1. Supplementary Material on Section 2

Proof of the asymptotic normal distribution of $\hat{B}$

By Central Limit Theorem, we have

$$\sqrt{n_{ij}}(\hat{\eta}_{ij} - \eta_{ij}) \xrightarrow{d} N(0, \eta_{ij}(1-\eta_{ij})), i = E, C, j = 0, 1$$

Since $\hat{\eta}_{ij}$s are independent of each other, let $\eta = (\eta_{E1}, \eta_{C1}, \eta_{E0}, \eta_{C0})^T$, then we have

$$\sqrt{n}(\hat{\eta} - \eta) \xrightarrow{d} N(0, \Omega)$$

where $\Omega = Diag(\frac{n}{n_{ij}}\eta_{ij}(1-\eta_{ij}))$

Note that $\hat{\pi} \xrightarrow{P} \pi$, let $\pi^* = (\pi, -\pi, 1-\pi, \pi-1)^T$, then we have $\hat{\pi}^* \xrightarrow{P} \pi^*$. Thus, by Slutsky's Theorem, we have

$$\begin{aligned}
\sqrt{n}(\hat{B} - B) &= \sqrt{n}(\hat{\pi}^{*T}\hat{\eta} - \pi^{*T}\eta) \\
&= \sqrt{n}(\hat{\pi}^{*T}(\hat{\eta} - \eta)) + \sqrt{n}(\hat{\pi}^{*T} - \pi^{*T})\eta \\
&\xrightarrow{d} N(0, \pi^{*T}\Omega\pi^*) + \sqrt{n}(\pi^{*T} - \pi^{*T})\eta \\
&= N(0, \pi^2(\frac{n\eta_{E1}(1-\eta_{E1})}{n_{E1}} + \frac{n\eta_{C1}(1-\eta_{C1})}{n_{C1}}) + (1-\pi)^2(\frac{n\eta_{E0}(1-\eta_{E0})}{n_{E0}} + \frac{n\eta_{C0}(1-\eta_{C0})}{n_{C0}}))
\end{aligned}$$

Thus

$$\begin{aligned}
var(\hat{B}) &= \pi^2\tfrac{\eta_{E1}(1-\eta_{E1})}{n_{E1}} + \pi^2\tfrac{\eta_{C1}(1-\eta_{C1})}{n_{C1}} + (1-\pi)^2\tfrac{\eta_{E0}(1-\eta_{E0})}{n_{E0}} + (1-\pi)^2\tfrac{\eta_{C0}(1-\eta_{C0})}{n_{C0}} \\
&= \pi^2 var(\hat{\eta}_{E1}) + \pi^2 var(\hat{\eta}_{C1}) + (1-\pi)^2 var(\hat{\eta}_{E0}) + (1-\pi)^2 var(\hat{\eta}_{C0}).
\end{aligned}$$

And we have

$$\frac{\hat{B} - B}{\sqrt{var(\hat{B})}} \sim N(0, 1)$$

When n is large, we can estimate $var(\hat{B})$ by $\widehat{var}(\hat{B})$ as shown in Section 2.1.

Supplementary Material on Section 4

Testing two hypotheses: Details of determining local optimal π_e, $\pi_e^{localopt}$

The solution for $n(\tilde{\pi}_e; H_{1a}) = n(\tilde{\pi}_e; H_{2a})$ is given as

$$\pi_e^{interact} = \frac{(\delta^2 - B_1^2)[\eta_{E1}(1-\eta_{E1}) + \eta_{C1}(1-\eta_{C1})]}{(\delta^2 - B_1^2)[\eta_{E1}(1-\eta_{E1}) + \eta_{C1}(1-\eta_{C1})] + B_1^2[\eta_{E0}(1-\eta_{E0}) + \eta_{C0}(1-\eta_{C0})]}$$

When $\pi_e^{interact} \in [\pi_e^{opt}, 1]$,

If $\pi_e^{interact} \in [min(\pi, PPV), max(\pi, PPV)]$, then $\pi_e^{localopt} = \pi_e^{interact}$ and $n_{max}^{opt} = n(\pi_e^{interact}; H_{1a}) = n(\pi_e^{interact}; H_{2a})$.

Else, $\pi_e^{localopt} = \pi$ or PPV, which is closer to $\pi_e^{interact}$, and $n_{max}^{opt} = max(n(\pi_e^{localopt}; H_{1a}), n(\pi_e^{localopt}; H_{2a}$

When $\pi_e^{interact} \in [0, \pi_e^{opt})$,

If $\pi_e^{opt} \in [min(\pi, PPV), max(\pi, PPV)]$, then $\pi_e^{localopt} = \pi_e^{opt}$ and $n_{max}^{opt} = n(\pi_e^{opt}; H_{2a})$.

Else, $\pi_e^{localopt} = \pi$ or PPV, which is closer to π_e^{opt}, and $n_{max}^{opt} = max(n(\pi_e^{localopt}; H_{1a}), n(\pi_e^{localopt}; H_{2a}))$.

When $\hat{\pi}_e^{*opt} \notin [0, 1]$,

If $\frac{var(\hat{B}_1; \pi_e = max(\pi, PPV))}{\hat{B}_1^2} > \frac{var(\hat{\delta}; \pi_e = max(\pi, PPV))}{\hat{\delta}^2}$, then $\pi_e^{localopt} = max(\pi, PPV)$ and $n_{max}^{opt} = n(\pi_e^{localopt}; H_{1a})$.

Else, if $\pi_e^{opt} \in [min(\pi, PPV), max(\pi, PPV)]$, then $\pi_e^{localopt} = \pi_e^{opt}$ and $n_{max}^{opt} = n(\pi_e^{localopt}; H_{1a})$, and if $\pi_e^{opt} \notin [min(\pi, PPV), max(\pi, PPV)]$, $\pi_e^{localopt} = \pi$ or PPV, which is closer to π_e^{opt}, and $n_{max}^{opt} = n(\pi_e^{localopt}; H_{1a})$.

Supplementary Material on Section 5

[Figure S1 about here.]

[Table S1 about here.]

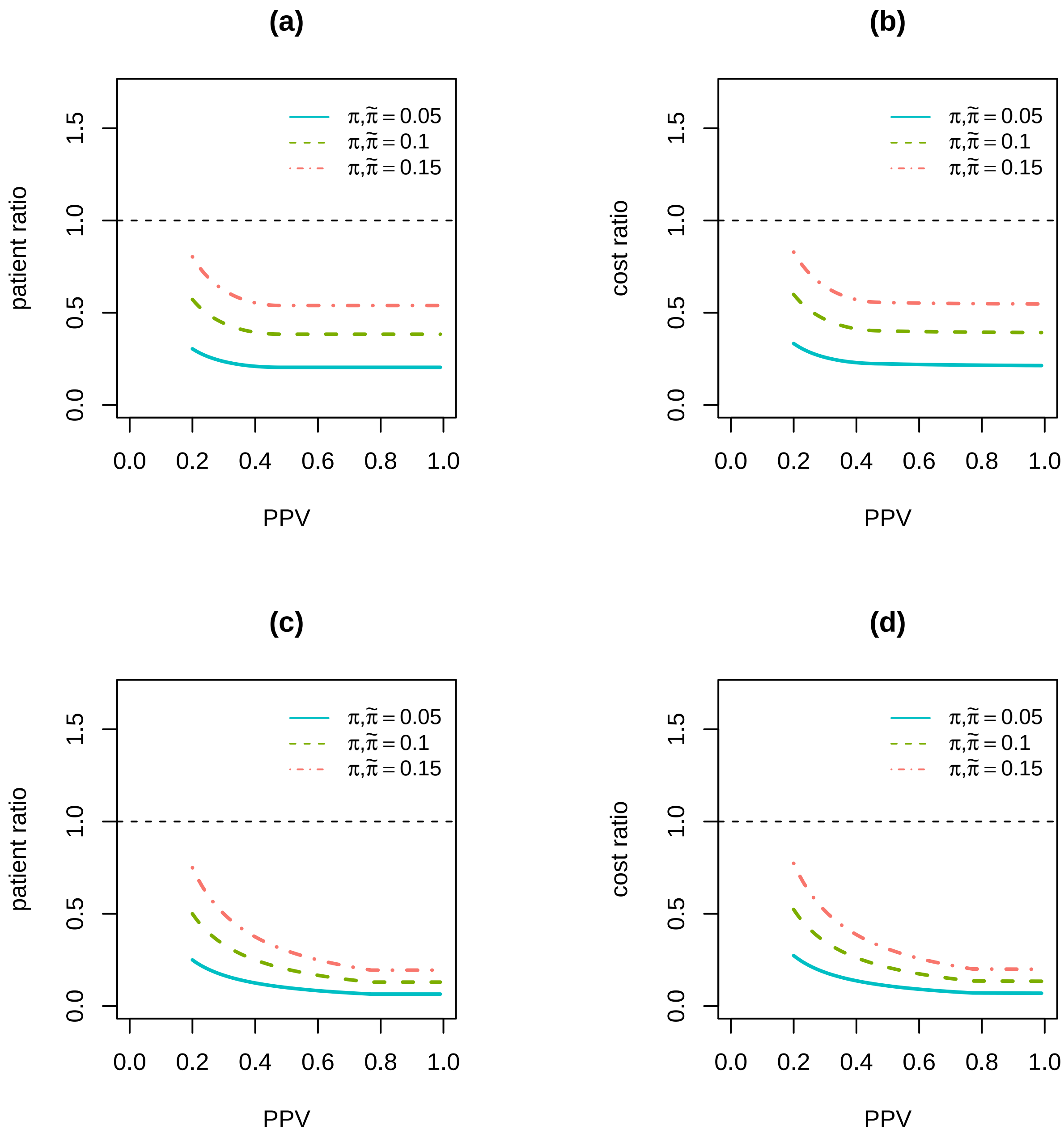

Figure S1: Relationship of patient ratio and cost ratio with PPV for testing B_1 and δ under AEBSD. (a) Patient ratio with quantitative interaction; (b) Cost ratio with quantitative interaction; (c) Patient ratio with qualitative interaction; (d) Cost ratio with qualitative interaction.

Table S1: Numerical results for AEBSD design for testing both B_1 and δ

π	$\tilde{\pi}$	PPV	$\tilde{\pi}_e^{opt}$	n_{aebsd}	ns_{aebsd}	n_{bsd}	n_{ratio}	c_{ratio}	ns_{ratio}
				quantitative interaction					
0.05	0.05	0.2	1.000	5108	102160	16772	0.305	0.334	6.091
		0.5	0.958	3428	65669	16772	0.204	0.223	3.915
		0.8	0.595	3428	40773	16772	0.204	0.216	2.431
0.1	0.1	0.2	1.000	5108	51081	8928	0.572	0.599	5.721
		0.5	0.955	3428	32739	8928	0.384	0.401	3.667
		0.8	0.589	3428	20178	8928	0.384	0.395	2.260
0.15	0.15	0.2	1.000	5108	34054	6356	0.804	0.829	5.358
		0.5	0.951	3428	21745	6356	0.539	0.556	3.421
		0.8	0.582	3428	13291	6356	0.539	0.549	2.091
				qualitative interaction					
0.05	0.05	0.2	1.000	2037	40740	8147	0.250	0.274	5.000
		0.5	1.000	815	16300	8147	0.100	0.110	2.000
		0.8	0.962	529	10182	8147	0.065	0.071	1.250
0.1	0.1	0.2	1.000	2037	20371	4074	0.500	0.524	5.000
		0.5	1.000	815	8150	4074	0.200	0.210	2.000
		0.8	0.962	529	5088	4074	0.130	0.136	1.249
0.15	0.15	0.2	1.000	2037	13580	2716	0.750	0.774	5.000
		0.5	1.000	815	5434	2716	0.300	0.310	2.000
		0.8	0.962	529	3390	2716	0.195	0.201	1.248

$\tilde{\pi}_e^{opt}$ is optimal enrichment proportion for auxiliary positive patient; n_{aebsd} is the number of randomized patients for AEBSD; n_{bsd} is the number of randomized patients for BSD; n_{bsd} is the number of randomized patients for BSD; n_{ratio} is the ratio of n_{EBSD} and n_{BSD}; ns_{ratio} is the ratio of the number of screened patients for AEBSD versus BSD; c_{ratio} is the cost ratio for conducting AEBSD and BSD. $\alpha_1 = \alpha_2 = 0.025, \beta_1 = \beta_2 = 0.1$. The unit cost is 500 for ascertaining the true biomarker, the average unit cost is $10,000$ for treatment and follow-up and the unit cost is 50 for ascertaining the auxiliary variable.