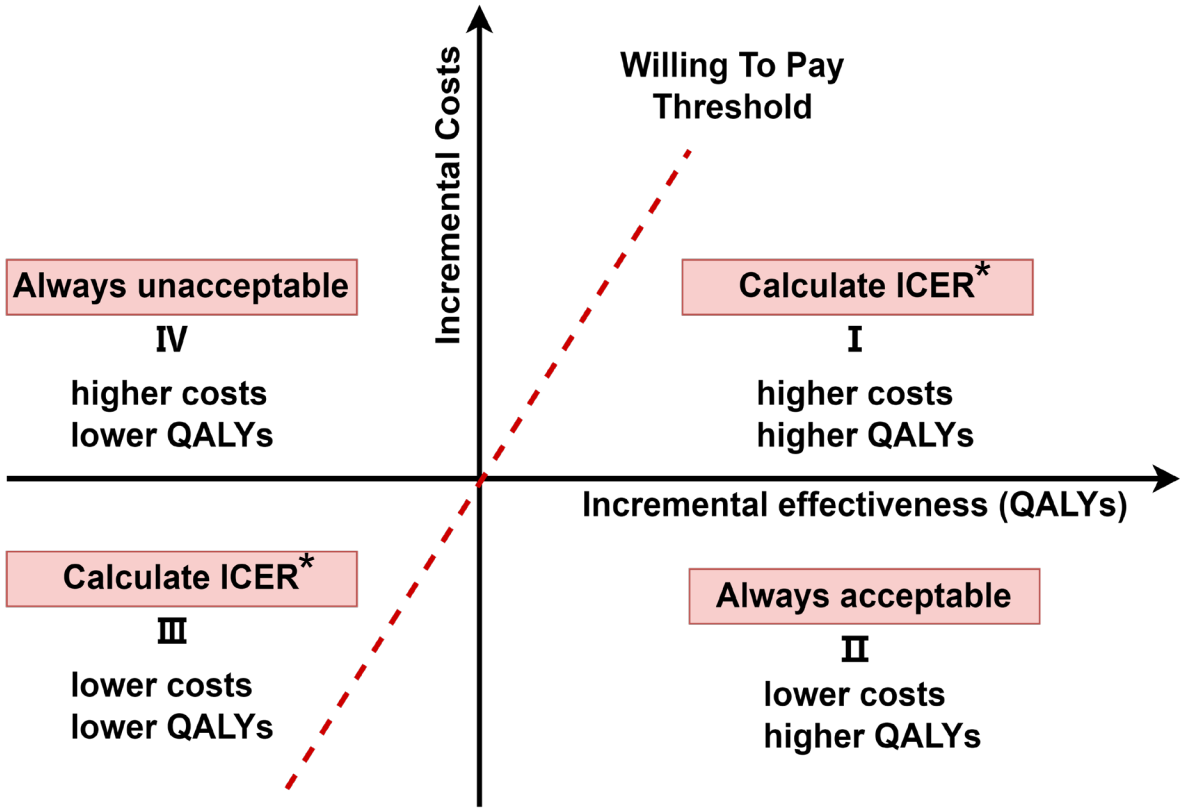
- **Transition probability from post-graft to post-graft failure is the most sensitive parameter**
- **The change of parameters does not reverse the outcome**

* Incremental cost-effectiveness ratio, ** Willing-to-pay threshold, † Gross domestic product

PE Evaluation - PSA

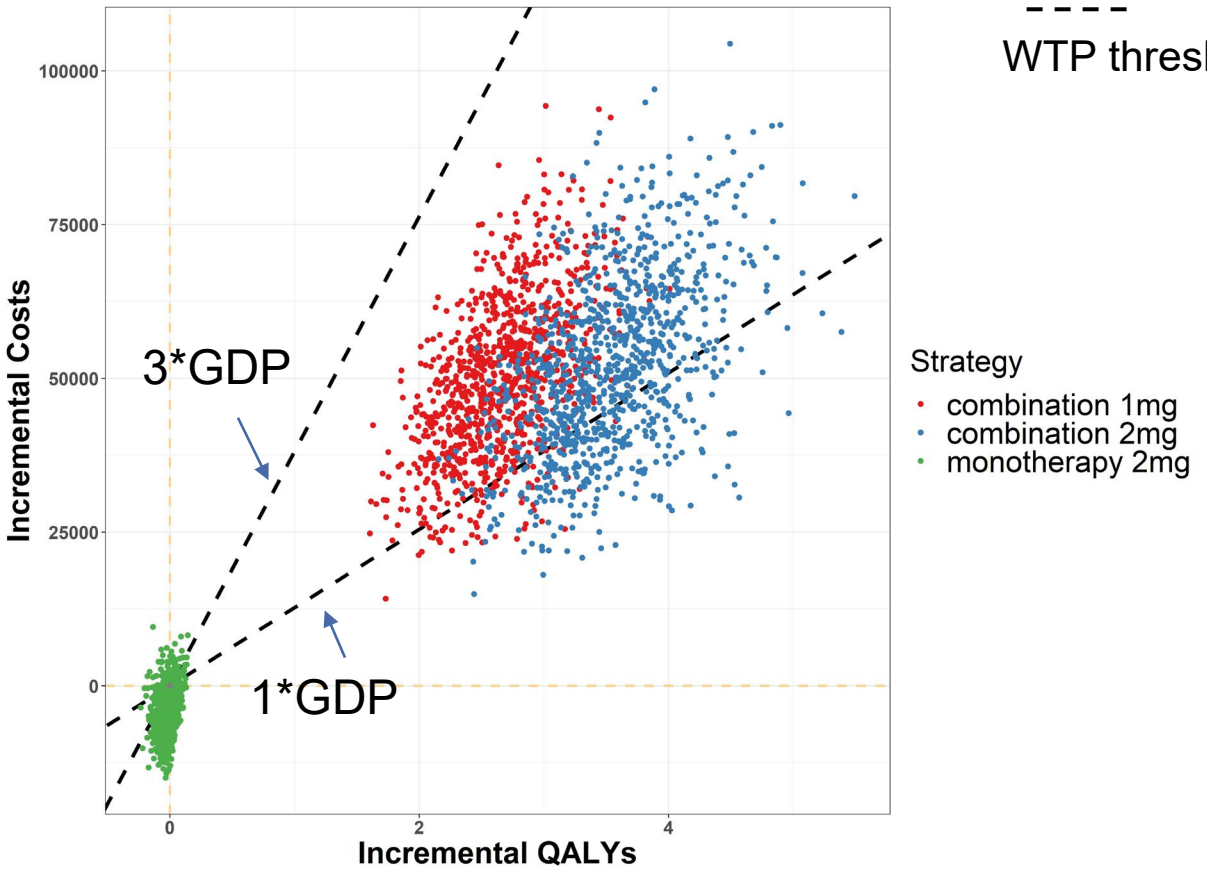
Probabilistic Sensitivity Analysis, PSA:

- A probability distribution is assigned to each parameter, reflecting uncertainty and correlation

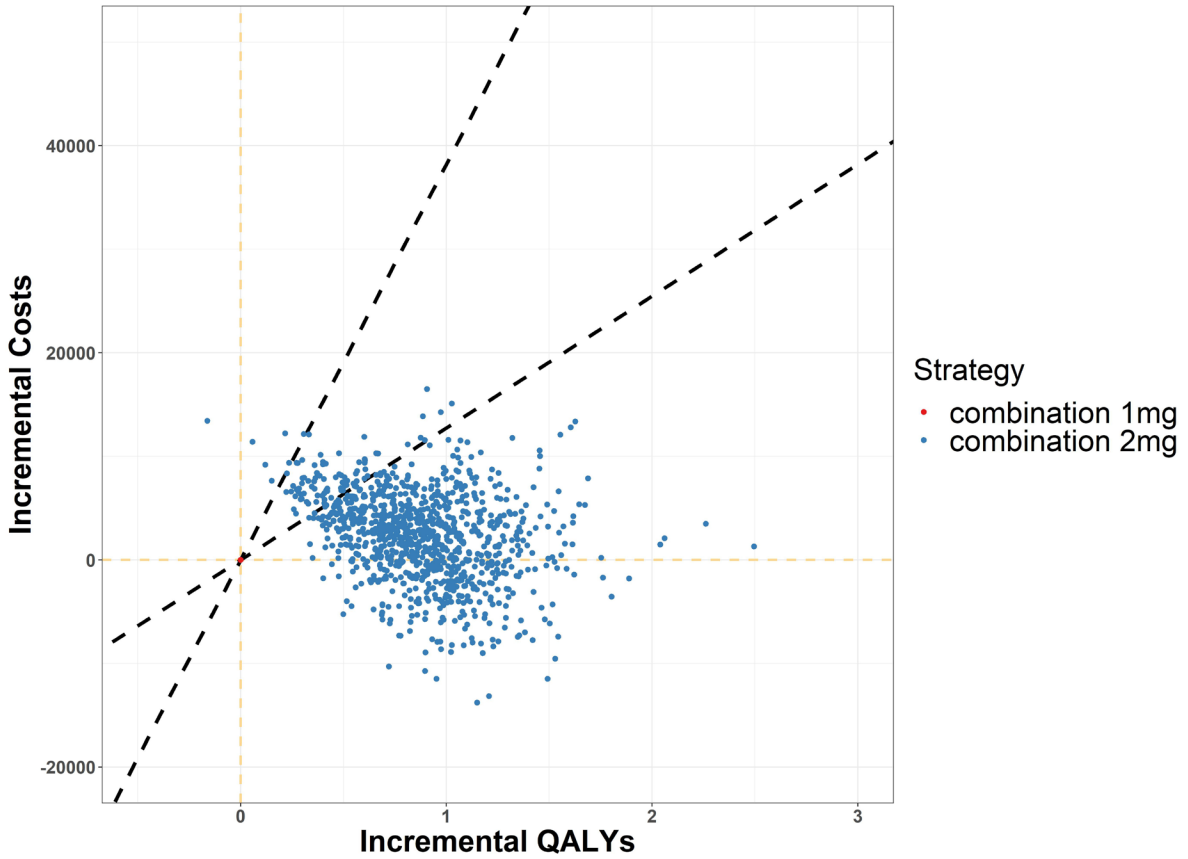


* Incremental cost-effectiveness ratio

PE Evaluation - PSA



*monotherapy 5mg as the comparator



*combination 1mg as the comparator

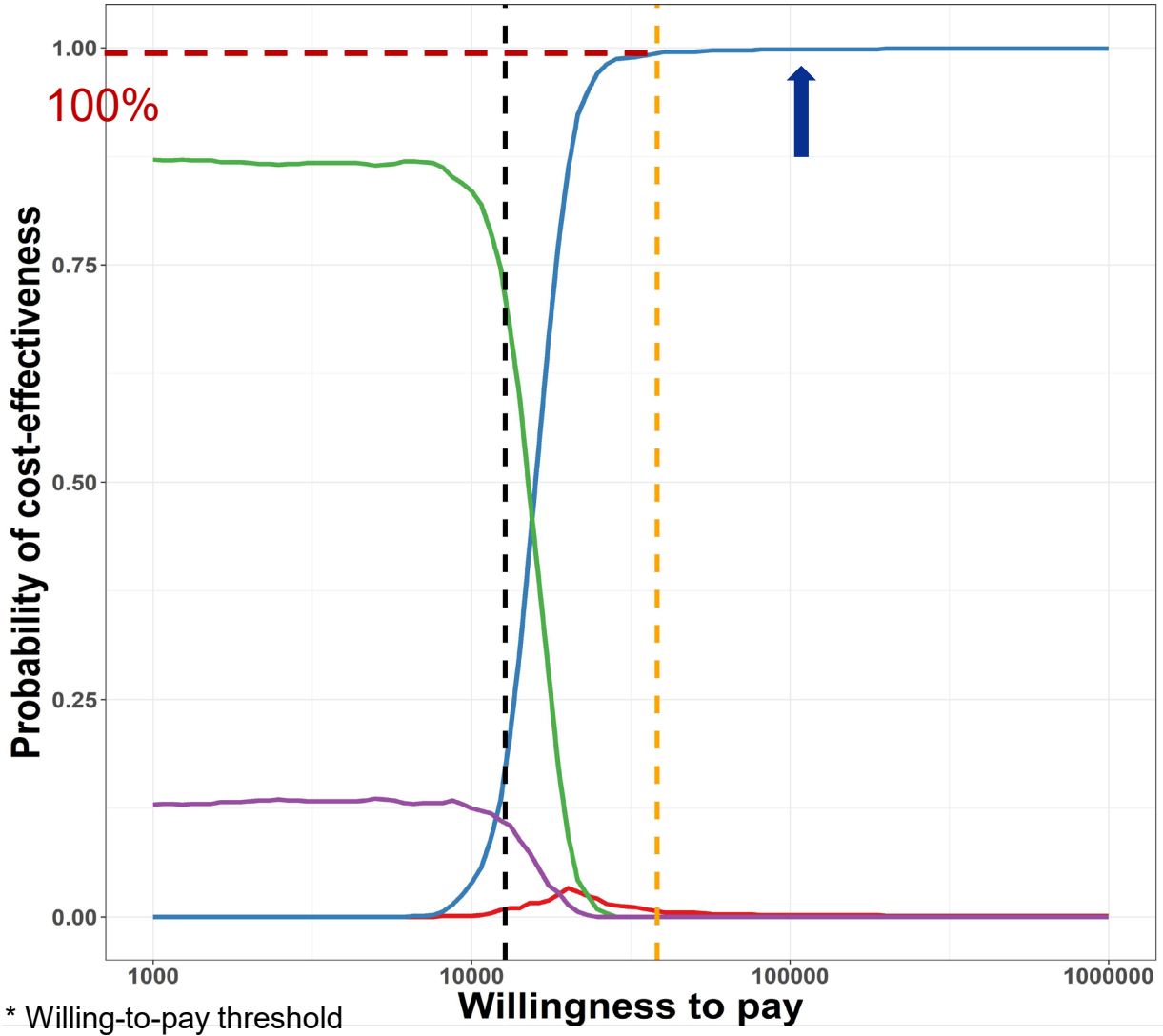
Both two combination therapies were cost-effective

Combination 2mg regimen is more cost-effective in most simulations

* Willing-to-pay threshold

PE Evaluation - CEAC

Cost-effectiveness Acceptability Curves, CEAC



WTP threshold*:
Black dashed line: 1*GDP
Orange dashed line: 3*GDP

Strategy
- combination 1mg
- combination 2mg
- monotherapy 2mg
- monotherapy 5mg

2/30 mg TAC-DTZ regimen has an almost 100% probability of being cost-effective at WTP threshold value of 3*GDP

* Willing-to-pay threshold

Conclusion

- How will Utility, Cost, Transition Probability, and Quality of Life change for untested regimens in clinical studies?
- Is there any unexplored but more cost-effective regimen?

✓ PMPE model predicts the specific change for different simulated regimens.

✓ Combination treatment in graft failure prevention, particularly the 2/30 mg TAC-DTZ regimen could be more cost-effective.

Acknowledgements

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- Stella Xu & & Min Chen & Xinyue Zhang
- Other group members

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Thanks for your attention!

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