On Cost-Effectivenes of Screening Using a Marker/Risk-model

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1 Introduction

Consider the problem of screening for cancer when a marker/risk-model is available. Each individual has a marker value or a risk score derived using a risk-model and the patient's characteristics. Individuals with high marker values or high risk scores are then tested for cancer. The problem is to identify an optimal cutoff value above which an individual needs to be tested for cancer. Notice that the lower the cutoff for the screening test is, the more likely a cancer case is detected (higher effectiveness), but also the higher the number of negative tests (higher costs).

2 Main

Katki **?** proposed a new measure of evaluating the risk before and after incorporating the marker information[1]. The mean risk classification (MRS) measure they proposed measure is the average change in risk (postttest - pretest). Briefly, their approach is to quantify the value of marker M to predict the outcome D by $P(D+|M+) - P(D+)$ if $M+$, and by $P(D-|M-) - P(D-)$ if $M-$, which yields (on average)

$$\begin{aligned} MRS &= [P(D+|M+) - P(D+)] \cdot P(M+) + [P(D-|M-) - P(D-)] \cdot P(M-) \quad (1) \\ &= 2[P(D+, M+) - P(D+) \cdot P(M+)]\,. \quad (2) \end{aligned}$$

Here $M+$ denotes the event $M \geq m_0$, for some cutoff value m_0, while $M-$ denotes the event $M < m_0$.

It follows from (2) that MRS is simply twice the covariance of $D+$ and $M+$. Therefore MRS is indeed a measure of association between the marker and the outcome, but it is not immediately clear how relevant it is if the goal is to find an optimal cutoff value m_0.

Katki **?** further show that

$$MRS = 2J \cdot \pi(1-\pi) = 4(AUC - 0.5) \cdot \pi(1-\pi)\,, \quad (3)$$

where $\pi = P(D+)$ and J is Youden's index. However, notice that π does not depend on the marker M, so that all three measures MRS, AUC and J are equivalent when it comes to choosing the marker cutoff value m_0.

Alternatively, one can introduce a cost-effectiveness framework for this problem as follows. Assume the effectiveness score for a subject who does not develop cancer is 1, and let e_1 denote the effectiveness score for a subject with a positive marker M which then tests positive for cancer; similarly, let e_2 be the effectiveness score for subject who is either not screened using the marker M or is $M-$, but then develops cancer. Since the cancer cases identified using the marker $M+$ are diagnosed earlier, it follows that $e_1 > e_2$, and both are less than 1.

Let c_m denote the cost of a marker evaluation, c_0 denote the cost of standard test for cancer, c_1 the cost of treatment for a cancer case diagnosed early (i.e., tested positive for M), and c_2 the treatment cost for a cancer case diagnosed late (i.e., either not screened with M or tested negative for M).

Two scenarios are considered at individual level:

[1] See the online MRS webtool.

1. No screening for M. There are two possibilities:
   (a) The individual has cancer ($D+$): cost is $c_0 + c_2$ and effectiveness is e_2
   (b) The individual does not have cancer ($D-$): cost is 0, effectiveness is 1.
2. Screening for M. There are four possibilities:
   (a) The screening is positive and the individual has cancer ($M+, D+$): cost is $c_m + c_0 + c_1$and effectiveness is e_1.
   (b) The screening is positive but the individual does not have cancer ($M+, D-$): cost is $c_m + c_0$and effectiveness is 1.
   (c) The screening is negative but the individual has cancer ($M-, D+$): cost is $c_m + c_0 + c_2$and effectiveness is e_2.
   (d) The screening is negative and the individual has not have cancer ($M-, D-$): cost is $c_m$and effectiveness is 1.

Let C and E denote the cost and effectiveness without screening, and C_M and E_M with screening. One has

$$\begin{aligned}
\mathcal{E}(C) &= (c_0 + c_2) \cdot P(D+) \\
\mathcal{E}(E) &= e_2 \cdot P(D+) + P(D-) \\
\mathcal{E}(C_M) &= c_m + [1 - P(D-, M-)] \cdot c_0 + P(D+, M-) \cdot c_2 + P(D+, M+) \cdot c_1 \\
\mathcal{E}(E_M) &= P(D-) + P(D+, M+) \cdot e_1 + P(D+, M-) \cdot e_2 \,,
\end{aligned}$$

so that the differences in cost and effectiveness between the two scenarios are

$$\begin{aligned}
\Delta C &= c_m + c_0 \cdot P(M+) + (c_1 - c_2 - c_0) \cdot P(D+, M+) \\
\Delta E &= (e_1 - e_2) \cdot P(D+, M+) \,.
\end{aligned}$$

One then selects m_0 based on both ΔC and ΔE. Notice that ΔE is maximized when $m_0 = -\infty$ (i.e., screen everybody).

3 Illustration

Let $\tilde{M}$ such that the true risk of cancer is

$$P(D = 1|\tilde{M} = \tilde{m}) = L(\alpha_0 + \alpha_1 \cdot \tilde{m}) \,, \tag{4}$$

where $L(x) = \exp(x)/(1 + \exp(x))$.

However, $\tilde{M}$ is not directly observed. Instead, one observes a marker M, where

$$M = \tilde{M} + \epsilon \,. \tag{5}$$

We further assume $\epsilon \sim N(0, \sigma_\epsilon^2)$, and $M \sim N(\mu_M, \sigma_M^2)$. One obtains

$$\begin{aligned}
P(M+) &= 1 - \Phi\left(m_0 - \mu_M, 0, \sigma_M^2 + \sigma_\epsilon^2\right) \\
P(D+, M+) &= \int_{m_0}^{\infty} \int_{\infty}^{\infty} L(\alpha_0 + \alpha_1 \cdot (m - \epsilon)) \cdot \phi(\epsilon, 0, \sigma_\epsilon^2) \cdot \phi(m, \mu_M, \sigma_M^2) d\epsilon \, dm
\end{aligned}$$

while $P(D+)$ is obtain by replacing m_0 by ∞ in the expression for $P(D+, M+)$ above.

The approaches are illustrated using $\alpha_0 = -6.67$, $\alpha_1 = 1$, $\mu_M = 1$, $\sigma_M = 1$, $c_m = 0.5$, $c_0 = 0.01$, $c_1 = 1$ and $c_2 = 2$.

The optimal m_0 with respect to the ICER (i.e., lowest ICER) and the corresponding ICER are

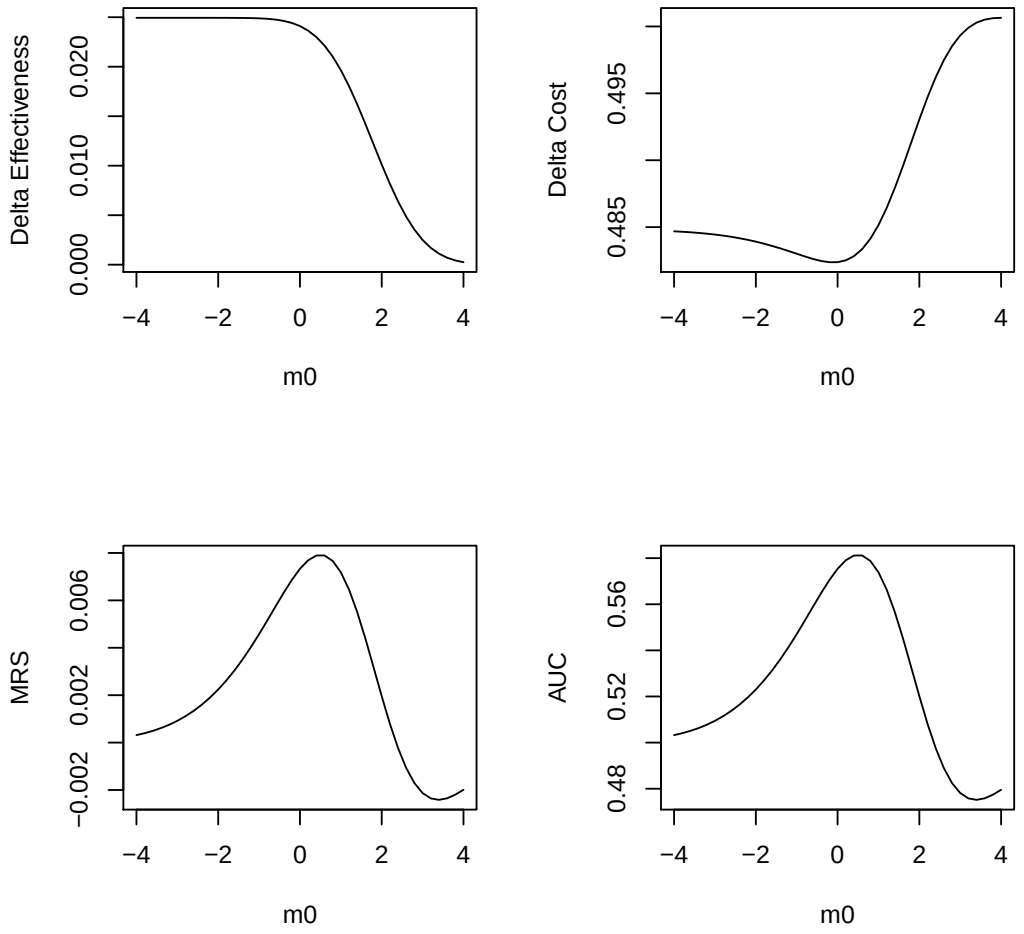

Figure 1: Effectiveness, cost, MRS and AUC as a function of the cutoff value m_0.

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[1] -1.4
```

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[1] 19.39465
```

The optimal m_0 with respect to the AUC (i.e., largest AUC) and the corresponding ICER are

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[1] 0.6
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[1] 0.5811674
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The optimal m_0 with respect to the MRS (i.e., largest MRS) and the corresponding ICER are

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[1] 0.6
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[1] 0.00789477
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As expected, MRS and AUC give identical results, but which are different than the ones for ICER. Moreover, the m_0 value selected by MRS/AUC has an ICER value of

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[1] 21.83748
```

or a

```
[1] 11.18642
```

percent (%) increase relative to the optimal ICER.

4 Discussion

Various approaches for calculating an optimal cutoff for a screening marker were considered. The MRS measure, which is twice the covariance between $D+$ and $M+$ is shown to be equivalent to AUC with respect to selecting this optimal cutoff m_0.

Note that the above calculations depend on the unobserved α_0, α_1 and σ_ϵ. However, for various values of σ_ϵ, one can estimate α_0 and α_1 based on the coefficients obtained by regressing $D = 1$ on M, which can then be used to find the optimal cutoff value m_0.

5 Incremental Net Benefit

A large Incremental Cost-Effectiveness Ratio (ICER) can mask a small difference, and vice-versa. For this reason, the Incremental Net Benefit (INB) is better:

$$INB \quad = \quad \Delta E - \Delta C.$$

This requires redefining Effectiveness as the dollar value of each life-year gained.

5.1 Application to deciding who should undergo *BRCA1/2* genetic testing

We previously applied MRS to the controversy over who should get tested for mutations in the *BRCA1/2* genes, which cause high risks of breast and ovarian cancer (**?**). The mutations are rare in the general population ($\approx 0.25\%$), but are 10 times more common among Ashkenazi-Jews (**?**). Currently, according to the UK National Institute for Health and Care Excellence (NICE) and the US Preventive Services Task Force, women are referred for mutation testing only if they have a strong family history of breast or ovarian cancer (**?**) as quantified by a risk model calculating that their risk of carrying a mutation exceeds 10% (**?**). However, as mutation-testing costs fall, prominent voices have called for testing *all* women (**??**). *BRCA1/2*

testing is already being offered to a large unselected Canadian population as a demonstration project (**?**). Testing all women would strain clinical resources by testing millions of women, 99.75% of whom will test negative. At US $500-$1,000 per test, testing millions of women has clear commercial implications.

In contrast, we recently demonstrated that 80% of Ashkenazi-Jewish mutation-carriers could be identified by testing only 44% of Ashkenazi-Jewish women (**?**). This is achieved by a low mutation-risk threshold of 0.78%, far lower than the current 10% UK NICE and US recommendation. However, we could not formally justify any choice of risk-threshold. To better understand the implications of different choices of risk threshold, we previously considered multiple metrics, including AUC, Net Benefit, and MRS/NBI (**?**). We showed that risk thresholds between 0.78% to 5.0% maximized the MRS ($\approx$ 1.7%) for Ashkenazi-Jewish women, and for the general population, thresholds between 0.07% to 0.56% maximized the MRS ($\approx$ 0.18%) (**?**). Here we compare risk thresholds that maximize MRS to risk thresholds that maximize the INB.

We use data on 4,589 volunteers (102 *BRCA1/2* mutation carriers) from the Washington Ashkenazi Study (WAS) (**?**). We calculated each volunteer's risk of carrying a mutation, based on their self-reported family-history of breast/ovarian cancers, using the BRCAPRO risk model (**?**). Here M is the BRCAPRO risk score, and because BRCAPRO is a well-calibrated risk model (**?**), $m_0 = R$, i.e. the cutpoint m_0 equals the risk threshold R. Disease D indicates the presence of a *BRCA1/2* mutation.

5.2 Costs and Effectiveness of *BRCA1/2* genetic testing, preventive interventions, and cancer treatments

Let us redefine Effectiveness as the dollar value of the life-years gained by undergoing genetic testing. Let us presume that women without mutations have a normal lifespan of age 80. *BRCA1/2* mutation-carriers have 5.7 fewer years of expected life (**?**), so we set their life-expectancy to age 74.

If mutation-carriers get genetic testing, they will act to reduce their cancer risks. Most mutation-carriers undergo oophorectomy, the removal of ovaries. Some also choose to have mastectomy, the removal of breasts. These surgeries reduce cancer risk drastically, but not entirely; there is typically a 10% chance that cancer occurs in each organ anyway. These women also undergo frequent screening, and if cancer is found early, hopefully treatment is more effective. I don't know what their life-expectancy is, but let me set it as age 78.

I set the dollar-value of each life-year gained as $100,000 per year. Thus Effectiveness is

$$e_1 - e_2 \quad = \quad (78 - 74) \times \$100,000 = \$400,000$$

For costs, c_m is the cost of using the BRCAPRO risk model. This is very low-cost, but you need to come to the doctor's office, your family history has to be elicited, it takes time. I will set it to the cost of a doctor's visit, say $100.

c_0 is the cost of the BRCA genetic test. Prices are falling, it is now about $1,000.

c_1 is the cost of interventions for BRCA mutation carrier found by screening. Generally they will undergo risk-reducting interventions, at least oophorectomy and perhaps also mastectomy, and then frequent lifetime cancer screening. But cancer can still occur, and those 25% (*should this be related to the 10% mentioned above?*) who still get cancer incur cancer treatment costs. For c_2, this is the cost of cancer treatment for mutation carriers who are not found until cancer is diagnosed. All of them will require full cancer treatment. I don't know how to specify c_1, c_2. Let me set them both equal to $100,000 for now.

Thus we have for Costs:

$$\begin{aligned} c_m &= \$100 \\ c_0 &= \$1,000 \\ c_1 &= \$100,000 \\ c_2 &= \$100,000. \end{aligned}$$

5.3 MRS vs. INB for *BRCA1/2* genetic testing

Figure 2 (left panels) show the increase in effectiveness and costs due to genetic testing for both Ashkenazi-Jews and the general population, as a function of the BRCAPRO risk threshold to offer women genetic testing. When the threshold is low, most everyone is offered testing. The cost is highest here, and decreases down to only marker testing cost (i.e. BRCAPRO risk model cost) if no one is offered genetic testing. Effectiveness is also highest if everyone is tested for mutations, and goes down to zero if no one is. Note that while the cost scale (y-axes) are the same, the effectiveness scale (right-axes) is about 10 times higher for Ashkenazi-Jews. This reflects that mutations are 10 times more common for Ashkenazi-Jews.

(Parenthetically, note that in the limits of testing no one or testing everyone, I should subtract out marker cost c_m because the marker is unnecessary. The limits of the INB curve don't equal the correct limits. I should probably add two points on the figures for the INBs of testing everyone or no one.)

Figure 2 (right panels) compare the MRS to INB. MRS is zero if no one, or everyone, gets mutation testing, and always peaks at threshold equals prevalence (dotted line). INB for Ashkenazi-Jews is highest at a threshold of zero, meaning everyone should get testing This happens because the of the high value attached to each life-year gained, and Ashkenazi-Jews are much more likely to gain this benefit. For the general population, note that $INB < 0$ for the lowest risk thresholds and for risk thresholds greater than 10% (recall that 10% is the current official threshold in the US and UK.). These are thresholds where net harm would be done to the population.

Importantly, for the general population, the INB curve is proportional to the MRS curve (i.e. the curves overlap, but note the very different scales on the left-axis and right-axis). Thus INB and MRS are maximized at the same risk-threshold and give the same answer. The next section shows that this happens because the costs and effectiveness balance each other in a special way.

5.4 When is INB proportional to MRS, so they have the same maximum?

$$\begin{aligned} INB &= \Delta E - \Delta C \\ &= [(e_1 - e_2) - (c_1 - c_2 - c_0)]P(D+, M+) - c_m - c_0 P(M+). \end{aligned}$$

Define $p = P(M+)$ and $\pi = P(D+)$. Recall that $P(D+, M+) = MRS/2 + p\pi$. Define the net effectiveness of early intervention: $e = (e_1 - e_2) - (c_1 - c_2)$. Then

$$\begin{aligned} INB &= (e + c_0)[MRS/2 + p\pi] - c_m - c_0 p \\ &= (e + c_0)MRS/2 - c_m + p[e\pi + c_0\pi - c_0] \\ &= (e + c_0)MRS/2 - c_m + p[e\pi - c_0(1 - \pi)]. \end{aligned}$$

Note that $INB \propto MRS$ if $e\pi - c_0(1 - \pi) = 0$, which happens when

$$\frac{\pi}{1 - \pi} = \frac{c_0}{e} = \frac{c_0}{(e_1 - e_2) - (c_1 - c_2)}, \quad or \quad \pi_{INB} = \frac{c_0}{c_0 + e}.$$

INB and MRS will have the same maximum if the odds of disease equals the ratio of confirmatory test cost to the net effectiveness of early intervention. Let us call this critical prevalence π_{INB} to indicate that this is the disease prevalence where MRS and INB yield the same optimal threshold. In Figure 2, $c_0/e = \$1,000/(\$400,000 - \$0) = 0.25\%$, and thus the critical prevalence is $\pi_{INB} = 0.25\%$. For the general population, $\pi = 0.26\%$, which is very close to the critical prevalence.

There is no reason for the confirmatory test cost and net effectiveness to balance in a way that their ratio equals the prevalence odds. However, it is useful to calculate the critical prevalence and compare to the observed disease prevalence, to qualitatively understand which way the threshold for maximum MRS changes when costs and effectiveness are accounted for. For example, for Ashkenazi-Jews, the prevalence is much higher than the critical prevalence ($2.5\% > 0.25\%$). Thus immediately you know that the optimal threshold will decrease from prevalence towards testing more women than MRS would indicate.

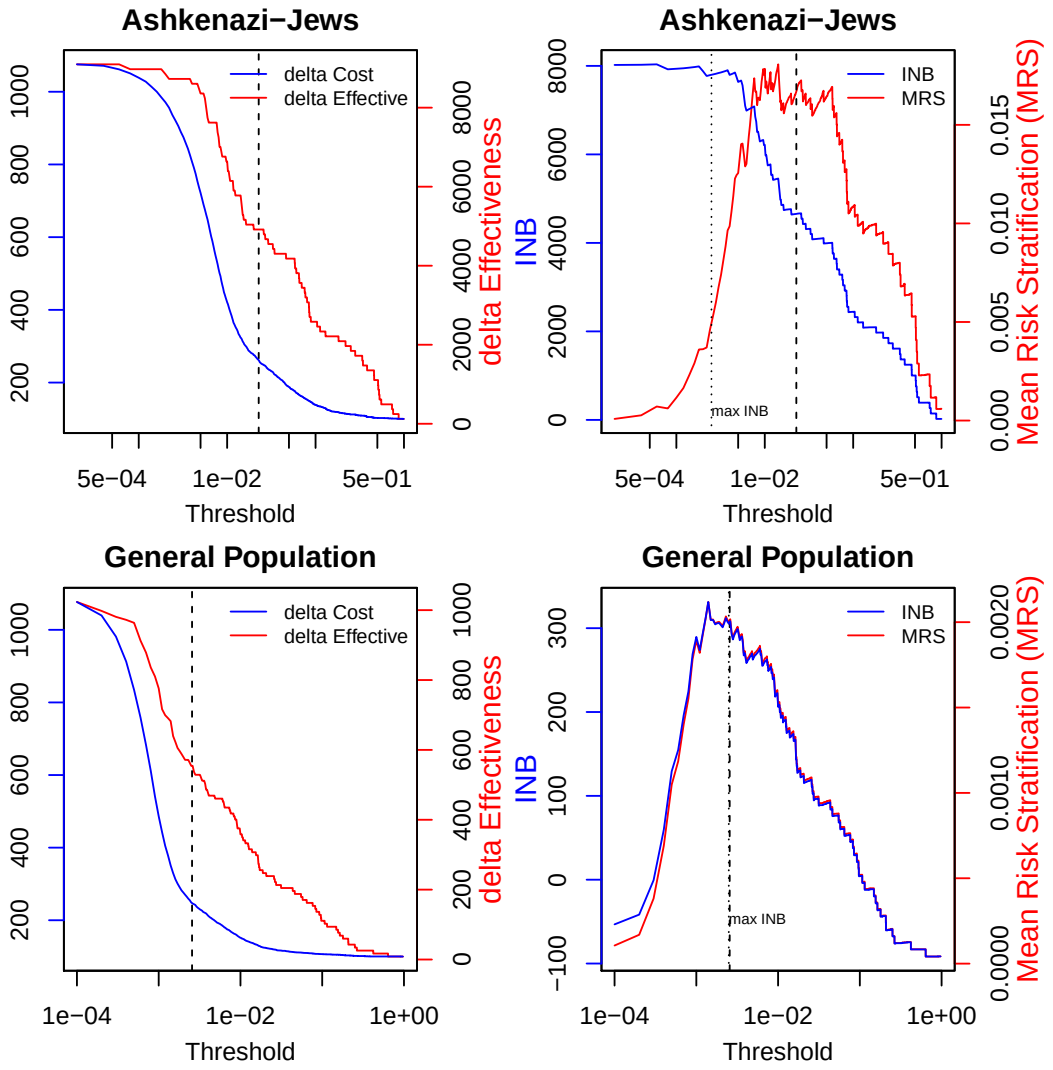

Figure 2: Effectiveness, cost, MRS and INB as a function of the cutoff Threshold values m_0. The marker is the BRCAPRO model score (cutoff at thresholds m_0), the confirmatory test is the BRCA genetic test itself. The outcome $D+$ is having a BRCA mutation. Costs c_1 and c_2 include risk-reducing interventions for the found BRCA mutation carriers, and cost of future cancer treatments. Effectiveness is the dollar value of the the life-years gained by early intervention. First row is for Ashkenazi-Jews, second row is for general population. Dashed line is where threshold equals mutation prevalence (2.3% for Ashkenazi-Jews, 0.26% for general population). Dotted line is the risk threshold that maximizes INB which is π_{INB}

6 Optimal cutoff threshold to maximize Incremental Net Benefit (INB)

Recall that the optimal threshold to maximize MRS is the same as that for Youden's index, which is risk threshold equals prevalence (**?**), see Appendix.

Here I derive the optimal threshold that maximizes INB. Recall that

$$INB \;=\; (e+c_0)MRS/2 - c_m + p[e\pi - c_0(1-\pi)] \;=\; (e+c_0)MRS/2 - c_m + p[\pi(e+c_0) - c_0].$$

INB increases as MRS increases, but the last term decreases INB as $p = P(M+)$ increases. To find the optimal threshold, let's find a simpler function with the same maximum Dividing both sides by the constant $e + c_0$ yields

$$\frac{INB}{e+c_0} \;=\; MRS/2 - \frac{c_m}{e+c_0} + p[\pi - \pi_{INB}].$$

Because $MRS = 2J\pi(1-\pi)$, then dividing by the constant $\pi(1-\pi)$ yields

$$\frac{INB}{(e+c_0)\pi(1-\pi)} \;=\; J - \frac{c_m}{(e+c_0)\pi(1-\pi)} + p\frac{\pi - \pi_{INB}}{\pi(1-\pi)}.$$

Explicitly writing INB, J, and p as functions of cutoff thresholds m_0,

$$INB(m_0) \;\propto\; J(m_0) + p(m_0)c,$$

where $c = \frac{\pi - \pi_{INB}}{\pi(1-\pi)}$. This is a simpler function to optimize. Following the Appendix, we optimize by differentiating $J(m_0) + p(m_0)c$

$$J(m_0) + p(m_0)c \;=\; \int_{m_0}^{\infty} P(M = m|D+) - P(M = m|D-) + cP(M = m)\; dm$$

with respect to the cutpoint m_0 using the Leibniz Integral Rule:

$$\frac{d(J(m_0) + p(m_0)c)}{dm_0} \;=\; P(M = m_0|D-) - P(M = m_0|D+) - cP(M = m_0).$$

Setting the derivative equal to zero, and using Bayes' rule:

$$cP(M = m_0) + \frac{P(D+|M = m_0)P(M = m_0)}{\pi} \;=\; \frac{P(D-|M = m_0)P(M = m_0)}{1-\pi}.$$

Note that the risk threshold is defined as $R(m_0) = P(D+|M = m_0)$. Note that $R(m_0) = m_0$ because M is a risk-model. Canceling $P(M = m_0)$,

$$\begin{aligned}
\frac{c\pi + R}{\pi} &= \frac{1-R}{1-\pi} \\
\pi(1-R) &= (c\pi + R)(1-\pi) \\
\pi(1-R) &= c\pi(1-\pi) + R(1-\pi) \\
R &= \pi - c\pi(1-\pi) \;=\; \pi - (\pi - \pi_{INB}) \;=\; \pi_{INB}
\end{aligned}$$

Thus INB is maximized at risk threshold $R = \pi_{INB} = c_0/(e+c_0)$.

Note that π_{INB} only requires the utilities: genetic test cost c_0 and the net effectiveness of early intervention $e = (e_1 - e_2) - (c_1 - c_2)$. None of the objective aspects of the problem matter, like disease prevalence, etc. This is unlike MRS, Youden's index, AUC, Vickers's Net Benefit gain, which are all maximized at risk threshold equals disease prevalence, regardless of your utilities.

Note that π_{INB} doesn't require the marker cost c_m. Thus you don't need to specify c_m to find the optimal risk threshold. Because c_m contributes to the INB level, we only need it to make sure that the INB is greater than the INBs for testing no one or testing everyone.

Figure 2, dotted line, is the optimal risk threshold cutoff for INB, $R = \pi_{INB} = 0.25\%$. For the general population, this coincides with disease prevalence, and thus $INB \propto MRS$ so they are maximized at the same risk threshold. For Ashkenazi-Jews, $R = \pi_{INB} = 0.25\%$ is to left of prevalence $\pi = 2.5\%$, which tests 85% of Ashkenazi-Jews to find 96% of BRCA mutation carriers. The INB at 0.25% is about \$7,800. INB for testing everyone is $INB_{all} = \$8,119$, which of course removes the \$100 cost of doing the marker, which is the BRCAPRO risk model. For Ashkenazi-Jews, INB is maximixed where everyone gets genetic testing for BRCA mutations, regardless of BRCAPRO risk score.

If we halve the dollar value of each life-year gained from \$100,000 to \$50,000, then the optimal risk-threshold doubles to $\pi_{INB} = 0.50\%$. For the general-population, the $INB > 0$ for risk threshlds from 0.17%-1.87% and the peak is indeed roughly at 0.50% (INB=\$33.94, barely positive). For Ashkenazi-Jews, the interior peak is at 0.50%, but testing everyone still has a slightly higher INB.

If we further halve the dollar value of each life-year gained to \$25,000, then the optimal risk-threshold doubles to $\pi_{INB} = 0.99\%$. For the general-population, all $INB < 0$, the least bad INB is for testing no one (this is a case where we can only minimize harm, there are no good options). For Ashkenazi-Jews, $INB > 0$ for risk-thresholds of 0%-5%, and the peak is around 0.99% (INB=\$1,235), although numerically 0.54% has best INB=\$1,400.

Ionut, why don't you calculate INB and the optimal π_{INB} for your logistic regression example?

7 Minimum MRS needed for a biomarker to be better than testing no one or testing everyone

How much MRS do we need to ensure that using the marker is better than testing no one or testing everyone? This would set the minimum MRS necessary, and give scientists an objective MRS goal to shoot for when designing new biomarker tests. Let's presume $MRS > 0$ and $e > 0$, else we never screen.

I've commented out some work below because I need to think about it more, and I just want to send you what I have right now.

8 Added

8.1 On Section 6, "Optimal cutoff threshold ..."

There are a lot of notations and changes in variables in Section 6, it seems difficult to follow. Here is a simplified version of your derivations.

Since M is an unbiased risk-model, one has

$$P(D+|M=m) = m\,. \tag{6}$$

Let f_M denote the density of M, so that one obtains

$$\begin{aligned} P(M+) &= \int_{m_0}^{\infty} f_M(m)\,dm \\ P(D+,M+) &= \int_{m_0}^{\infty} P(D+|M=m)\cdot f_M(m)\,dm \\ &= \int_{m_0}^{\infty} m\cdot f_M(m)\,dm\,. \end{aligned} \tag{7}$$

INB can be writen as

$$INB = A\cdot P(D+,M+) - B\cdot P(M+) - C\,, \tag{8}$$

where $A = (e_1 - e_2) - (c_1 - c_2 - c_0)$, $B = c_0$ and $C = c_m$. Replacing (7) in (8) yields

$$INB = A \cdot \int_{m_0}^{\infty} m \cdot f_M(m)\, dm - B \cdot \int_{m_0}^{\infty} f_M(m)\, dm - C\,. \tag{9}$$

Taking derivative with respect to m_0 and setting it to zero yields

$$-A \cdot m_0 \cdot f_M(m_0) + B \cdot f_M(m_0) = 0\,,$$

so that INB is maximized at $m_0 = B/A$.

8.2 Statistical Inference for INB

Consider a random sample of individuals with both marker (M) values and disease status (D) available, and let n denote the sample size. Then, given a cutoff marker value m_0, the quantities $P(D+, M+)$ and $P(M+)$ can be obtained as the sample proportions of the individuals with positive marker and disease present (denoted by $\hat{P}(D+, M+)$), and positive marker (denoted by $\hat{P}(M+)$), respectively. Moreover, the joint distribution of these sample proportions is asymptotically bivariate normal,

$$\left(\hat{P}(D+, M+), \hat{P}(M+)\right)' \sim N\left((P(D+, M+), P(M+))', \Sigma/n\right)\,, \tag{10}$$

where $\Sigma_{11} = P(D+, M+)[1 - P(D+, M+)]$, $\Sigma_{22} = P(M+)[1 - P(M+)]$, and $\Sigma_{12} = P(D+, M+) \cdot P(M+)$. It follows that $\widehat{INB}$, the sample estimate of INB obtained by replacing $P(D+, M+)$ and $P(M+)$ by their sample estimates, is asymptotically normally distributed with mean INB and variance

$$\sigma^2_{INB} = A^2 \cdot \Sigma_{11}/n + B^2 \cdot \Sigma_{22}/n - 2 \cdot A \cdot B \cdot \Sigma_{12}/n\,. \tag{11}$$

The results are presented in Figure 3 for Ashkenazi-Jewish population. *Hormuzd, INB in Figure 3 looks a little different than in your Figure 2, not sure whether I got the variables right... Also, I didn't know the sample size for the sample from the general population (I used n = 4589 for AJ) so couldn't plot for the general population.*

Notice that a model-based estimator can be obtained as well by employing the joint model for M and D described in (7), and statistical inference can be based on the asymptotic normality of the MLE.

8.3 Sensitivity Analyses

8.3.1 With respect to input parameters

It is common in cost-effectiveness to see how sensitive the results are (i.e., INB herein) with respect to changes in input parameters. The input parameters are the cost (i.e., c_0, c_1, c_2 and c_m)and the effectiveness (i.e., e_1 and e_2) parameters. Since INB is linear in these parameters and $P(D+, M+)$ and $P(M+)$ are assumed fixed, it is straightforward to assess the sensitivity of the results (e.g., assuming these cost and effectiveness input parameters are normally distributed yields a normally distributed INB).

8.3.2 With respect to the risk-model

Now that I look at it in this way, the model in Section 3 could be thought of as allowing for error in the risk-model (still unbiased, but with some random error), hence it is a sensitivity analysis. Could you please provide density plots for the risk marker M in AJ and the general population? Separately, we want to see whether we could employ some parametric model.

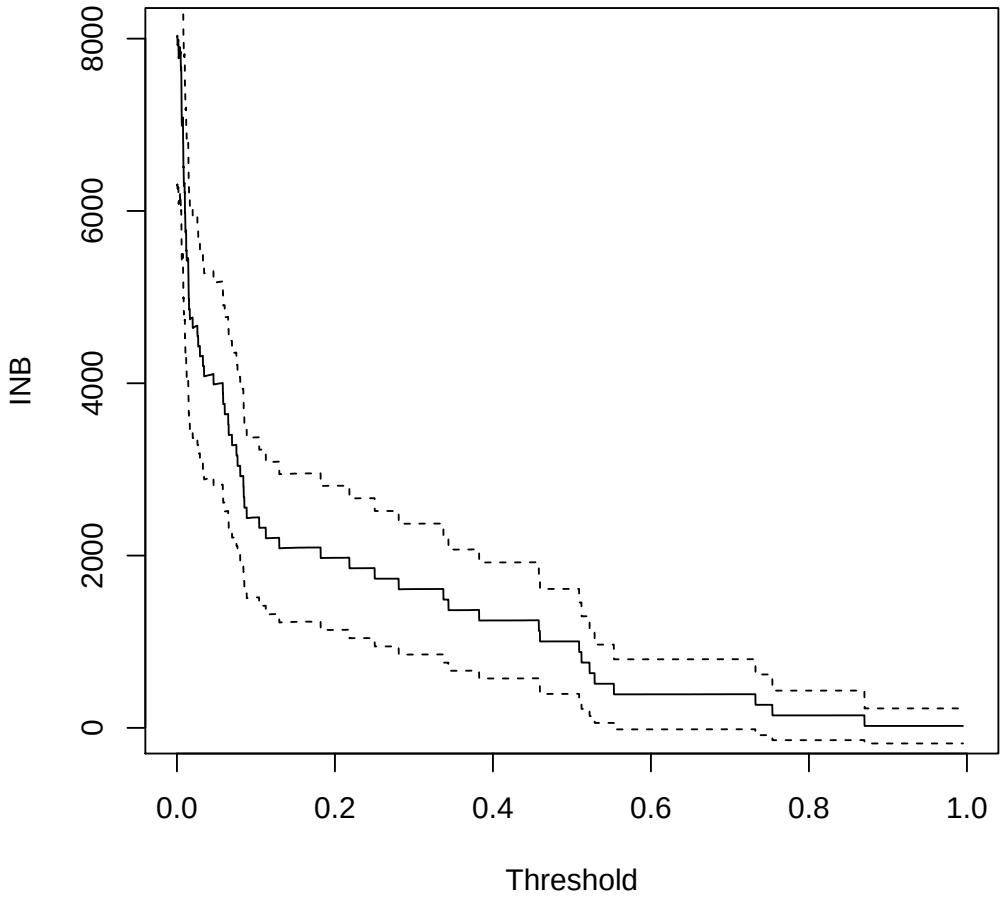

Figure 3: INB (solid line) with 95% confidence intervals (dashed lines) for Ashkenazi-Jews.

Appendix

MRS is maximized when dichotomizing at disease prevalence

Recall that $MRS(m_0) = 2J(m_0)\pi(1-\pi)$, where $J(m_0)$ is Youden's index calculated at cutpoint m_0. MRS is maximized as a function of cutpoint m_0 when Youden's index $J(m_0)$ is maximized, which occurs when dichotomizing at disease prevalence: $P(D+|M = m_0) = P(D+) = \pi$. To prove this we differentiate Youden's index as a function of m_0

$$J(m_0) \quad = \quad \int_{m_0}^{\infty} P(M = m|D+) - P(M = m|D-)\ dm$$

with respect to the cutpoint m_0 using the Leibniz Integral Rule:

$$\frac{dJ(m_0)}{dm_0} \quad = \quad P(M = m_0|D-) - P(M = m_0|D+).$$

Setting the derivative equal to zero, and using Bayes' rule:

$$\begin{aligned} \frac{P(D+|M = m_0)P(M = m_0)}{\pi} &= \frac{P(D-|M = m_0)P(M = m_0)}{1-\pi} \\ P(D+|M = m_0) &= \pi \end{aligned}$$

Thus dichotomizing marker/model M at m_0 at disease prevalence π maximizes Youden's index and thus MRS. Thus the "sweetspot" of risk-thresholds that maximize MRS will always include disease prevalence. At this cutpoint, MRS equals Total Gain (**?**).