SISCER 2023 Module 5: Evaluation of Biomarkers and Risk Models

Part V: Target Performance for
Early Phase Biomarker Research

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Early-Phase Biomarker Research

- Early phase biomarker research project
  - "We seek a biomarker with 80% sensitivity and 90% specificity"…. What makes a reasonable goal?
  - We can borrow principles from risk model assessment to inform and set performance targets

Early-Phase Biomarker Research

- If the marker is used to inform a clinical decision about an intervention, the context can help set performance standards
- Example: Seek a biomarker to select women for mammography
  - Let B be the benefit of mammography to a women with undiagnosed breast cancer
  - Let C be the cost/harms of mammography to a women without breast cancer
  - Let ρ be the prevalence of undiagnosed breast cancer in the target population
  - Total benefit derives from positive mammogram in cases: ρ · TPR · B
  - Total harm derives from positive mammogram in controls: (1−ρ) · FPR · C

Early-Phase Biomarker Research

- For the marker to have net positive value:

$$\rho \cdot TPR \cdot B > (1-\rho) \cdot FPR \cdot C$$

i.e., $\frac{TPR}{FPR} > \frac{1-\rho}{\rho}\frac{C}{B} = \frac{1-\rho}{\rho}r$, where r is the Cost/Benefit ratio $\frac{C}{B}$.

Specifying or soliciting $\mathrm{r} = \frac{C}{B}$ is difficult

Intuitive Measures of the Cost/Benefit Ratio

One can articulate $\mathrm{r} = \frac{C}{B}$ in terms of the maximum number of controls N_{max} we are willing to work up in order to receive the benefit of working up one case.

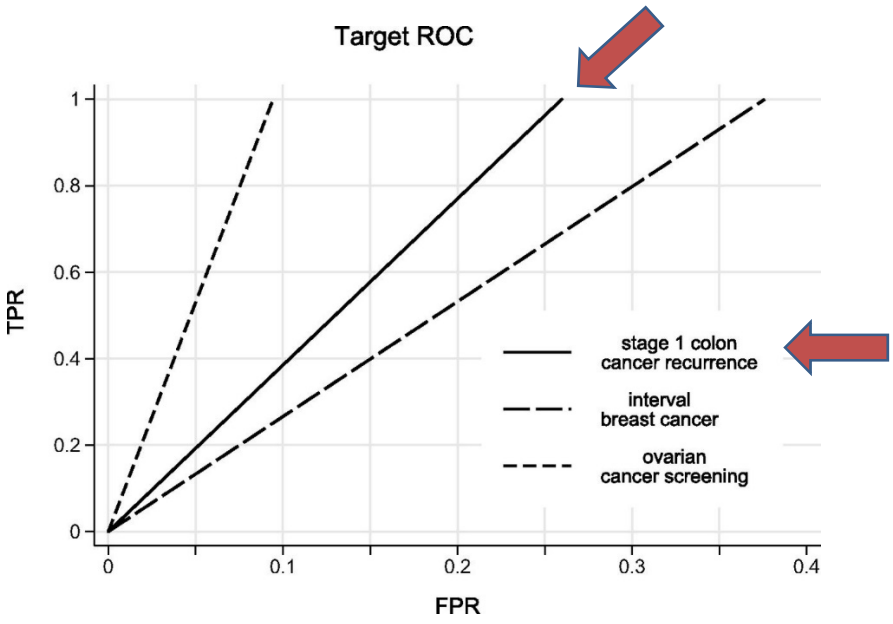
- The cost of working up N_{max} controls is $N_{max} \cdot C$.
- From the definition of N_{max}: $N_{max} \cdot C = B$.
- So $\mathrm{r} = \frac{C}{B} = \frac{1}{N_{max}}$

Intuitive Measures of the Cost/Benefit Ratio

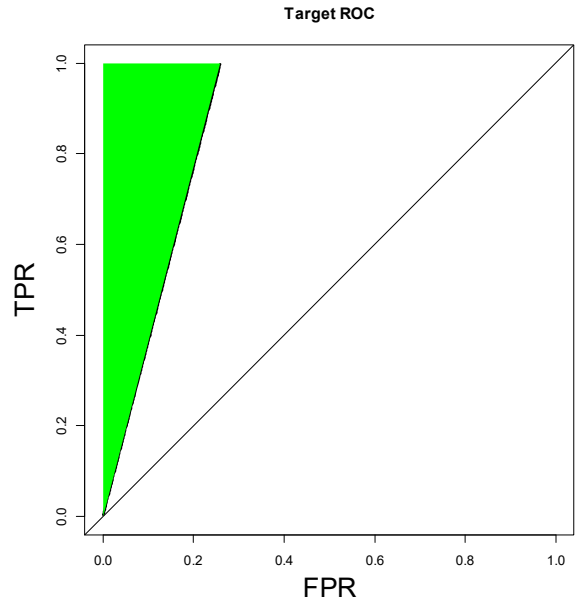
- What is the minimum level of risk R at which work-up is warranted?
- E.g., a woman might feel a mammogram is warranted if her risk of having breast cancer is at least 5/1000 but not if it is less.
- $\frac{C}{B} = \frac{R}{1-R}$

Example: Chemotherapy for Stage 1 Colon Cancer

- Consider biomarker for risk of recurrence within the first year after surgery for stage 1 colon cancer patients.
- Stage 1 patients are not normally offered chemotherapy, which would reduce risk of recurrence.
- The 1-year recurrence rate for stage 1 patients is 10% (ρ).
- Stage 3 colon cancer patients are routinely offered chemotherapy; without it, their risk of recurrence is 30%.
- Therefore, R≤30%. If we take R=30%, then $r = \frac{C}{B} = \frac{0.3}{1-0.3} = 0.43$.
- Thus $\frac{TPR}{FPR} \geq \frac{1-0.1}{0.1} \times 0.43 = 3.85$.



A marker with a single (FPR, TPR) above the target could have clinical utility.
Since TPR cannot exceed 1, markers with FPR>1/3.85=26% cannot have clinical utility.



Example: Interval Breast Cancer Screening

- Women 50-74 are recommended for screening mammography every two years.
- Suppose we seek a biomarker to identify women for additional screening (mammograms) 8 and 16 months after a negative mammogram.
- During this interval, the expected incidence of breast cancer is 0.15% (0.0015).
- A panel decides that the health care system should support 500 additional mammograms (250 women getting 2 "extra" mammograms) to catch 1 woman with interval cancer.
  - N_{max}=250 → $r = \frac{1}{250} \rightarrow \frac{TPR}{FPR} \geq \frac{1-0.0015}{0.0015} \times \frac{1}{250} = 2.66.$

Example: Interval Breast Cancer Screening

- N_{max}=250 → $r = \frac{1}{250} \rightarrow \frac{TPR}{FPR} \geq \frac{1-0.0015}{0.0015} \times \frac{1}{250} = 2.66.$
- If we limit FPR at 5%, then the TPR must exceed 2.66 · 0.05 = 13% for the biomarker to be useful

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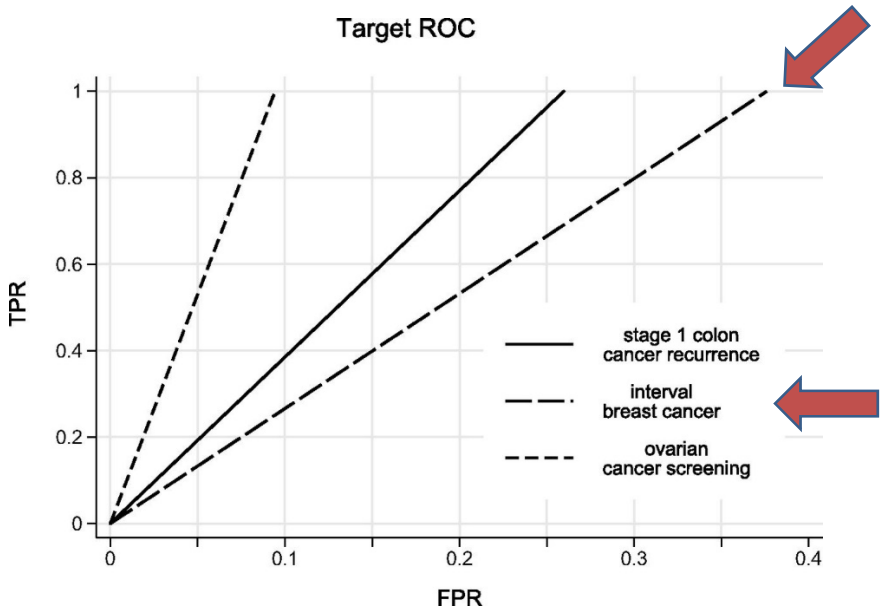
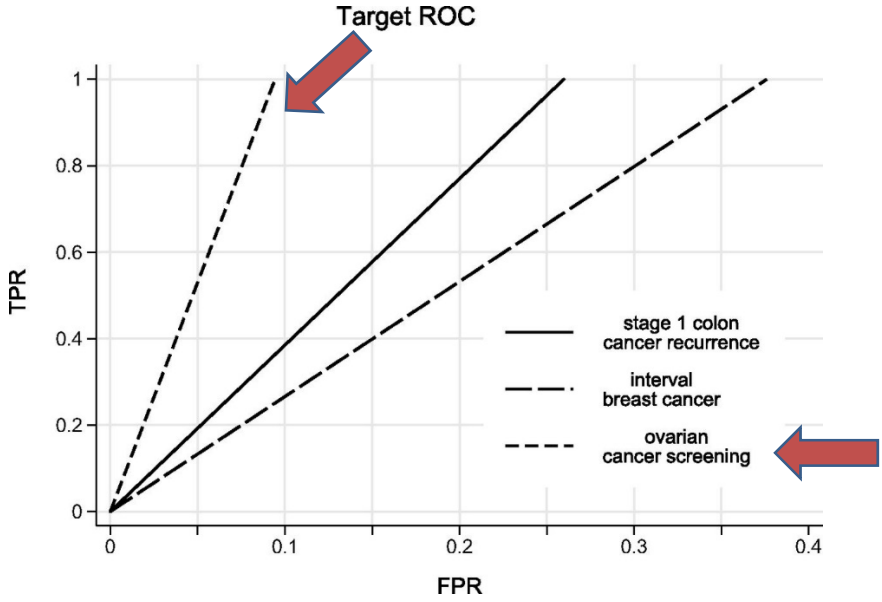


Example: Ovarian Cancer Screening

- Incidence of ovarian cancer in women 50-64 is 25 in 100,000
- We seek a biomarker for annual screening; biomarker positive women will receive surgery for definitive diagnosis.
- We require 1 discovery of ovarian cancer for every 10 surgeries. That is, we tolerate 9 unnecessary surgeries to find one cancer.
- $N_{max}=9 \rightarrow r = \frac{1}{9} \rightarrow \frac{TPR}{FPR} \geq \frac{1-0.00025}{0.00025} \times \frac{1}{9} = 444.$

Example: Ovarian Cancer Screening

- More realistically, marker positive women would receive transvaginal ultrasound to decide on surgery. If TVS is also positive, then surgery.
- If marker results and TVS results are independent (big assumption), then the TPR for the combined test is the TPR for ultrasound (0.755) times the TPR for the marker; the FPR for the combined test is the FPR for ultrasound (0.018) times the FPR for the marker.
- $\frac{0.755 \times TPR}{0.018 \times FPR} \geq 444 \rightarrow \frac{TPR}{FPR} \geq 10.6.$
- A biomarker that detects 80% of cancers must have an FPR ≤ 0.075.



Reference

Clinical Chemistry 62:5
737–742 (2016)

Cancer Diagnostics

Early-Phase Studies of Biomarkers: What Target Sensitivity and Specificity Values Might Confer Clinical Utility?

Margaret S. Pepe,[1*] Holly Janes,[2] Christopher I. Li,[3] Patrick M. Bossuyt,[4] Ziding Feng,[5] and Jørgen Hilden[6]