Dynamic prediction for time-to-death under the joint frailty-copula model

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Joint work with
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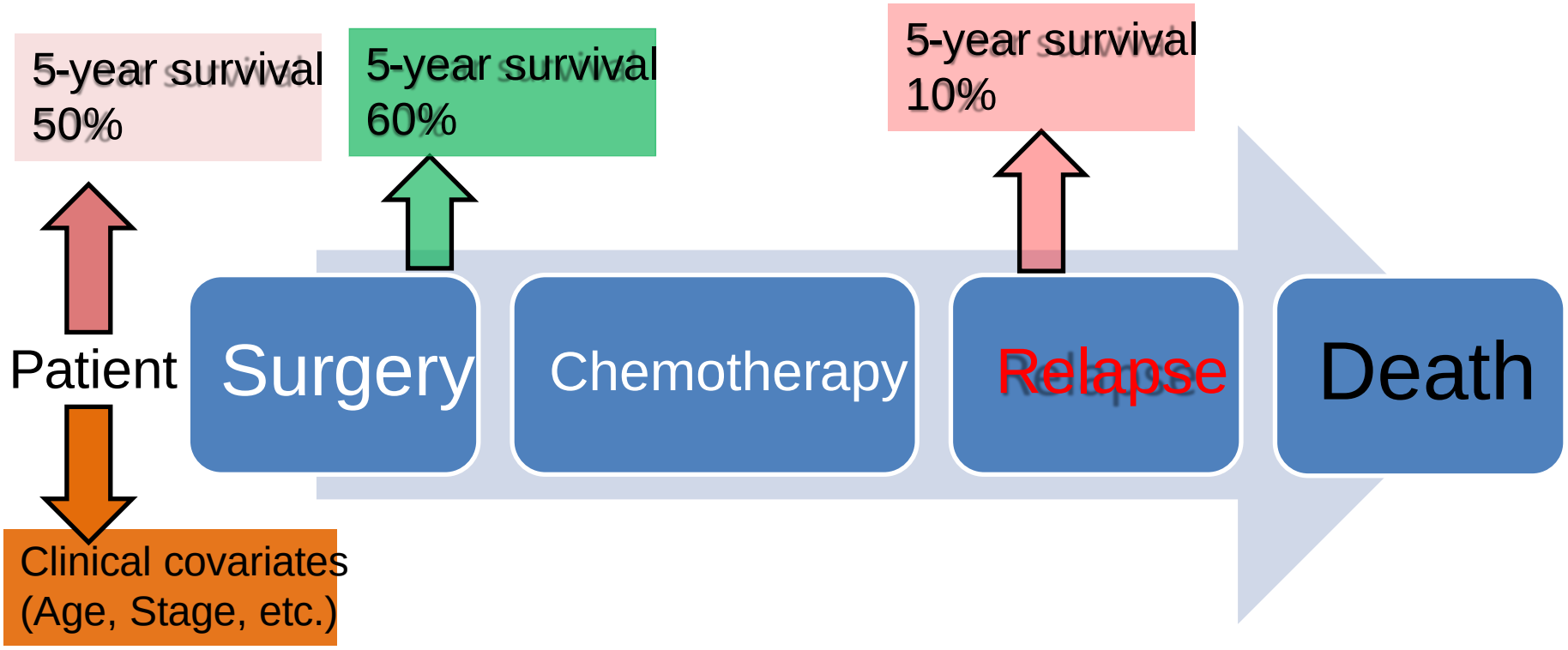
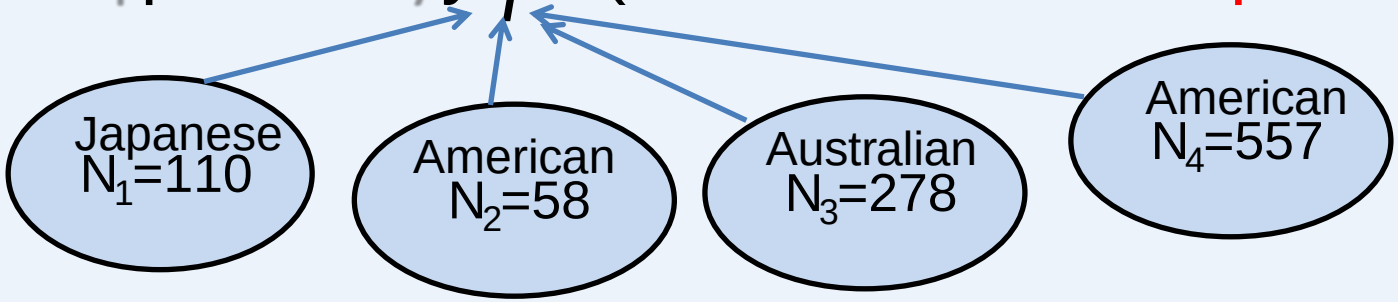
Follow-up for a cancer patient

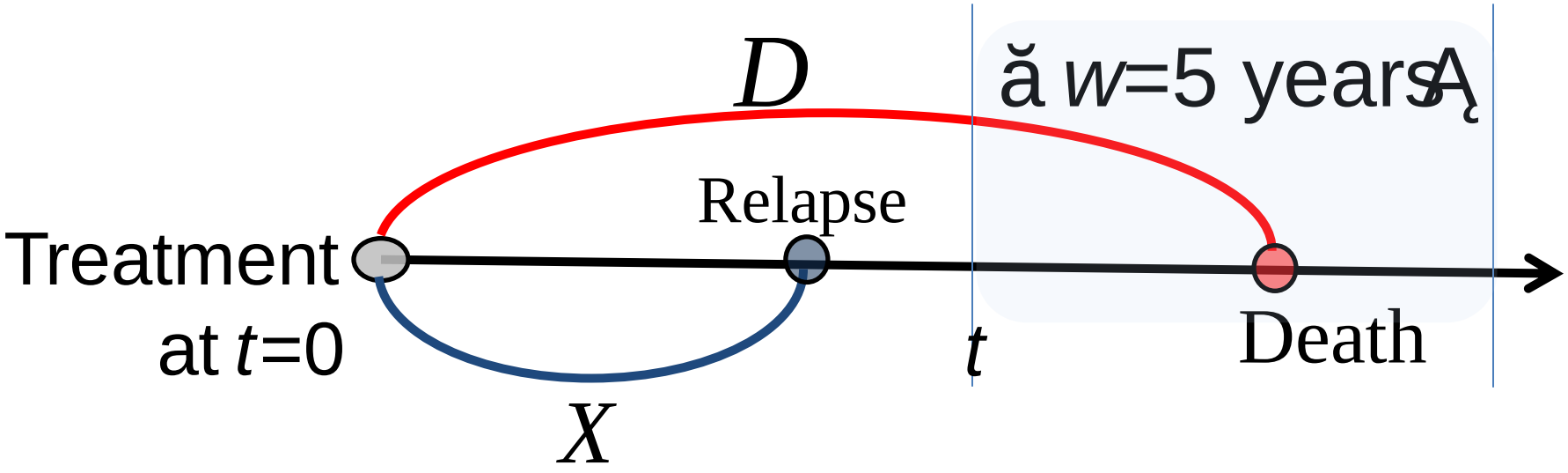


Survival probability = $f^{\check{E}}$ (Clinical, Gene, Relapse, Timing)



EmuraT*, NakatochiM, Matsui S, Michimae H, Rondeau V (2017) Personalized dynamic prediction of death according to tumour progre
and high-dimensional genetic factors: meta-analysis with a joint model, Stat Methods Med Res, doi:10.1177/0962280216688032

Dynamic Prediction



Å Conditional failure function (van Houwelingen and Putter 2013)

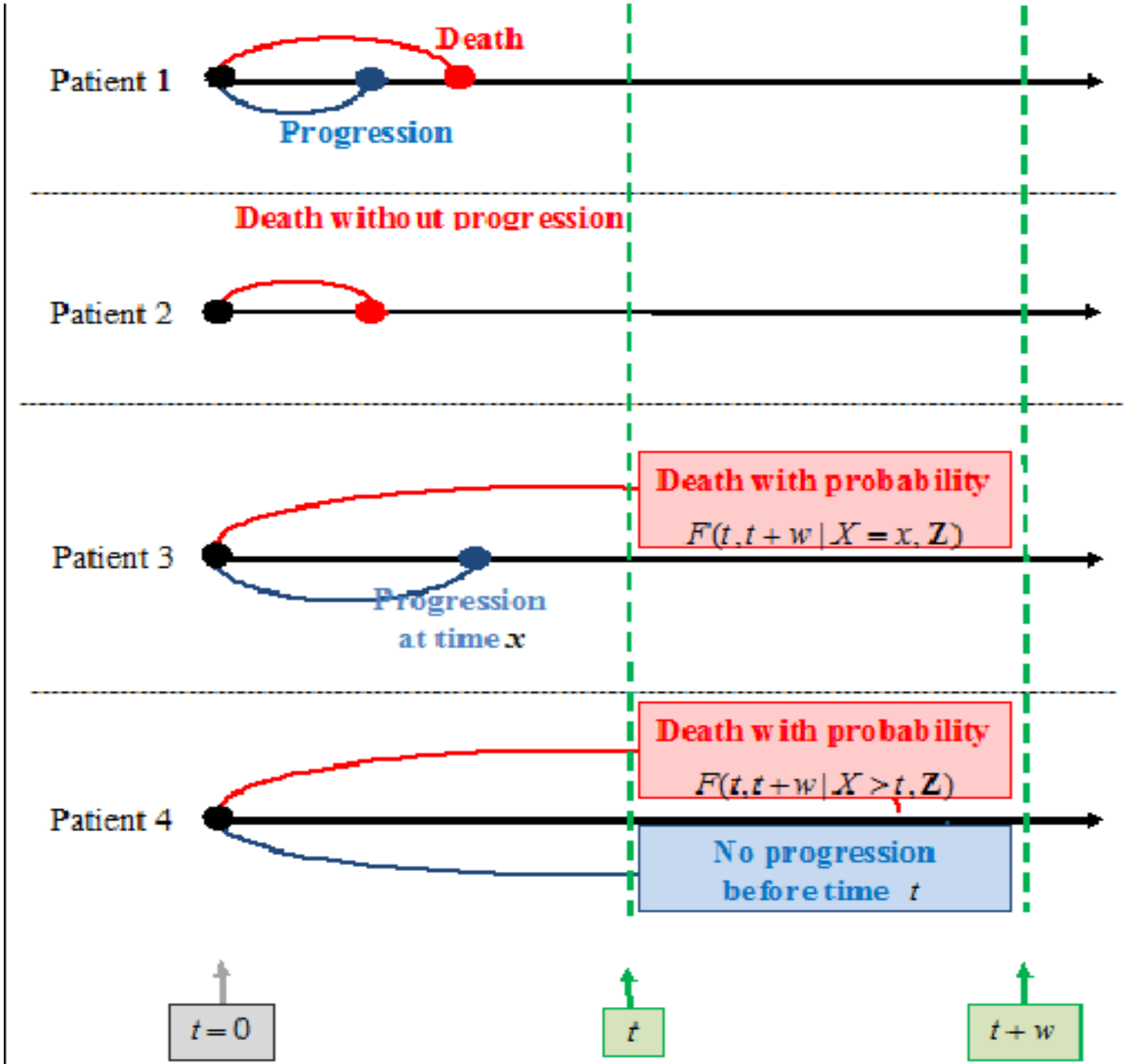
$$F(t, t+w \mid X, \mathbf{Z}) = \Pr(D \leq t+w \mid D > t, X, \mathbf{Z})$$

Two major approaches to obtain $\hat{F}$

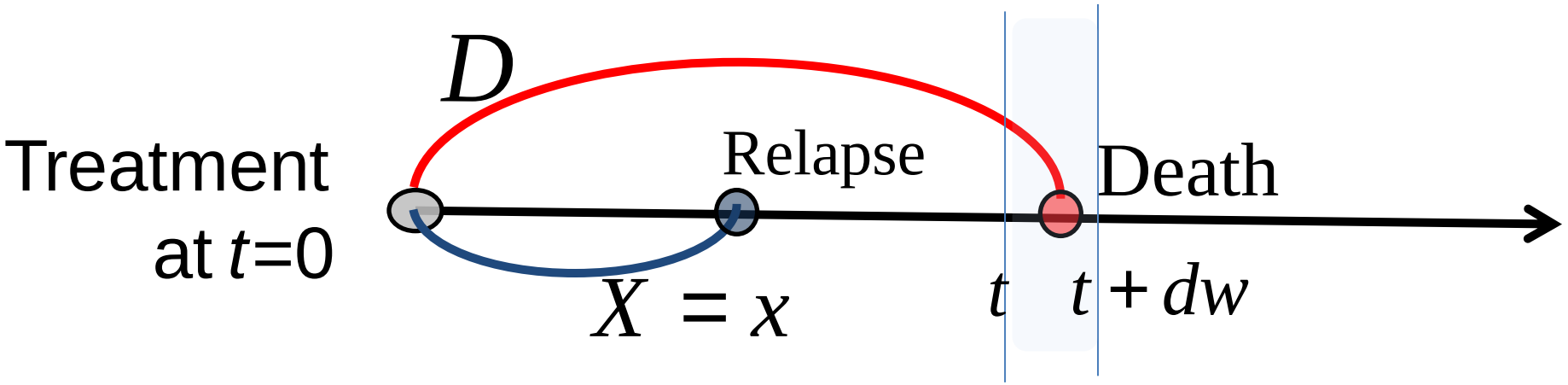
1) Landmark model

   (fit the Cox models by left truncation at time t)

2) Joint model (use a copula on (X, D))


Patient 1
Death
Progression
Death without progression
Patient 2
Patient 3
Death with probability
$F(t, t+w \mid X = x, \mathbf{Z})$
Progression
at time x
Patient 4
Death with probability
$F(t, t+w \mid X > t, \mathbf{Z})$
No progression
before time t
$t = 0$
t
$t+w$

Dynamic Prediction via Hazard



Å Conditional hazard (Clayton1978Biometrika)

$$\lambda(t \mid X = x, \mathbf{Z}) = F(t, t + dw \mid X = x, \mathbf{Z}) / dw$$

1) Used in Landmark model (Day et al.1997Biometrika)
2) Used under Joint model (Emura et al.2017SMMR)

$$\text{Relative risk} = \frac{\lambda(t \mid X = t, \mathbf{Z})}{\lambda(t \mid X > t, \mathbf{Z})} = \begin{cases} > 1 & : \text{relapse increases death rate} \\ = 1 & : \text{relapse is independent of death rate} \\ < 1 & : \text{relapse increases death rate} \end{cases}$$

Dynamic prediction via joint models

Method	Response	Dependence	Heterogeneity
Rizopoulos (2011, Biometrics) Taylor et al. (2013, SMMR) Sènecat al. (2014, SMMR) Proust-Lima (2014, SMMR)	Longitudinal measurements + Time-to-events	Frailty	No
Mauguenet al. (2013, 2015) Król et al. (2016, Biometrics) Mazroui et al. (2015 LTDA)	Recurrent events + Time-to-death	Frailty	No
Rondeau et al (2017, SMMR)	Clustered failure events	Frailty	No
Our method	Time-to-relapse + Time-to-death	Copula	Frailty

Copula model

$$\Pr(X > x, D > y) = C_q[\Pr(X > x), \Pr(D > y)]$$

Clayton copula: $C_q(v, w) = (v^{-q} + w^{-q} - 1)^{-1/q}$

$$q+1 = \frac{\Pr(X = x, D = y)\Pr(X > x, D > y)}{\Pr(X = x, D > y)\Pr(X > x, D = y)} = \text{Odds ratio in } 2^3 \text{ 2table}$$

$q > 0$: Positive dependence

$-1 < q < 0$: Negative dependence

¶ Kendall's tau $= \frac{q}{q+2}$

¶ $\frac{I(t \mid X = x, \mathbf{Z})}{I(t \mid X > x, \mathbf{Z})} = 1 + q$

: constant hazard ratio

	Relapse	Relapse-free
Death	$X=x, D=y$	$X>x, D=y$
Alive	$X=x, D>y$	$X>x, D>y$

Example: Ovarian cancer data (Ganzfried et al. 2013)

T_i : time-to-tumour progression or censoring

d_i : progression status (0 or 1)

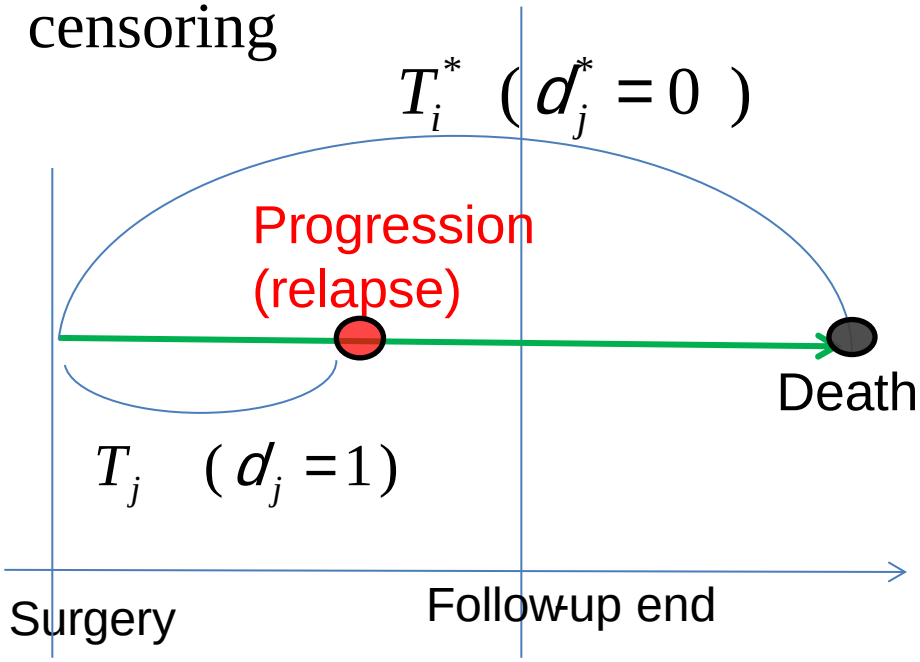
T_i^* : time-to-death or censoring

d_i^* : vital status (0 or 1)

Z_i : residual tumour size

(1cm < vs. 1cm > ∋)

$\mathbf{V}_i = (V_{i1}, ..., V_{ip})$¡: gene expressions



T_i^* Time-to-death	d_i^* Vital status	AP3S1	APMAP	ARHGAP28	CXCL12	……..	ASB7	B4GALT5
1650	0	-0.52	1.12	-0.37	1.30	……	0.354	-1.015
30	1	-0.18	-0.69	-0.93	3.52	……	0.026	0.38
ể	ể					……		
1800	1	-1.08	0.70	-0.29	-0.529	……..	-0.50	-1.09

Clustered semi-competing risks data

: Progression=0 or No progression=1

: Alive =0 or Death=1