Generalized pairwise comparisons for precision medicine

Tomasz Burzykowski
IDDI & Hasselt University, Belgium
tomasz.burzykowski@iddi.com

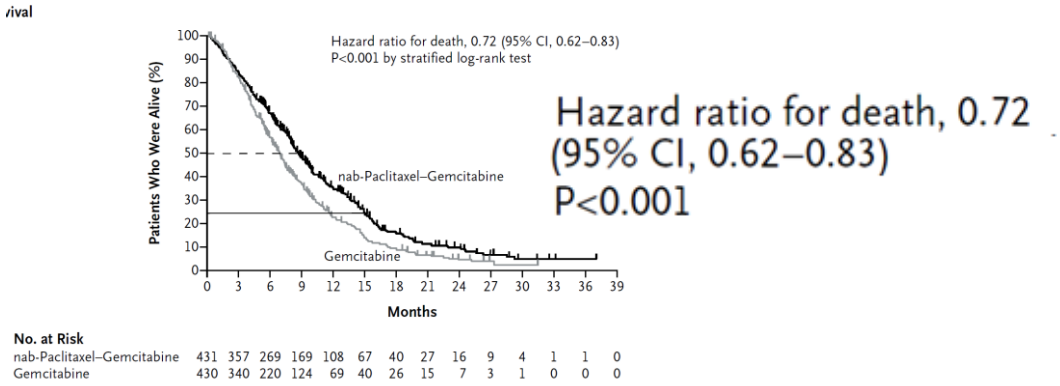
Personalizing Treatment Choices

- *Evidence-based medicine*
  - (Meta-analyses of) randomized control trials
  - Subgroup analyses, if appropriate
- *Precision medicine*

  "Giving the right treatment to the right patient at the right time"
- *Personalized medicine*
  - Precision medicine with personalized/patient-centric choices for therapeutic decisions

An Unmet Statistical Need

Consider the following results



Worst grade related AE	Monotherapy (n=430)	Combination (n=431)
Grade 3 Grade 4	**23%**	**54%**

A patient might reason:

- Taking combination, I'm more likely to live longer (by how much?)
- Taking combination, I'm more likely to have grade 3/4 adverse events (AEs)
- I'm willing to experience AEs for a survival benefit of at least *m* months…

Von Hoff et al, N Engl J Med 2013;369:1691

Limitations of Standard Analyses

- A single (primary) endpoint drives decision-making
- Other endpoints are analyzed descriptively
- Safety informally balanced against efficacy, resulting in debatable risk / benefit analyses
- Patient preferences are not formally taken into account

Research Article

Statistics in Medicine

Received 27 October 2009, Accepted 2 March 2010 Published online in Wiley Online Library

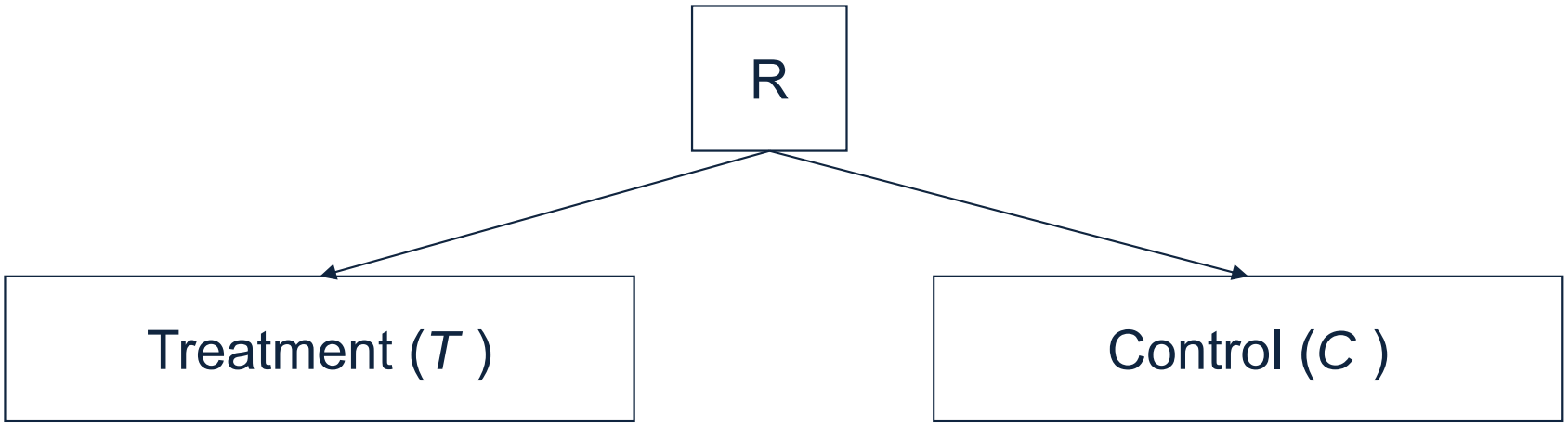
(wileyonlinelibrary.com) DOI: 10.1002/sim.3923

Generalized pairwise comparisons of prioritized outcomes in the two-sample problem

Marc Buyse[a,b*†]

Buyse, Stat Med 2010;29:3245

Randomized Trial



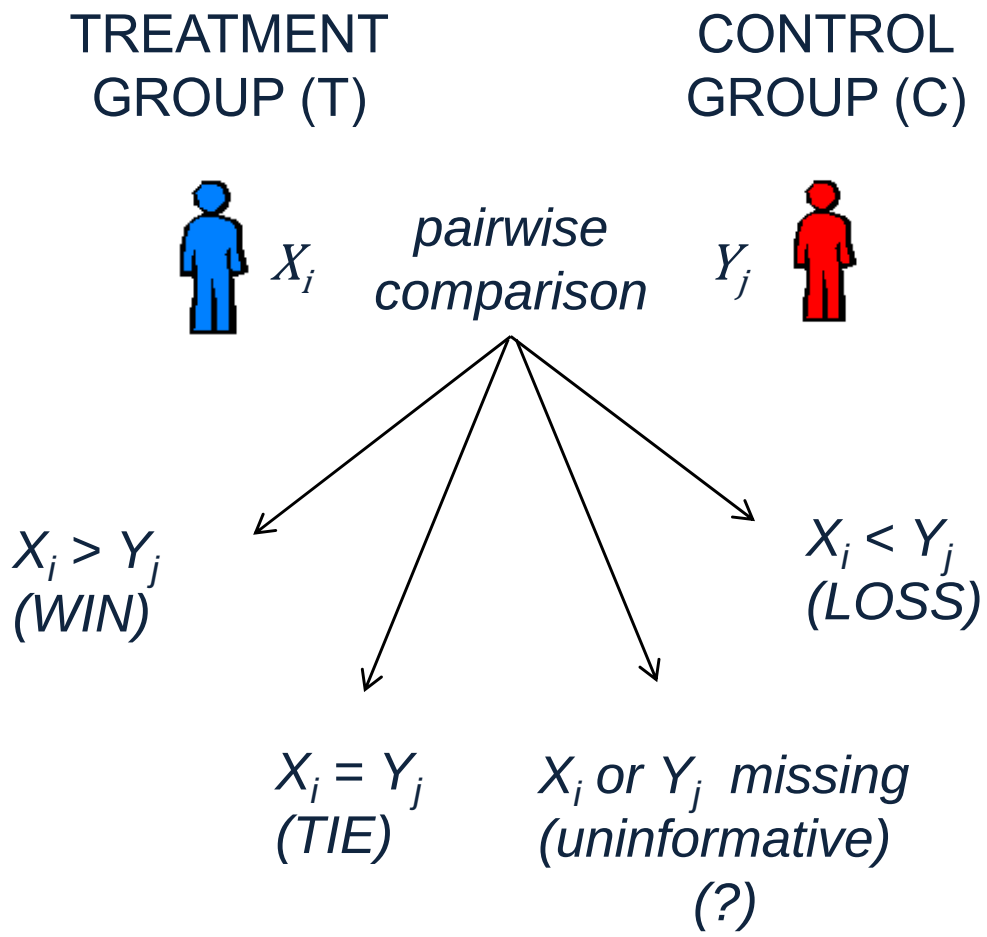
Let X_i be the outcome of i^{th} subject in T ($i = 1, \ldots, n$)

Let Y_j be the outcome of j^{th} subject in C ($j = 1, \ldots, m$)

Buyse, Stat Med 2010;29:3245

Pairwise Comparisons

Let X_i and Y_j be the observed values of a continuous outcome



Buyse, Stat Med 2010;29:3245

Net Benefit

- Let p_{ij} be equal to

  1 if the pair is a win

  -1 if the pair is a loss

  0 if the pair is a tie/?

- Then

$$U = \sum_{ij} p_{ij}/(nm)$$

  - A generalization of the Wilcoxon-Mann-Whitney test-statistic

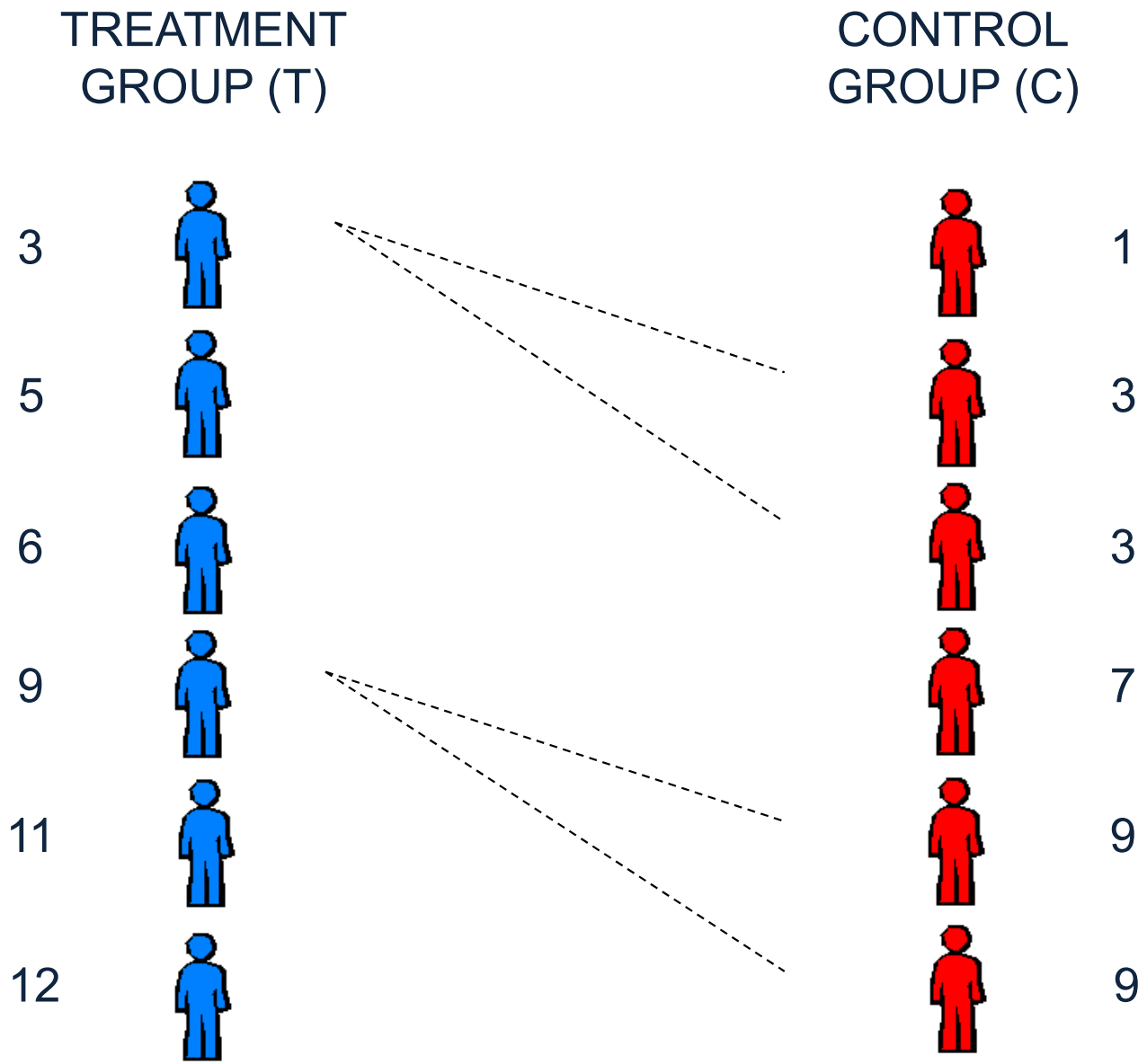
- And (if no missing data)

$$\Delta = E(U) = P(X>Y)-P(X<Y) = P(T \text{ better})-P(C \text{ better})$$

Illustration

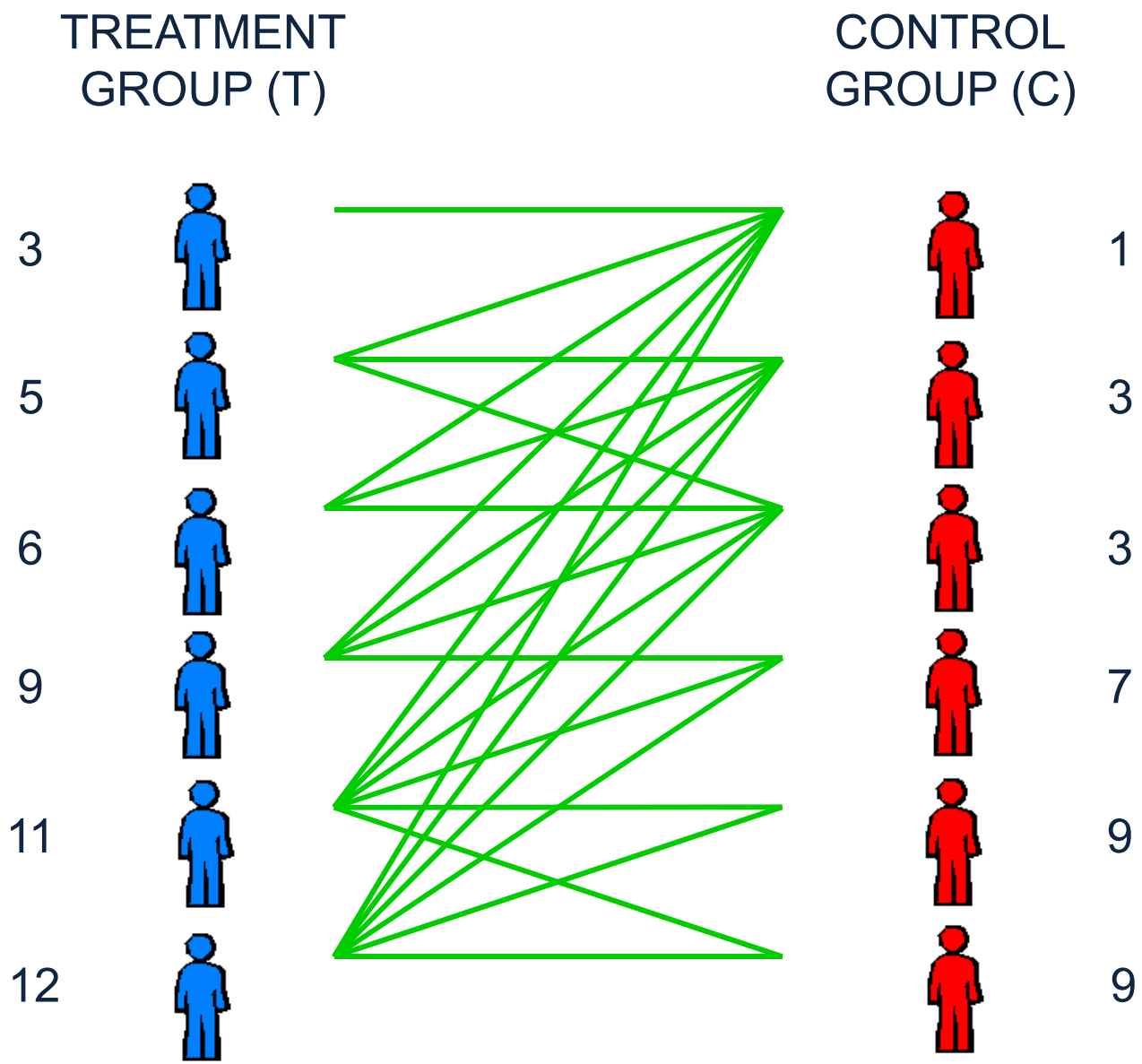
TREATMENT GROUP (T)	CONTROL GROUP (C)
3	1
5	3
6	3
9	7
11	9
12	9

Ties



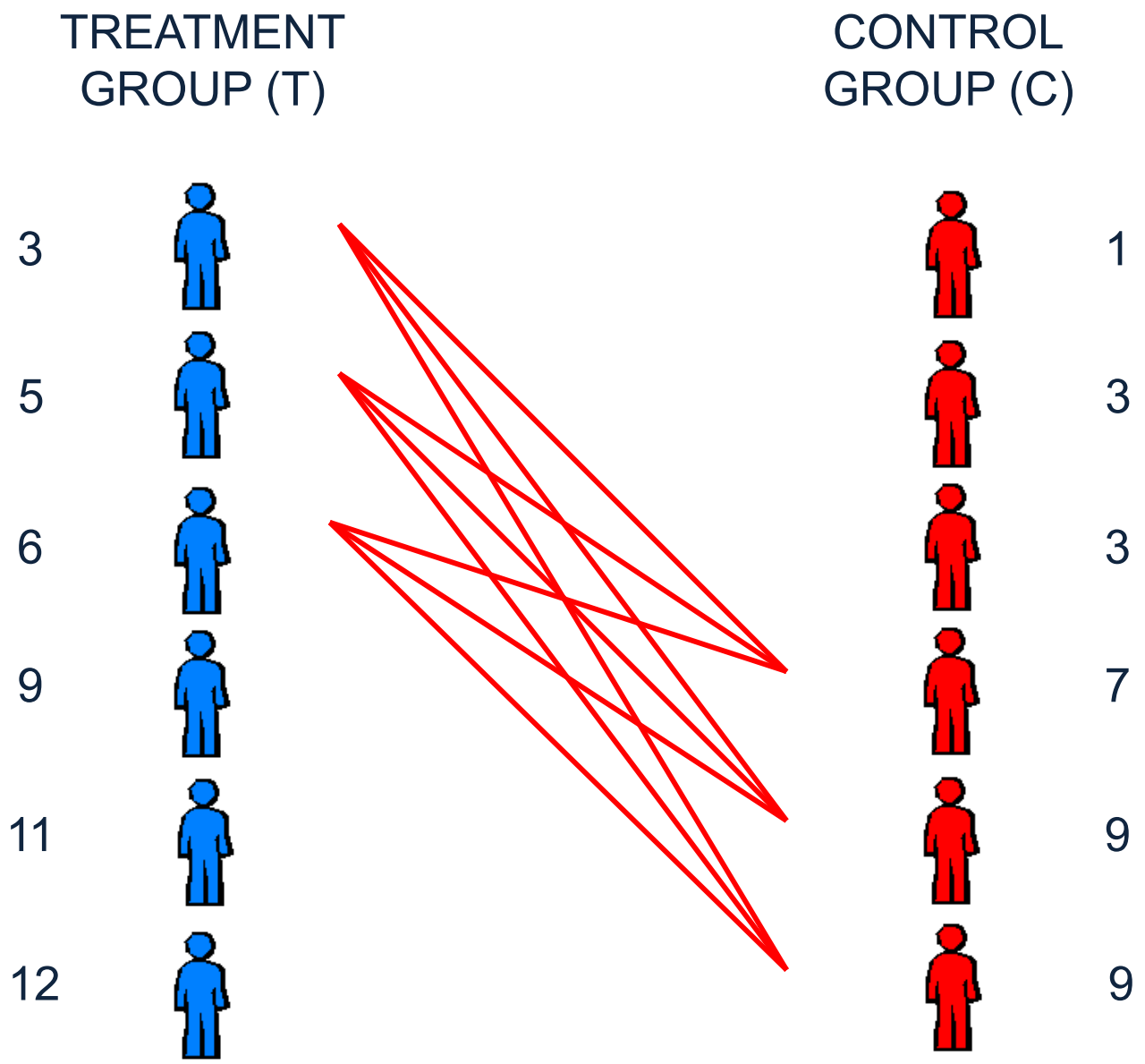
4 TIES

Wins



23 WINS

Losses



9 LOSSES

Net Benefit

Ties	Wins	Losses	Net benefit
4 / 36 = 0.11	23 / 36 = 0.64	9 / 36 = 0.25	0.64 – 0.25 = 0.39

The probability of a patient having a better outcome

- if on treatment is 0.64
- if on control is 0.25

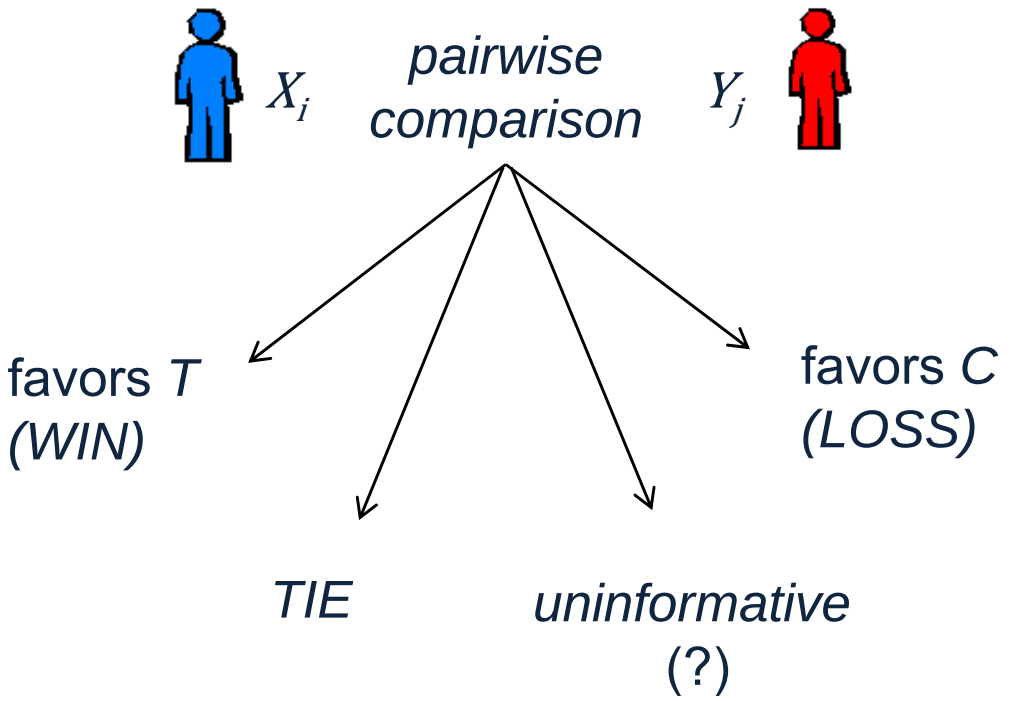
The ”net benefit” is 0.39

Note: the ”win ratio” is 0.64 / 0.25 = 2.56

Pocock et al. Eur Heart J 2012; 33: 176

Generalized Pairwise Comparisons

Now let X_i and Y_j be the observed values of any outcome measure (continuous, time-to-event, binary, categorical, …)



Buyse, Stat Med 2010;29:3245

Time to Event

X_i censored	Y_j censored	$X_i > Y_j$	$X_i < Y_j$	$X_i = Y_j$
No	No	Win	Loss	Tie
Yes	No	Win	?	?
No	Yes	?	Loss	?
Yes	Yes	?	?	?

Buyse, Stat Med 2010;29:3245

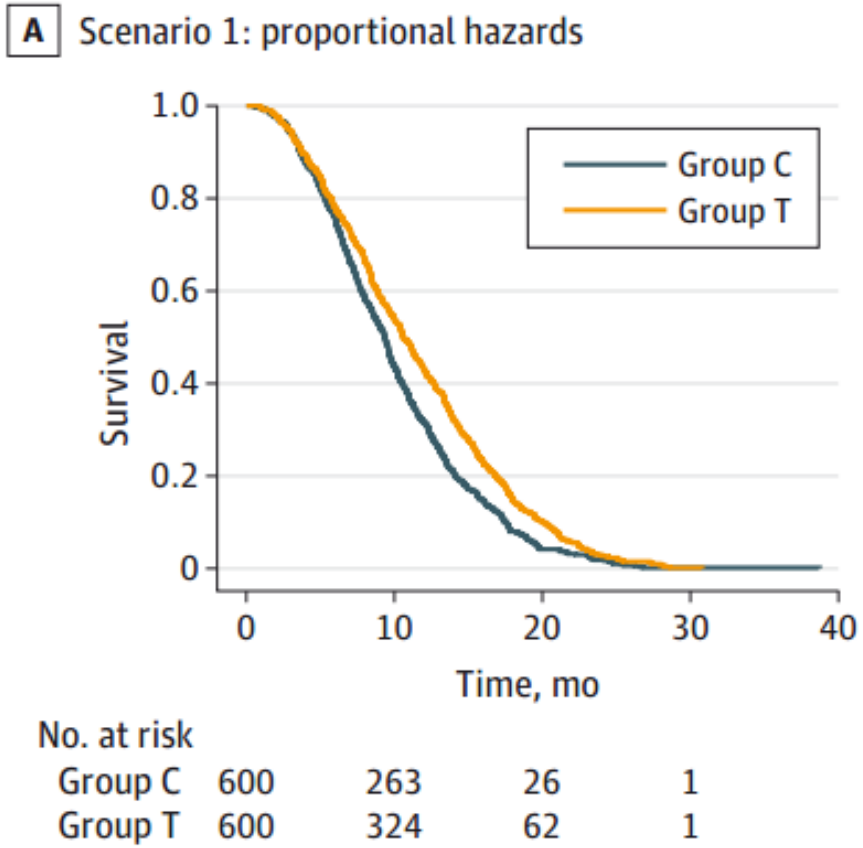
Thresholds of Clinical Relevance

X_i censored	Y_j censored	$X_i - Y_j > m$	$X_i - Y_j < -m$	$\lvert X_i - Y_j \rvert \leq m$
No	No	Win	Loss	Tie
Yes	No	Win	?	?
No	Yes	?	Loss	?
Yes	Yes	?	?	?

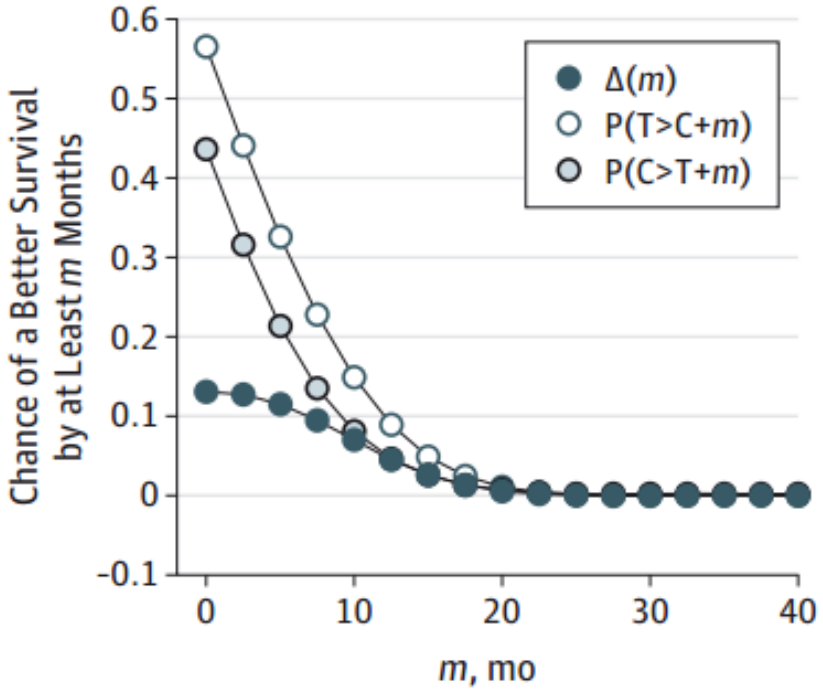
Buyse, Stat Med 2010;29:3245

Net Benefit – Proportional Hazards

KAPLAN-MEIER CURVES



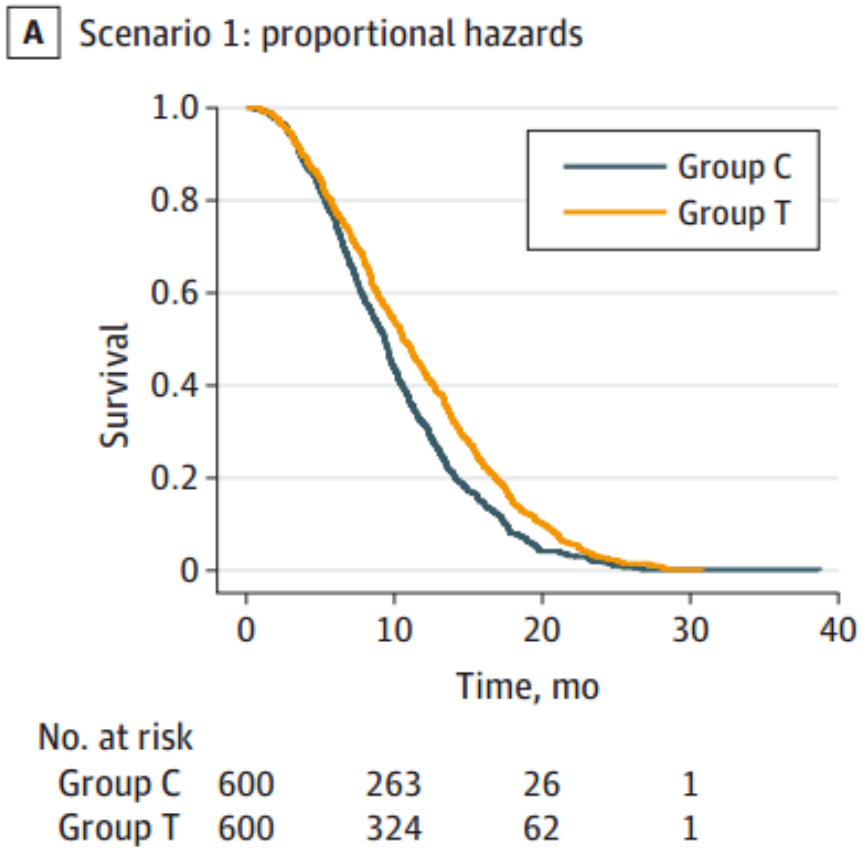
NET BENEFIT OF AT LEAST m MONTHS



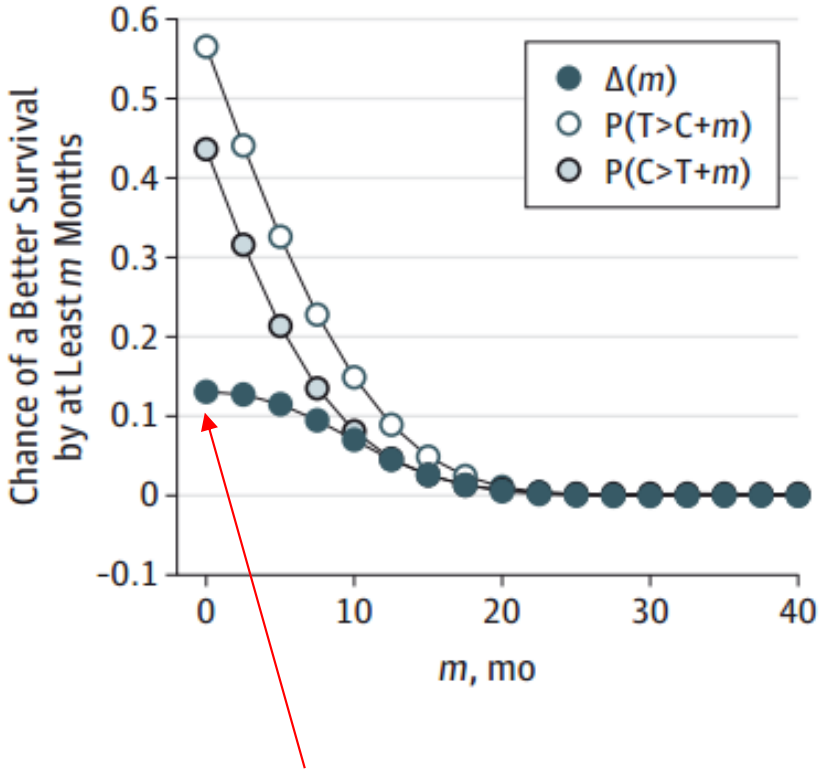
Péron et al, JAMA Oncol 2016;2:901

Net Benefit – Proportional Hazards

KAPLAN-MEIER CURVES



NET BENEFIT OF AT LEAST m MONTHS



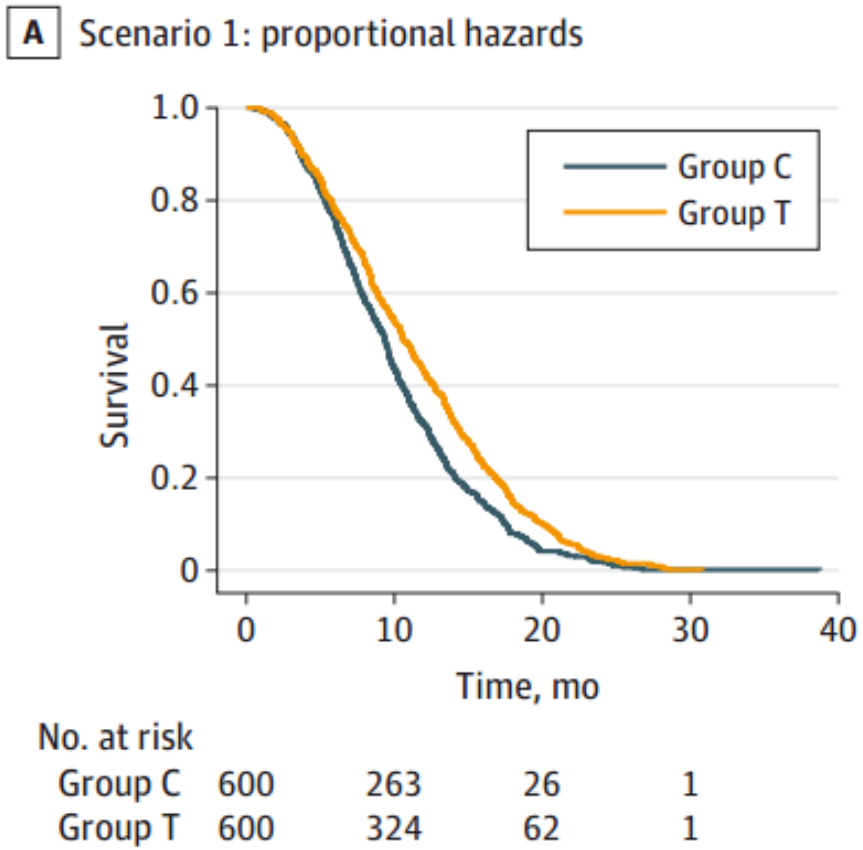
There is a 13% net probabilty that survival will be longer on T than C

The "net benefit" of T is 13%

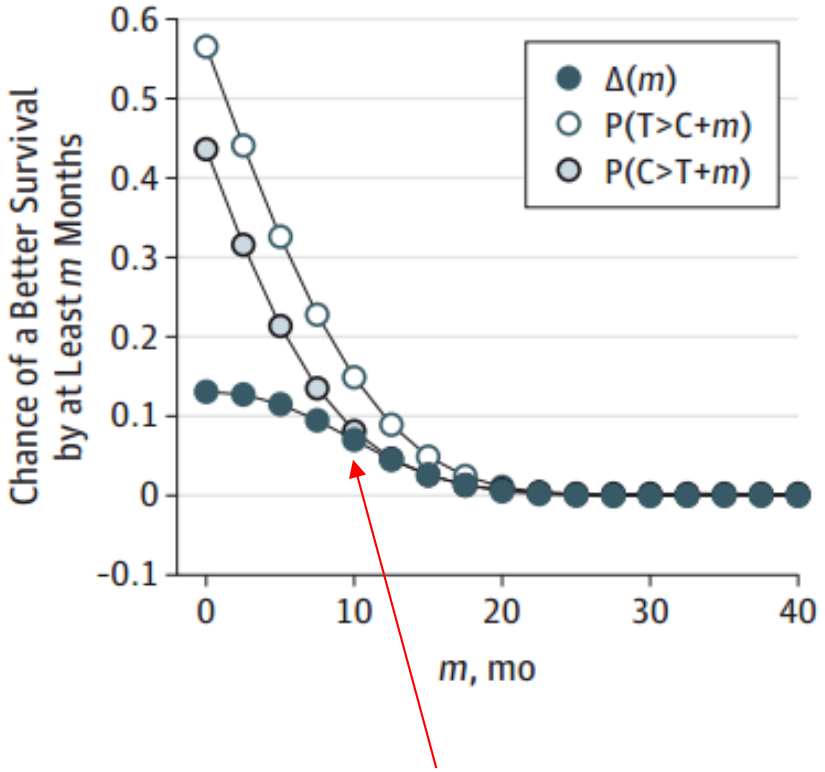
Péron et al, JAMA Oncol 2016;2:901

Net Benefit – Proportional Hazards

KAPLAN-MEIER CURVES



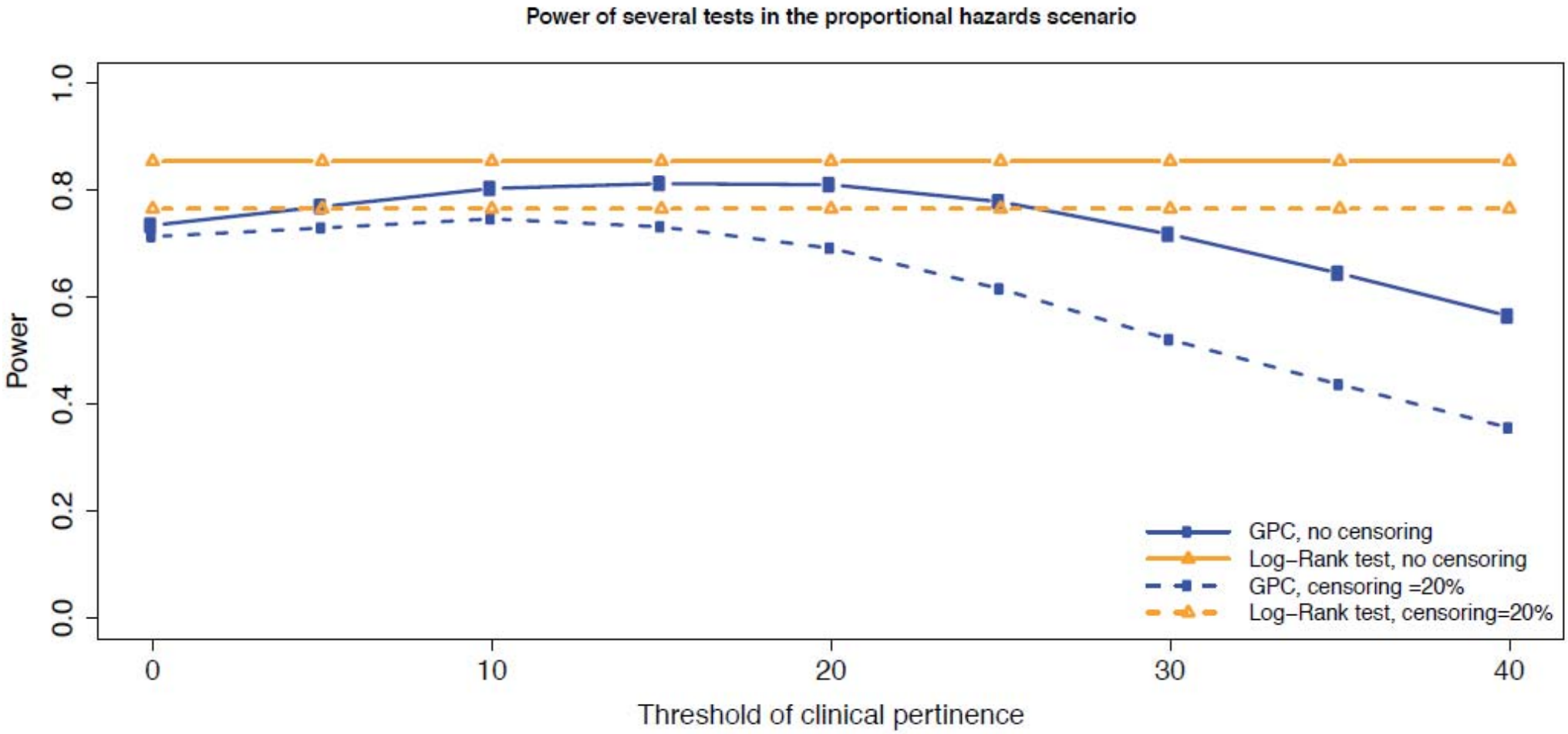
NET BENEFIT OF AT LEAST m MONTHS



There is an 8% net benefit of at least 10 months in favor of T

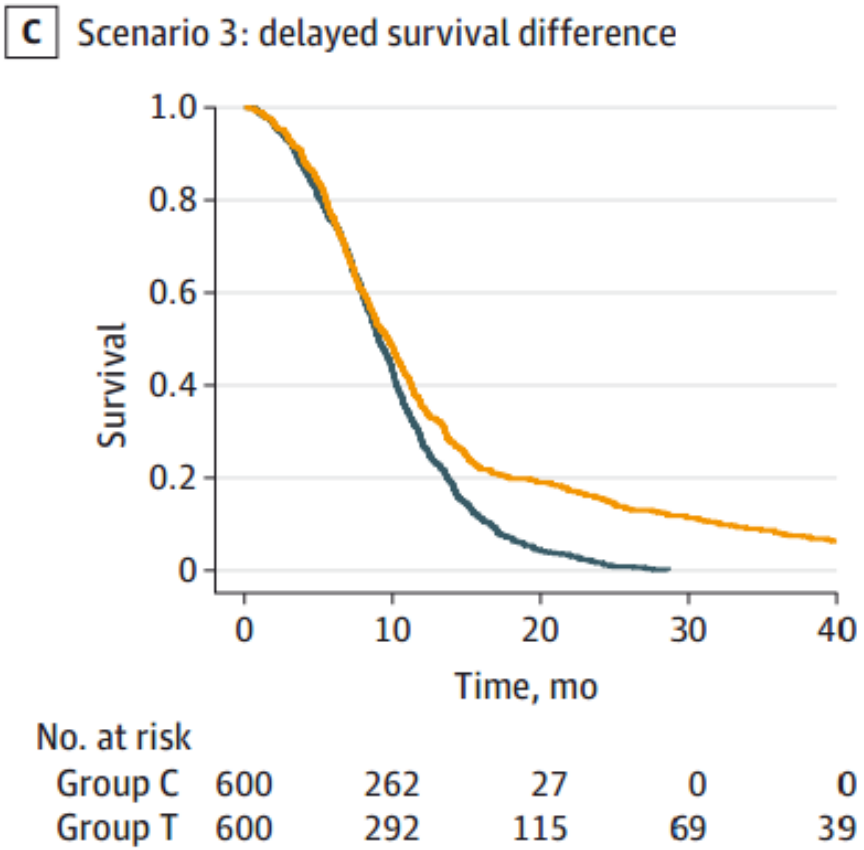
Péron et al, JAMA Oncol 2016;2:901

Power – Proportional Hazards

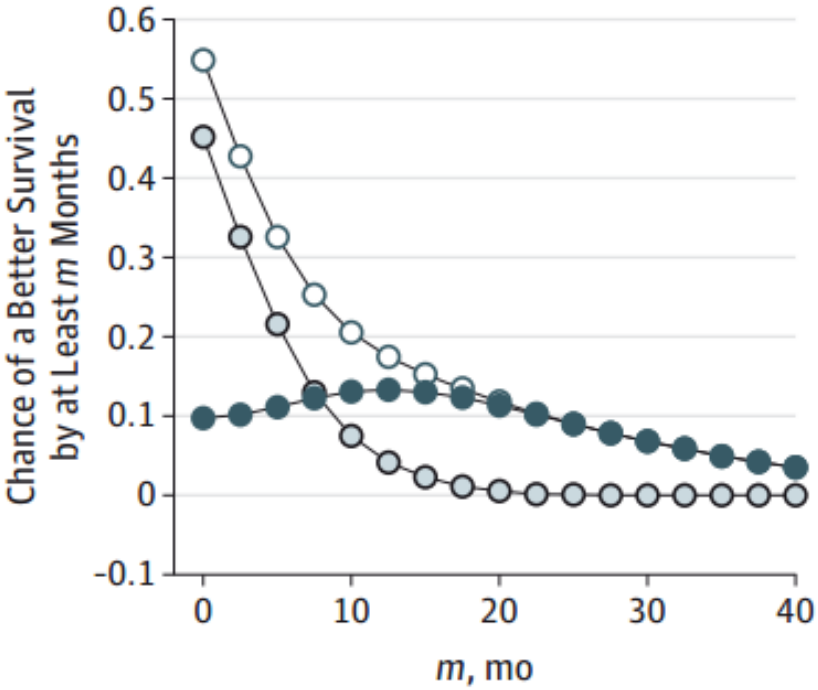


Net Benefit – Delayed Difference

KAPLAN-MEIER CURVES



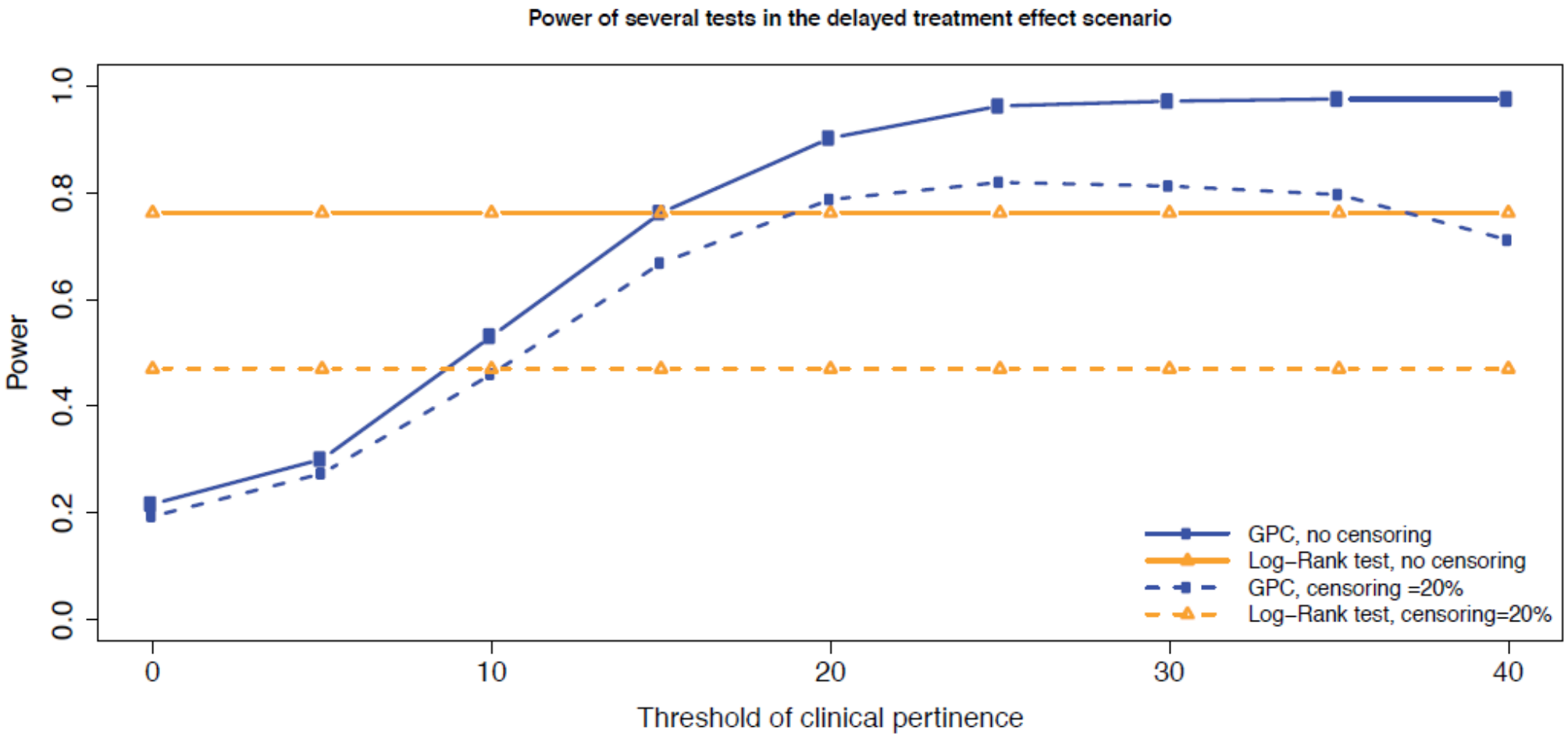
NET BENEFIT OF AT LEAST m MONTHS



Example: immunotherapy for advanced solid tumors

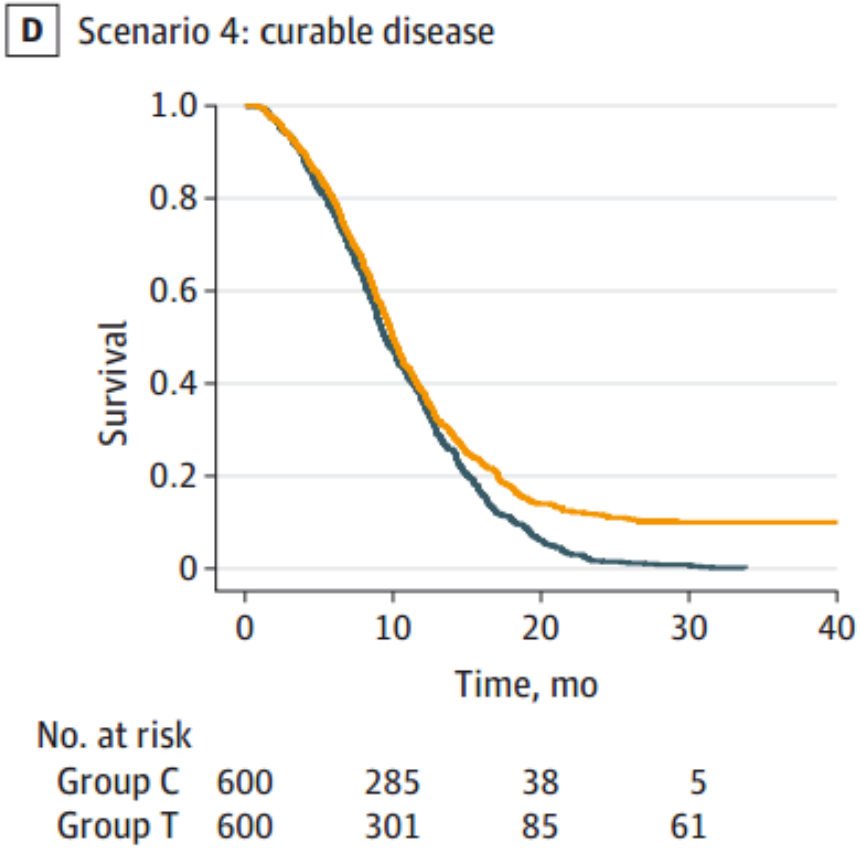
Péron et al, JAMA Oncol 2016;2:901

Power – Delayed Difference

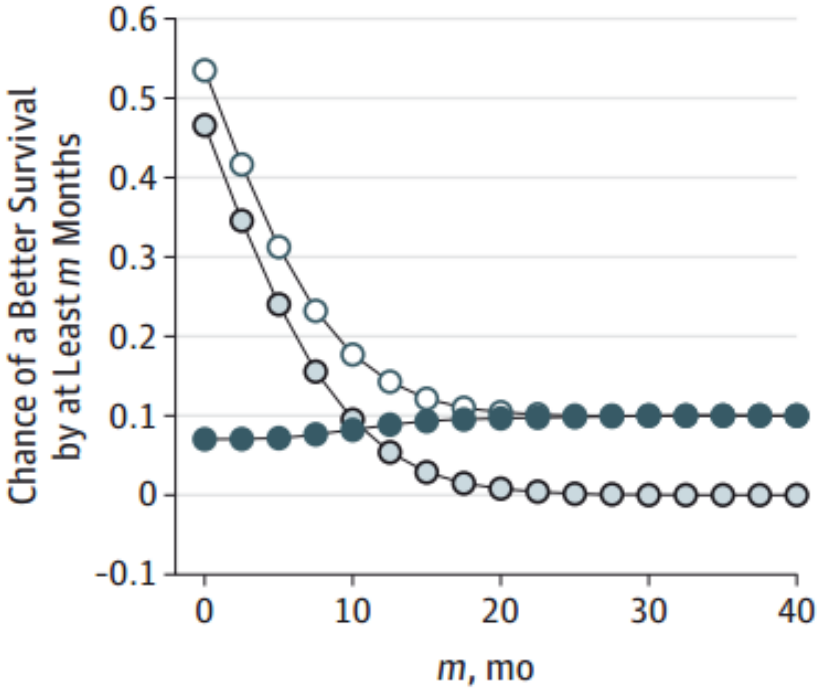


Net Benefit – Cure Rate

KAPLAN-MEIER CURVES



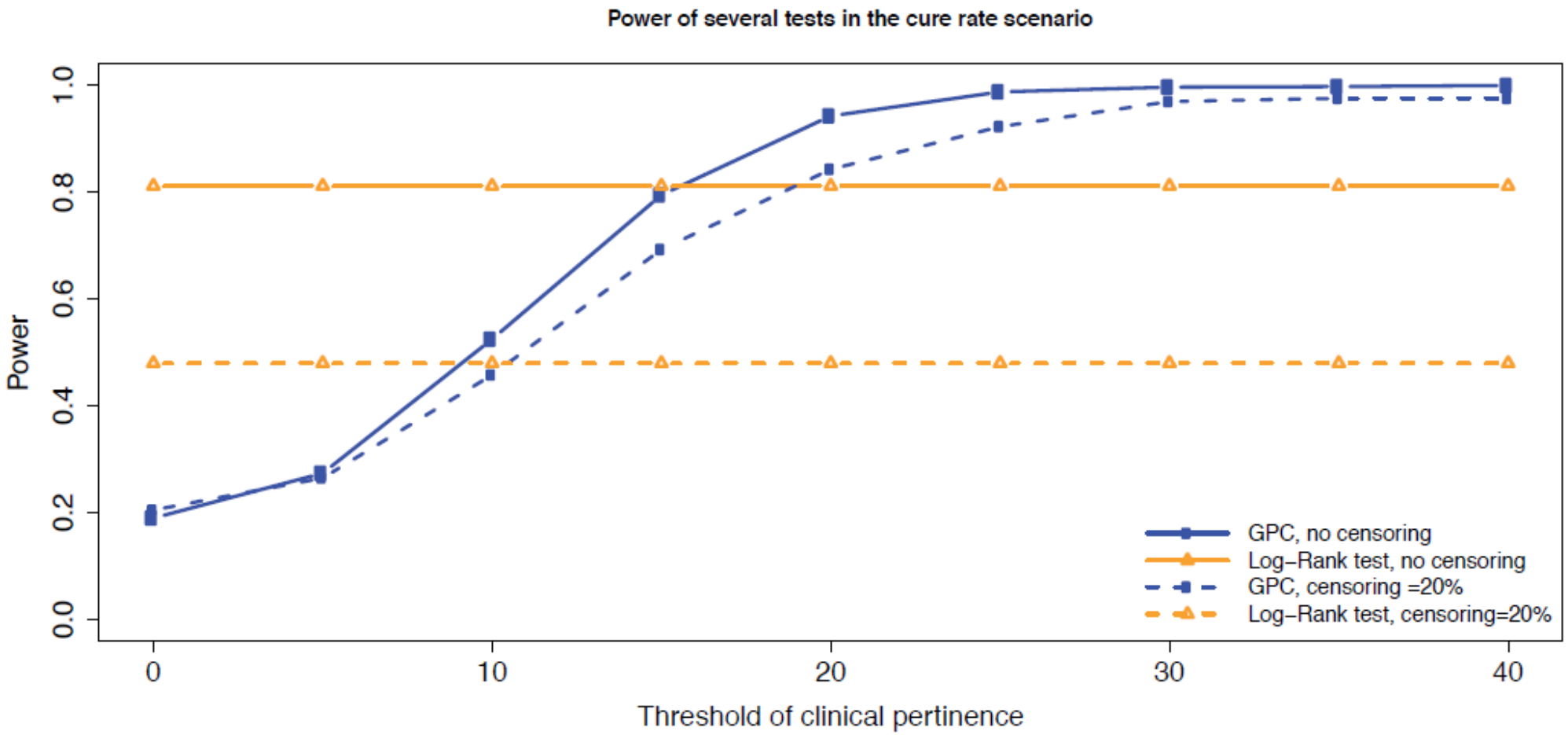
NET BENEFIT OF AT LEAST m MONTHS



Example: allografts in childhood tumors

Péron et al, JAMA Oncol 2016;2:901

Power – Cure Rate



Net Benefit

- Related to the ‘probabilistic index’, P(X > Y), [Acion et al. 2006, De Neve et al. 2013].

- The probabilistic index and related measures do not automatically generalize to other settings or different patient populations, where the variability of the outcome(s) of interest could be quite different [Senn 2011, Thas et al. 2012].

- These measures of benefit may be best seen as complementary to traditional (parametric) measures of benefit.

Prioritized Outcomes

Now let (X_i, X'_i) and (Y_j, Y'_j) be observed values of two outcome measures, with X (Y) being prioritized over X' (Y')


X_i, X'_i *pairwise comparison* Y_j, Y'_j


X_i *vs.* Y_j	X_i' *vs.* Y_j'	Pair is
WIN		WIN
LOSS		LOSS
TIE or ?	WIN	WIN
TIE or ?	LOSS	LOSS
TIE or ?	TIE or ?	TIE or ?

Buyse, Stat Med 2010;29:3245

Net Benefit

- Assume K outcomes
- Let p_{ijk} (k=1, …, K) be equal to

  1 if the pair is a win for the k-th outcome

  -1 if the pair is a loss for the k-th outcome

  0 if the pair is a tie for the k-th outcome
- Define u_{ijk}= I(the pair is ? for the k-th outcome)

- Let

$$U(K) = \sum_{ij}\{p_{ij1}(1-u_{ij1})+\ldots+p_{ijK}u_{ij1}\ldots u_{ij,K-1}(1-u_{ijK})\}/(nm)$$

- And

$$\Delta = E\{U(K)\}$$

A Recent Example

N Engl J Med 2018;378:35-47.
DOI: 10.1056/NEJMoa1703327

Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma

K.M. Sullivan, E.A. Goldmuntz, L. Keyes-Elstein, P.A. McSweeney, A. Pinckney, B. Welch, M.D. Mayes, R.A. Nash, L.J. Crofford, B. Eggleston, S. Castina, L.M. Griffith, J.S. Goldstein, D. Wallace, O. Craciunescu, D. Khanna, R.J. Folz, J. Goldin, E.W. St. Clair, J.R. Seibold, K. Phillips, S. Mineishi, R.W. Simms, K. Ballen, M.H. Wener, G.E. Georges, S. Heimfeld, C. Hosing, S. Forman, S. Kafaja, R.M. Silver, L. Griffing, J. Storek, S. LeClercq, R. Brasington, M.E. Csuka, C. Bredeson, C. Keever-Taylor, R.T. Domsic, M.B. Kahaleh, T. Medsger, and D.E. Furst, for the SCOT Study Investigators*

METHODS

We randomly assigned adults (18 to 69 years of age) with severe scleroderma to undergo myeloablative autologous stem-cell transplantation (36 participants) or to receive cyclophosphamide (39 participants). The primary end point was a global rank composite score comparing participants with each other on the basis of a hierarchy of disease features assessed at 54 months: death, event-free survival (survival without respiratory, renal, or cardiac failure), forced vital capacity, the score on the Disability Index of the Health Assessment Questionnaire, and the modified Rodnan skin score.

RESULTS

In the intention-to-treat population, global rank composite scores at 54 months showed the superiority of transplantation (67% of 1404 pairwise comparisons favored transplantation and 33% favored cyclophosphamide, P=0.01). In the per-protocol population

BENEFIT Project

- Biostatistical Estimation of Net Effects For Individualization of Therapy

- Funds: the Walloon Region, Biowin – the Health Cluster of Wallonia and Innoviris, the Brussels Institute for Research and Innovation.

- Partners
  - International Drug Development Institute (IDDI)
  - Bristol-Myers Squibb
  - European Organization for Research and Treatment of Cancer (EORTC)
  - Université Catholique de Louvain (UCL)
  - Université Claude Bernard Lyon 1 (Lyon, France)

BENEFIT Project: Goals

- Methods
  - Extensions of GPC (missing data, longitudinal, cross-over, ...)
  - "Optimal" GPC (censoring, risk/benefit, ...)
  - Comparisons with traditional methods
  - Use for trial design
- Applications (oncology, ophthalmology, ...)
- Software
  - Open
  - Proprietary (design, analysis, patient)

Net Benefit for Longitudinal Data

- Normally-distributed outcome Y
- Two measurements: "earlier" Y_1 and "later" Y_2
- Y_2 "primary"
- For uncorrelated Y_1 and Y_2

$$\Delta = \theta_2 + \theta_1 * \left\{ \Phi\left(\frac{\mu_{20} + \tau_2 - \mu_{21}}{\sigma_2\sqrt{2}}\right) - \Phi\left(\frac{\mu_{20} - \tau_2 - \mu_{21}}{\sigma_2\sqrt{2}}\right) \right\}$$

= {P(T better for Y_2)-P(C better for Y_2)} +
{P(T better for Y_1)-P(C better for Y_1)}·P(tie on Y_1)

= (Net benefit for Y_2) + (Net benefit for Y_1)·P(tie on Y_2)

Net Benefit Under MCAR Dropout

- Data for Y_1 complete
- Data for Y_2 missing completely at random in each treatment group
  - $\omega_0 = P(Y_2 \text{ observed for control})$, $\omega_1 = P(Y_2 \text{ observed for treatment})$

- Then, for uncorrelated Y_1 and Y_2,

$$\Delta_{MCAR} = \omega_0\omega_1\Delta + \theta_1(1-\omega_0\omega_1)$$

- Hence, estimation ignoring missing data (even for MCAR) is biased!

- A corrected estimator obtained from

$$\Delta = \{\Delta_{MCAR} - \theta_1(1-\omega_0\omega_1)\}/(\omega_0\omega_1)$$

Net Benefit Under Dropout/Correlation

- Formulae quickly complicate for correlated Y_1 and Y_2
  - MCAR:

$$\begin{aligned}\Delta = {} & \theta_2\Phi(\beta_0)\Phi(\beta_0+\gamma) + \theta_1(1-\Phi(\beta_0)\Phi(\beta_0+\gamma)) + \\ & + \Phi(\beta_0)\Phi(\beta_0+\gamma)\left(\frac{1}{\sigma_1^2}\int_{-\infty}^{\infty}\phi\left(\frac{y_{11}-\mu_{11}}{\sigma_1}\right)\left(BvN(h_{11},\frac{y_{11}-\tau_1-\mu_{10}}{\sigma_1};\rho_3) - \right.\right. \\ & \left.\left. BvN(h_{12},\frac{y_{11}-\tau_1-\mu_{10}}{\sigma_1};\rho_3)\right)dy_{11} - \right. \\ & \left. + \frac{1}{\sigma_1}\int_{-\infty}^{\infty}\phi\left(\frac{y_{10}-\mu_{10}}{\sigma_1}\right)\left(BvN(h_{13},\frac{y_{10}-\tau_1-\mu_{11}}{\sigma_1};-\rho_3) - \right.\right. \\ & \left.\left. BvN(h_{14},\frac{y_{10}-\tau_1-\mu_{11}}{\sigma_1};\rho_3)\right)dy_{10}\right)\end{aligned}$$

- Even more for MAR…
- Nevertheless, IPW estimators can be constructed

Closing Remarks (1)

- GPCs are attractive
  - In terms of patient centricity:
    - “Net benefit”, a patient-relevant measure
    - Accommodate prioritized outcomes
  - In statistical terms:
    - Equivalent to standard non-parametric tests in simple cases
    - May have better power than, e.g., the logrank test
    - Allow for testing of clinically relevant differences

Closing Remarks (2)

- GPCs require more fundamental research
  - In terms of theoretical properties:
    - sufficiency, completeness?
    - robustness to missing data
    - handling multiple relevance-thresholds
    - generalizability beyond the available sample?
    - …
  - In terms of applicability:
    - Disease domains where additional insight can be obtained?