Evaluating dynamic treatment strategies

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Objectives

- Define dynamic treatment strategies
- Describe when g-methods are needed
- Review an application of the parametric g-formula to cancer research
  - Causal inference perspective
- Discuss the AI Clinician
  - Reinforcement learning perspective

WHAT ARE DYNAMIC TREATMENT STRATEGIES?

Treatment strategies

Point interventions	Sustained strategies	
	Static	Dynamic
		
1. Initiate treatment at baseline 2. Do not initiate treatment at baseline	1. Initiate treatment at baseline and continue over follow-up 2. Do not initiate treatment over follow-up	1. Initiate treatment at baseline and continue over follow-up, unless a contraindication occurs 2. Do not initiate treatment over follow-up, unless an indication occurs

Dynamic treatment strategies

- Take into consideration a patient's evolving characteristics before making a decision
  - Decisions about prevention, screening, or treatment interventions over time may depend on evolving comorbidities, screening results, or treatment toxicity
- Strategies in clinical guidelines and practice are often dynamic
- The optimal strategies will be dynamic

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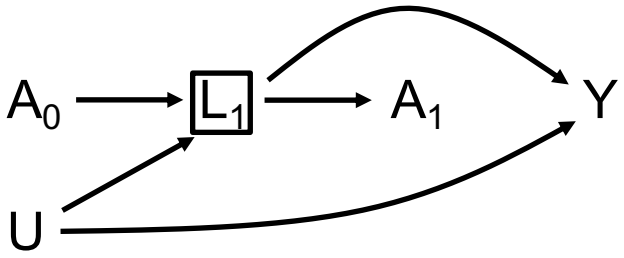
WHEN ARE G-METHODS NEEDED?

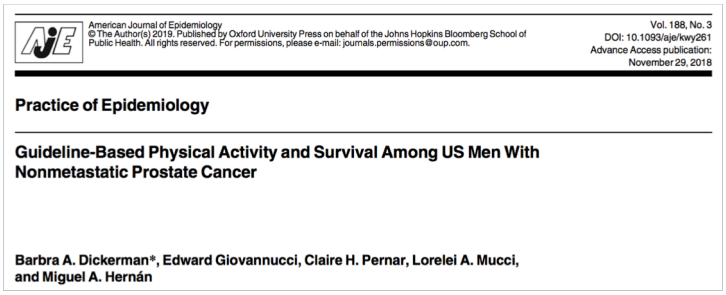
Conventional statistical methods cannot appropriately compare dynamic strategies with treatment-confounder feedback



A_t	Vasopressors
L_1	Systolic blood pressure
Y	Survival
U	Disease severity

G-methods

- Parametric g-formula
- G-estimation of structural nested models
- Inverse probability weighting of marginal structural models



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Practice of Epidemiology

Guideline-Based Physical Activity and Survival Among US Men With Nonmetastatic Prostate Cancer

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CASE STUDY: PHYSICAL ACTIVITY AND SURVIVAL AMONG MEN WITH PROSTATE CANCER

Case study: Physical activity and survival among men with prostate cancer

Question

- What is the effect of adhering to guideline-based physical activity strategies on survival among men with nonmetastatic prostate cancer?

Data

- Health Professionals Follow-up Study (HPFS)

Physical activity and survival among men with prostate cancer

Eligibility criteria	• Diagnosed with nonmetastatic prostate cancer at age 50-80 between 1998-2010 • No cardiovascular/neurological condition limiting physical ability • Data on all potential confounders measured in the past 2 years
Treatment strategies	Initiate 1 of 6 physical activity strategies at diagnosis and continue it over follow-up until the development of a condition limiting physical ability
Follow-up	Starts at diagnosis and ends at death, loss to follow-up, 10 years after diagnosis, or administrative end of follow-up (June 2014), whichever happens first
Outcome	All-cause mortality within 10 years of diagnosis
Causal contrast	Per-protocol effect
Statistical analysis	Parametric g-formula

Parametric g-formula

- Generalization of standardization to time-varying exposures and confounders
- Conceptually, the g-formula risk is a **weighted average of risks** conditional on a specified intervention history and observed confounder history
  - The **weights** are the probability density functions of the time-varying confounders, estimated using parametric regression models
  - The weighted average is approximated using Monte Carlo simulation

Steps of the parametric g-formula

1. **Fit parametric regression models** for treatment, confounders, and death at each follow-up time *t* as a function of treatment and covariate history among those under follow-up at time *t*
2. **Monte Carlo simulation** to generate a 10,000-person population under each strategy by sampling with replacement from the original study population (to estimate the standardized cumulative risk under a given strategy)
3. **Repeat in 500 bootstrap samples** to obtain 95% confidence intervals (CIs)

Estimated risk of all-cause mortality under several physical activity strategies

All strategies excuse men from following the recommended physical activity levels after development of metastasis, MI, stroke, CHF, ALS, or functional impairment

Strategy	10-year risk (%)	95% CI	Risk ratio	95% CI
No intervention	15.4	(13.3, 17.7)	1.0	--
Vigorous activity				
≥1.25 h/week	13.0	(10.9, 15.4)	0.84	(0.75, 0.94)
≥2.5 h/week	11.1	(8.7, 14.1)	0.72	(0.58, 0.88)
≥3.75 h/week	10.5	(8.0, 13.5)	0.68	(0.53, 0.85)
Moderate activity				
≥2.5 h/week	13.9	(12.0, 16.0)	0.90	(0.84, 0.94)
≥5 h/week	12.6	(10.6, 14.7)	0.81	(0.73, 0.88)
≥7.5 h/week	12.2	(10.3, 14.4)	0.79	(0.71, 0.86)

Potential unmeasured confounding by chronic disease (*i.e.* reverse causation)

- Severe enough to affect both physical activity and risk of death
- G-formula provides a natural way to partly address this
  - By estimating risk under physical activity interventions that are only applied at each time point to those who are sufficiently healthy at that time
  - Main analysis: excused men from following the intervention after developing metastasis, MI, stroke, CHF, ALS, or functional impairment

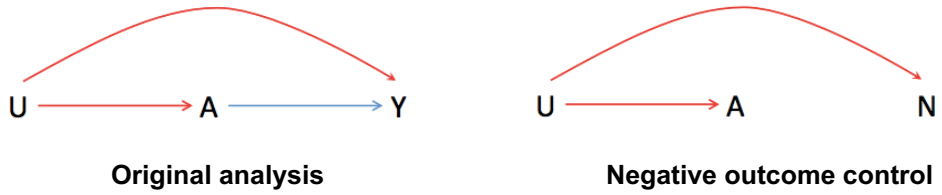
Sensitivity analyses for unmeasured confounding: Expanded definition of "serious condition"

All strategies excuse men from following the recommended physical activity levels after development of metastasis, MI, stroke, CHF, ALS, or functional impairment, angina pectoris, pulmonary embolism, heart rhythm disturbance, diabetes, chronic renal failure, rheumatoid arthritis, gout, ulcerative colitis or Crohn's disease, emphysema, Parkinson's disease, and multiple sclerosis

Strategy	10-year risk (%)	95% CI	Risk ratio	95% CI
No intervention	15.5	(13.8, 17.4)	1.0	--
Vigorous activity				
≥1.25 h/week	14.2	(12.4, 16.2)	0.92	(0.85, 0.97)
≥2.5 h/week	13.1	(11.2, 15.3)	0.84	(0.75, 0.93)
≥3.75 h/week	12.8	(10.9, 14.9)	0.83	(0.72, 0.92)
Moderate activity				
≥2.5 h/week	14.3	(12.7, 16.4)	0.93	(0.89, 0.96)
≥5 h/week	13.7	(11.9, 15.6)	0.89	(0.83, 0.92)
≥7.5 h/week	13.4	(11.8, 15.5)	0.87	(0.81, 0.91)

Sensitivity analyses for unmeasured confounding: Lag and negative outcome control

- **Lagged** physical activity and covariate data by two years
- **Negative outcome control** to detect potential unmeasured confounding by clinical disease
  - Questionnaire non-response



Original analysis **Negative outcome control**

G-methods let us validly estimate the effect of pre-specified dynamic strategies

- And estimate adjusted absolute risks
  - Appropriately adjusted survival curves
  - Not only hazard ratios
  - Even in the presence of treatment-confounder feedback
- Under the assumptions of exchangeability, consistency, positivity, no measurement error, no model misspecification
- Powerful approach to estimate the effects of currently recommended or proposed strategies
- But, these pre-specified strategies may not be the optimal strategies

ARTICLES
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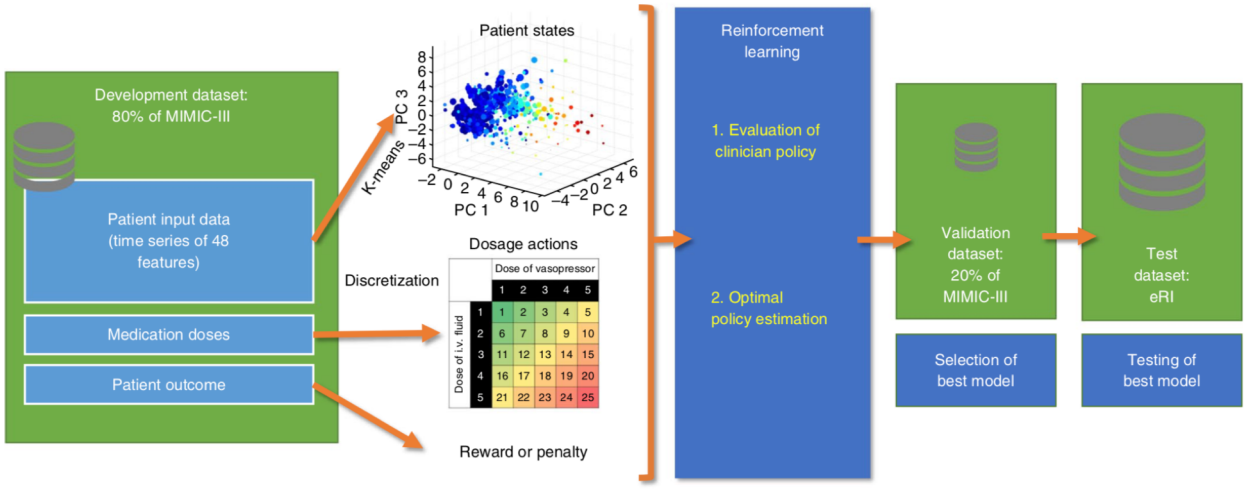
nature medicine

The Artificial Intelligence Clinician learns optimal treatment strategies for sepsis in intensive care

Matthieu Komorowski[1,2,3], Leo A. Celi[3,4], Omar Badawi[3,5,6], Anthony C. Gordon[1*] and A. Aldo Faisal[2,7,8,9*]

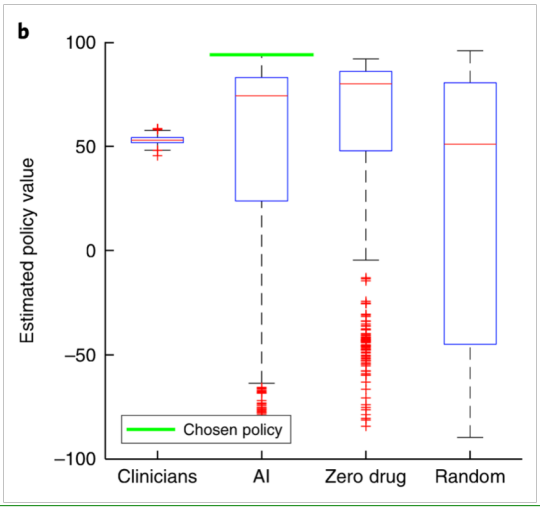
DISCUSSION: THE AI CLINICIAN

Figure 1 Data flow of the AI Clinician



Komoroski et al. *Nat Med* 2018

Figure 2b Distribution of the estimated value of the clinicians' actual treatments, the AI policy, a random policy and a zero-drug policy across the 500 models in the MIMIC-III test set (*n* = 500 models in each boxplot).



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Discussion

- Study overview
- System representation
- Policy evaluation
- Interpretability
- Future directions