Supplemental Material

Conditions When the Parameter *f* is lose to 1

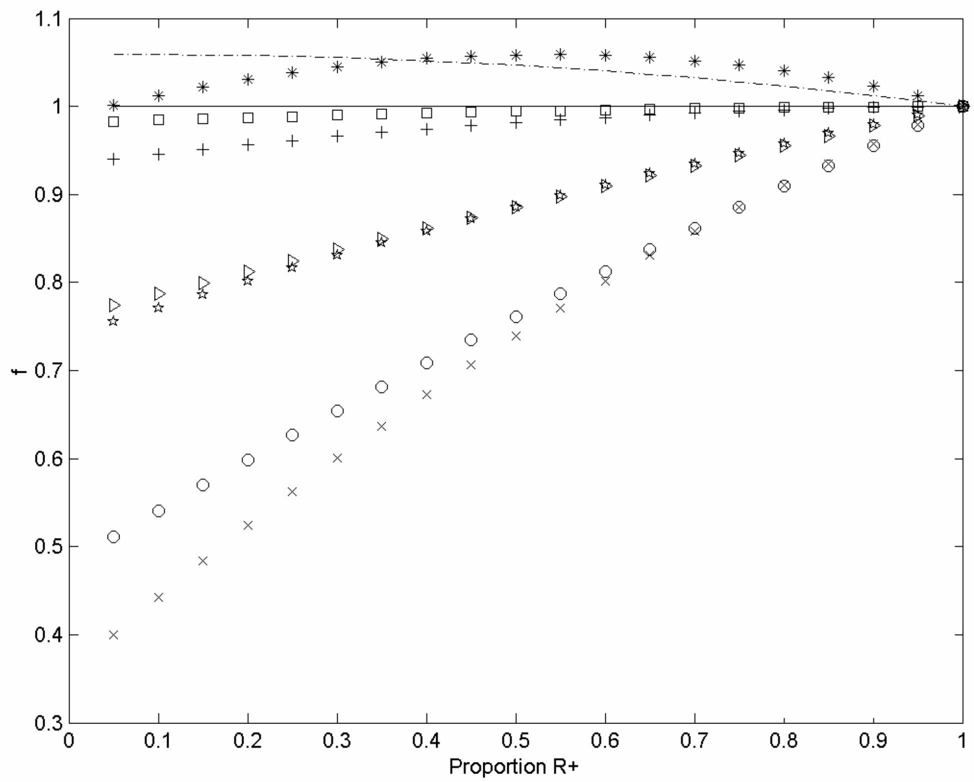

Fig.3

Fig. 3 Legend

Factor $f = \left\{ \dfrac{z_\alpha\sqrt{2\overline{pq}} + z_\beta\sqrt{p_e(1-p_e)+p_c(1-p_c)}}{z_\alpha\sqrt{2\overline{p}_T\overline{q}_T} + z_\beta\sqrt{p_e^T(1-p_e^T)+p_c(1-p_c)}} \, \dfrac{1+\sqrt{1+2w}}{1+\sqrt{1+2w_T}} \right\}^2$ intervening in the relative efficiency of the untargeted and targeted designs with regard to number of randomized patients, $n/n^T = \left[\dfrac{\delta_1}{\gamma\delta_0 + (1-\gamma)\delta_1}\right]^2 f$, with w and w_T respectively defined by $w = \dfrac{(\gamma\delta_0 + (1-\gamma)\delta_1)}{(z_\alpha + z_\beta)^2\,\overline{pq}}$ and $w_T = \dfrac{\delta_1}{(z_\alpha + z_\beta)^2\,\overline{p}_T\overline{q}_T}$. γ is the proportion of R- patients . p_c denotes the response probability in control group and is assumed to be the same for R- and R+ patients. The response probability in the treatment group is $p_c + \delta_0$ and $p_c + \delta_1$ for the R- and R+ patients respectively. The response probability p_e for the experimental treatment group in the untargeted design is a weighted average of $p_c + \delta_0$ and $p_c + \delta_1$ with weights γ and (1-γ) respectively. The response probability in the experimental group in the targeted design is $p_e^T = p_c + \delta_1$. $\overline{p} = (p_e + p_c)/2$, $\overline{q} = 1 - \overline{p}$ and $\overline{p}_T = (p_e^T + p_c)/2$, $\overline{q}_T = 1 - \overline{p}_T$. The constants z_α and z_β denote the 100α and 100β percentiles of the standard normal distribution. The horizontal axis represents the proportion of patients who express the target and are expected to be responsive to the new treatment.

Case 0: No Treatment effect for R- patients

○ : $\delta_0 = 0, \delta_1 = 0.2, p_c = 0.1$

× : $\delta_0 = 0, \delta_1 = 0.4, p_c = 0.1$

+ : $\delta_0 = 0, \delta_1 = 0.2, p_c = 0.5$

✳ : $\delta_0 = 0, \delta_1 = 0.4, p_c = 0.5$

Case 1: Treatment effect for R- patients is half as large as that for R+ patients

▷ : $\delta_0 = 0.1, \delta_1 = 0.2, p_c = 0.1$

☆ : $\delta_0 = 0.2, \delta_1 = 0.4, p_c = 0.1$

□ : $\delta_0 = 0.1, \delta_1 = 0.2, p_c = 0.5$

–·– : $\delta_0 = 0.2, \delta_1 = 0.4, p_c = 0.5$

Assay Imprecision

Let R be a binary indicator of true tumor status; R=1 for R+ and R=0 for R-.

Let A be a binary indicator of assay result; A=1 for R+ and A=0 for R-.

Let Resp denote binary response; Resp=1 for response and Resp=0 for no response.

Let T denote the treatment group; T=c for control and e for the experimental treatment.

In the paper we have assumed that

$\text{Prob}\{\text{Resp}=1 \mid R=0, T=c\} = \text{Prob}\{\text{Resp}=1 \mid R=1, T=c\}$.

That is, the R- and R+ patients on the control treatment have the same probability of response. Consequently, it is easy to show that

$\text{Prob}\{\text{Resp}=1 \mid T=c, A=0\} = \text{Prob}\{\text{Resp}=1 \mid T=c, A=1\} = p_c$.   (A1)

$$\begin{aligned}\text{Prob}\{\text{Resp}=1 \mid T=e, A=0\} &= \text{Prob}\{\text{Resp}=1, R=0 | T=e, A=0\} + \text{Prob}\{\text{Resp}=1, R=0 | T=e, A=0\} \\ &= \text{Prob}\{\text{Resp}=1 | T=e, R=0\} * \text{Prob}\{R=0 | A=0\} \\ &\quad + \text{Prob}\{\text{Resp}=1 | T=e, R=1\} * \text{Prob}\{R=1 | A=0\}. \\ \\ &= (p_c + \delta_0) * \text{NPV} + (p_c + \delta_1)(1-\text{NPV}) \\ &= p_c + \delta_0 * \text{NPV} + \delta_1 * (1-\text{NPV}) \qquad \text{(A2)}\end{aligned}$$

Where NPV denotes the negative predictive value of the assay.

Subtracting (A1) from (A2), the treatment effect for assay negative patients is

Treatment effect for assay negative patients = $\delta_0 * \text{NPV} + \delta_1 * (1-\text{NPV})$.   (A3)

The quantity δ_0 is the treatment effect for R- patients. If that is zero, then the treatment effect for assay negative patients is $\delta_1 * (1-\text{NPV})$ as indicated in the manuscript.

Similar to the derivation of (A1) and (A2) we can show that:

$\text{Prob}\{\text{Resp}=1 \mid T=c, A=1\} = p_c$

and

$$\text{Prob}\{\text{Resp}=1 \mid T=e, A=1\} = \text{Prob}\{\text{Resp}=1|T=e,R=0\}*\text{Prob}\{R=0|A=1\} + \text{Prob}\{\text{Resp}=1|T=e,R=1\}*\text{Prob}\{R=1|A=1\}$$

$$= (p_c+ \delta_0)*(1\text{-PPV}) + (p_c+ \delta_1)\ \text{PPV}$$
$$= p_c + \delta_0*(1\text{-PPV}) + \delta_1*\text{PPV}.$$

Consequently, the treatment effect for assay positive patients is $\delta_0*(1\text{-PPV}) + \delta_1*\text{PPV}$ which equals $\delta_1*\text{PPV}$ when the treatment effect is limited to R+ patients.