The Ideal Evaluation of a Risk Prediction Model: A Randomized Clinical Trial

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Context

Often a risk prediction model is developed to identify high risk subjects who can benefit from preventative therapy

- E.g. Framingham risk model to identify subjects to treat with statins for CVD prevention
- E.g. Gail risk model to identify women to treat with tamoxifen for the prevention of breast cancer
Concept

The assumption is that the cost vs. benefit of treatment is favorable only for subjects at high risk.

In CVD prevention, the mantra has become “match the intensity of treatment to the risk of the event"
(American College of Cardiology/American Heart Association Guideline on the Assessment of Cardiovascular Risk)
Implicit Assumption

Implicit is that the net benefit of treatment varies as a function of risk of the event

Net benefit = Benefit - Cost of treatment,

Cost = side effects/toxicity, burden, and/or monetary cost
Benefit = reduction in event rate

Otherwise, a uniform treatment strategy would be optimal.
More precisely (Gail JNCI, 2009),

\[ T = 1 \text{ indicates treatment, } T = 0 \text{ no treatment} \]
\[ D = 1 \text{ indicates an event, } D = 0 \text{ no event} \]
\[ X = \text{marker(s)} \]
\[ \text{Risk}(X) = P(D = 1|T = 0, X) \]
\[ RR = \frac{P(D=1|T=1)}{P(D=1|T=0)}, \text{ assumed constant} \]
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**Cost** = cost of treatment vs. no treatment, assumed constant

**Benefit** = benefit of treatment vs. no treatment

\[ = P(D = 1 \mid T = 0, X) - P(D = 1 \mid T = 1, X) \]
\[ = \text{Risk}(X)(1 - RR) \]
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\textbf{Cost} = \text{cost of treatment vs. no treatment, assumed constant}
\textbf{Benefit} = \text{benefit of treatment vs. no treatment}
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\[ = \text{Risk}(X)(1 - RR) \]

\text{NB}(X) = \text{Benefit} - \text{Cost} = \text{Risk}(X)(1 - RR) - \text{Cost}
Net Benefit vs. Risk

\[ NB(X) = \text{Benefit} - \text{Cost} \]
\[ = \text{Risk}(X)(1 - RR) - \text{Cost} \]
Optimal treatment rule is:

\[
treat \text{ if } \text{NB}(X) = \text{Risk}(X)(1 - RR) - \text{Cost} > 0,
\]
i.e. \[
\text{Risk}(X) > \frac{\text{Cost}}{1 - RR}
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\]

- Well-known decision-theoretic result, for special case where Benefit = Risk(X)(1 - RR) (Pauker and Kassirer, 1975)
The Value of the Risk Model

\[ \text{Value} = \text{reduction in event rate}, \text{less the cost of treatment} \]

Estimated using

- Data for cohort of untreated subjects \((T = 0)\), to estimate distribution of Risk\((X)\)
- RCT estimates of \(RR\) and Cost of treatment
Example

Gail (JNCI, 2009) assessed the value of the Gail model* for identifying healthy older white women at high risk of developing breast cancer over the next year, who can be recommended tamoxifen for breast cancer prevention.

*Gail model predicts risk of breast cancer given age at menarche, age at first live birth, number of previous breast biopsy examinations, total number of first-degree relatives with breast cancer
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Benefit of tamoxifen = reduction in risk of breast cancer = Risk($X$)(1 – RR),

where Risk($X$) = Gail risk, distribution based on NHIS data

RR = 0.51 based on RCT data
Cost of tamoxifen = change in risk of “secondary events”– hip fracture, endometrial cancer, stroke, and pulmonary embolism– due to tamoxifen, based on RCT data

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\(RR = 0.51\) based on RCT data

Value of Gail model is a very modest 0.2% reduction in the composite event rate.
Assumptions

- All events—breast cancers and others—are of equal importance and mutually exclusive.
- Tamoxifen can cause other events but not breast cancer.
- \( RR \) and Cost of tamoxifen are constant in \( X \).
  E.g. Cost does not vary with age.

If these assumptions are incorrect, the optimal treatment rule and its value are incorrect.
Ideal Evaluation of a Risk Model

To avoid Cost/Benefit assumptions, assess value of risk model in a randomized trial comparing $T = 0$ to $T = 1$.

Requires baseline Risk($X$) values for all or a random sample of participants*

- Measured prospectively, at trial initiation
- Or retrospectively, given baseline data/samples

*Risk($X$) function might come from another study, or be estimated using RCT data.
Specifically, given RCT data:

**Fit models for Benefit and Cost**

\[
\text{Benefit}(X) = P(D = 1|T = 0, \text{Risk}(X)) - P(D = 1|T = 1, \text{Risk}(X))
\]

\[
\text{Cost}(X) = \text{a constant, or a function of } X
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**Evaluate the net benefit of treatment**

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**Identify the optimal treatment rule**

Treat if \( \text{NB}(X) > 0 \), i.e.

\[
P(D = 1 | T = 0, \text{Risk}(X)) - P(D = 1 | T = 1, \text{Risk}(X)) > \text{Cost}(X)
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Is net benefit really linear in Risk($X$)?

$$\text{NB}(X) = \text{Benefit} - \text{Cost}$$

$$= P(D = 1|T = 0, \text{Risk}(X)) - P(D = 1|T = 1, \text{Risk}(X)) - \text{Cost}(X)$$
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Net benefit may be non-linear if

- $RR$ due to treatment is not constant in $X$
  - E.g. different treatment effects by race/ethnicity, BMI, ...
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Net benefit may be non-linear if

- $RR$ due to treatment is not constant in $X$
  E.g. different treatment effects by race/ethnicity, BMI, ...
- Cost of treatment is not constant in $X$
  E.g. Cost increases with age
Example

Cost increases with $X = \text{age}$, so net benefit is $< 0$ for highest risk
Does the risk model have population value?

Value of the model is affected by

- Benefit and Cost of treatment
- Its predictive capacity: proportions of cases ($D = 1$) and controls ($D = 0$) designated “high risk” and recommended treatment
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Most risk models have limited predictive capacity and therefore modest value.
Even a perfectly predictive risk model has limits as to its value—
markers that predict treatment effect have greater potential value

- In Gail example, perfect model would reduce composite event rate by 20%
- Less than if treatment effect varied widely with marker value, i.e. $P(D = 1|T = 0, X) - P(D = 1|T = 1, X)$ varied in $X$
Practical difficulties with RCT evaluation

- Requires RCT with marker(s) measured at baseline on trial participants
- Large sample size required to evaluate treatment effect as a function of risk, vs. trial sized only to estimate overall treatment effect
  - Except for very strong markers/risk models
But such evaluation has been performed


- Framingham risk model evaluated in JUPITER trial of rosvastatin for CVD prevention (Dorresteijn et al. BMJ 2011)

- Lung cancer death risk model evaluated in NLST of low-dose CT screening for lung cancer (Kovalchik et al. NEJM 2013)
Summary and Discussion

Risk prediction models are often developed to guide the use of treatment.

Evaluating such usage given only cohort data requires making strong assumptions about the consequences of high risk designation:

- Cost of treatment, and whether/how this varies
- Benefit of treatment, and whether/how this varies.

The validity of the treatment rule and its value depend on these assumptions.
Summary and Discussion, cont’d.

Model evaluation in an RCT avoids these assumptions
- Cost and Benefit assessed as a function of Risk
- Optimal treatment rule identified and evaluated

Ideal confirmatory study is a “biomarker strategy" trial
(Mandrekar et al. 2005; Sargent et al. 2005)
- Randomize subjects to marker-based treatment or standard of care
- Contrast event rate and Cost across arms to measure *effectiveness* of marker-based treatment strategy—taking into account imperfect adherence
References


Extra Slides
Merits of Biomarker Strategy Design

- Measures the “effectiveness" of marker-based treatment policy, allowing for non-adherence

- But requires committing to the marker-based treatment rule in advance of the study – therefore best-suited to confirmatory studies of marker
Examples of Biomarker Strategy Designs

- UK trial of tumor-chemosensitivity-assay-directed chemo to treat recurrent platinum-resistant ovarian cancer (Cree et al. 2007)
- PREDICT-1 study of HLA-B*5701 screening for hypersensitivity to abacavir to treat HIV (Mallal et al. NEJM 2008)
- EU-PACT study of genotype-guided dosing of warfarin to treat thromboembolism (Pirmohamed et al. NEJM 2013)