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Cut-off Selections for Biomarkers in Observational Studies

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دانشگاه علوم پزشکی و خدمات بهداشتی درمانی ایران

Contents of this presentation

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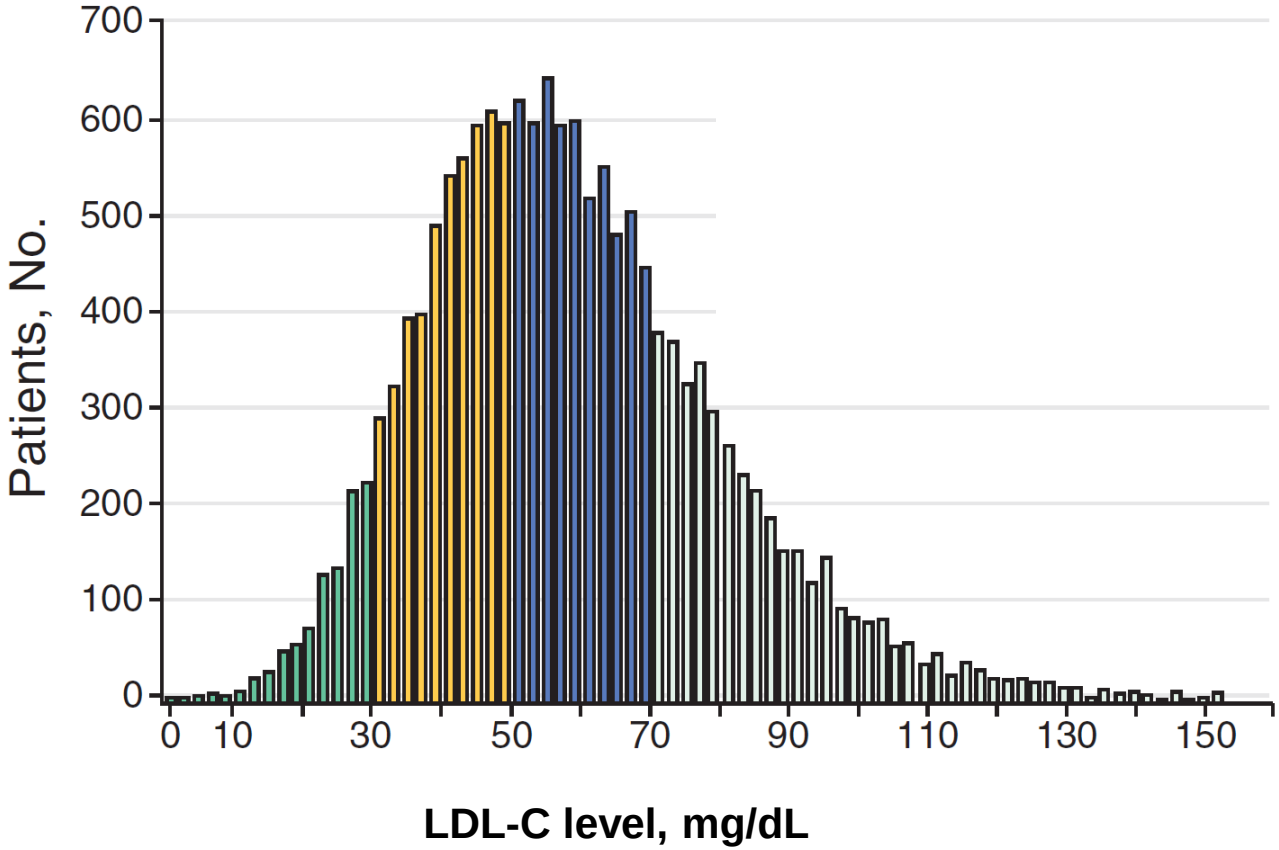
Methods	Different Methods for cut-off selection
Practical example	Cutoff for fasting blood sugar
Conclusion	Practical tool for cut-off selection

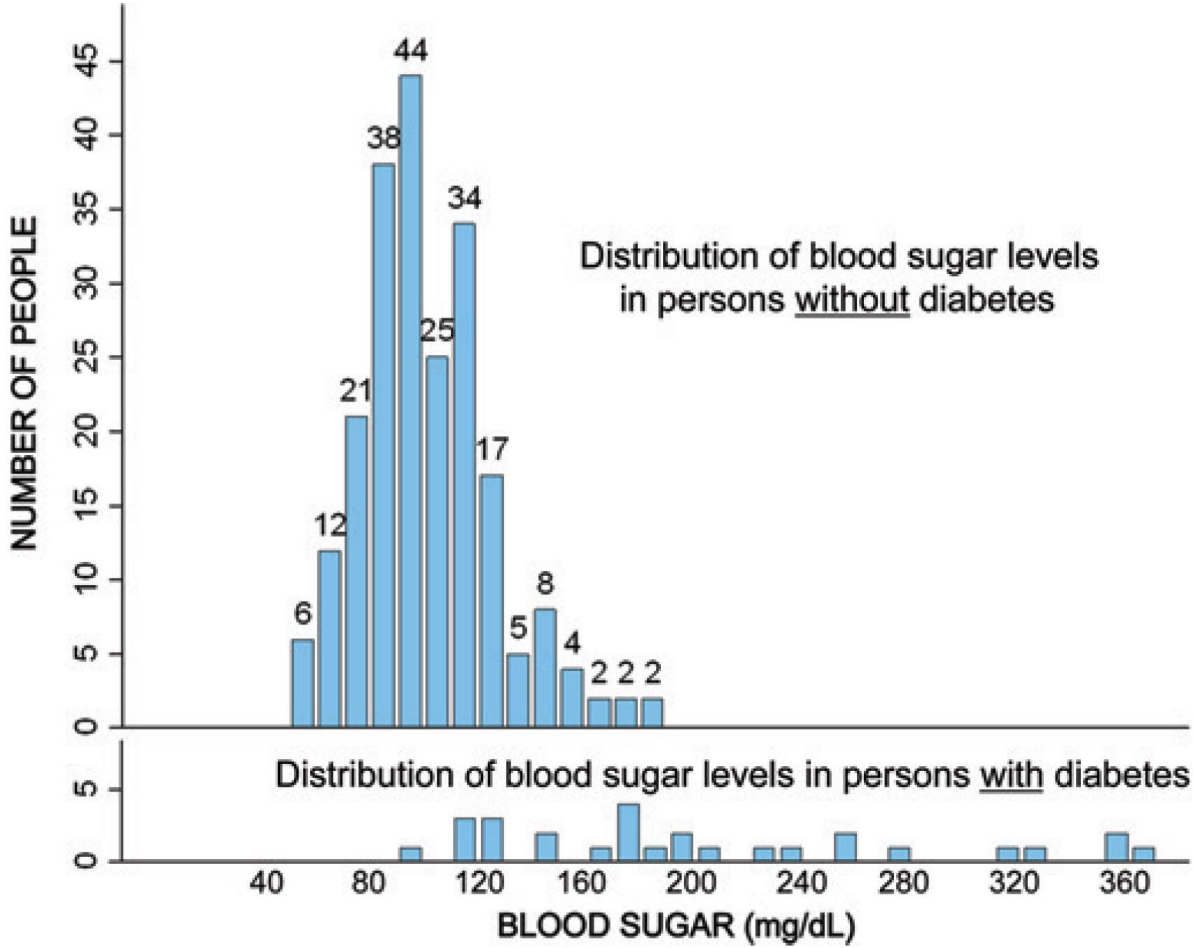
Concept of Cutoff (Threshold)

- Dichotomizing continuous biomarkers into **“positive”** or **“negative”** is common in medicine

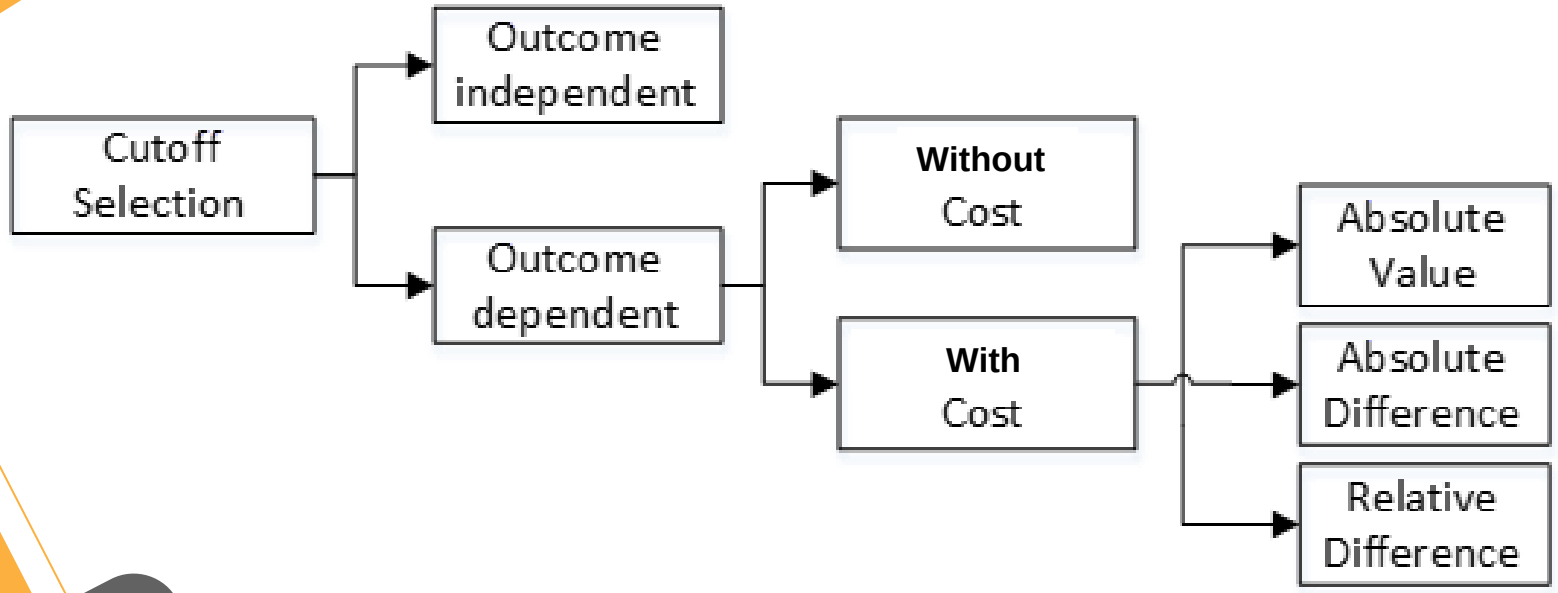
- ***despite its disadvantages such as information loss !***

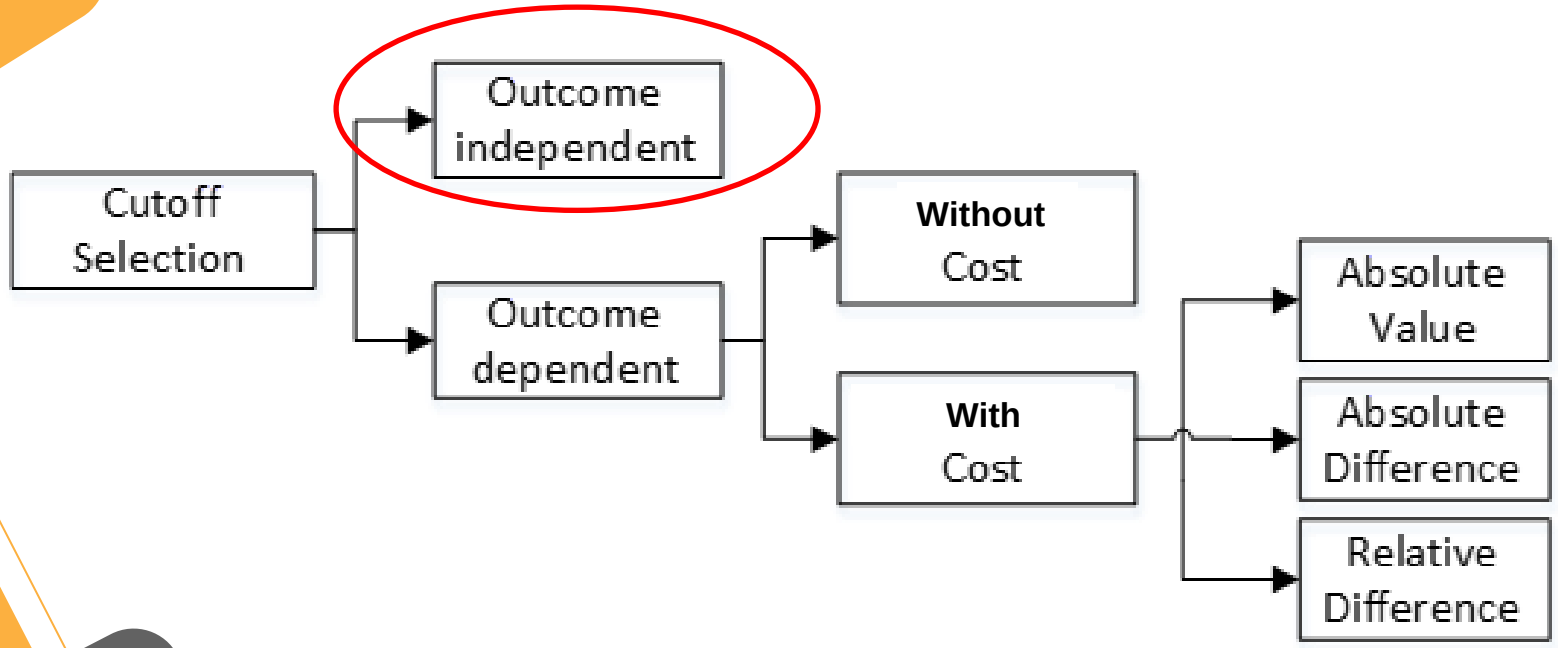

Patients, No.
700
600
500
400
300
200
100
0
0
10
30
50
70
90
110
130
150
LDL-C level, mg/dL

Gordis 2019

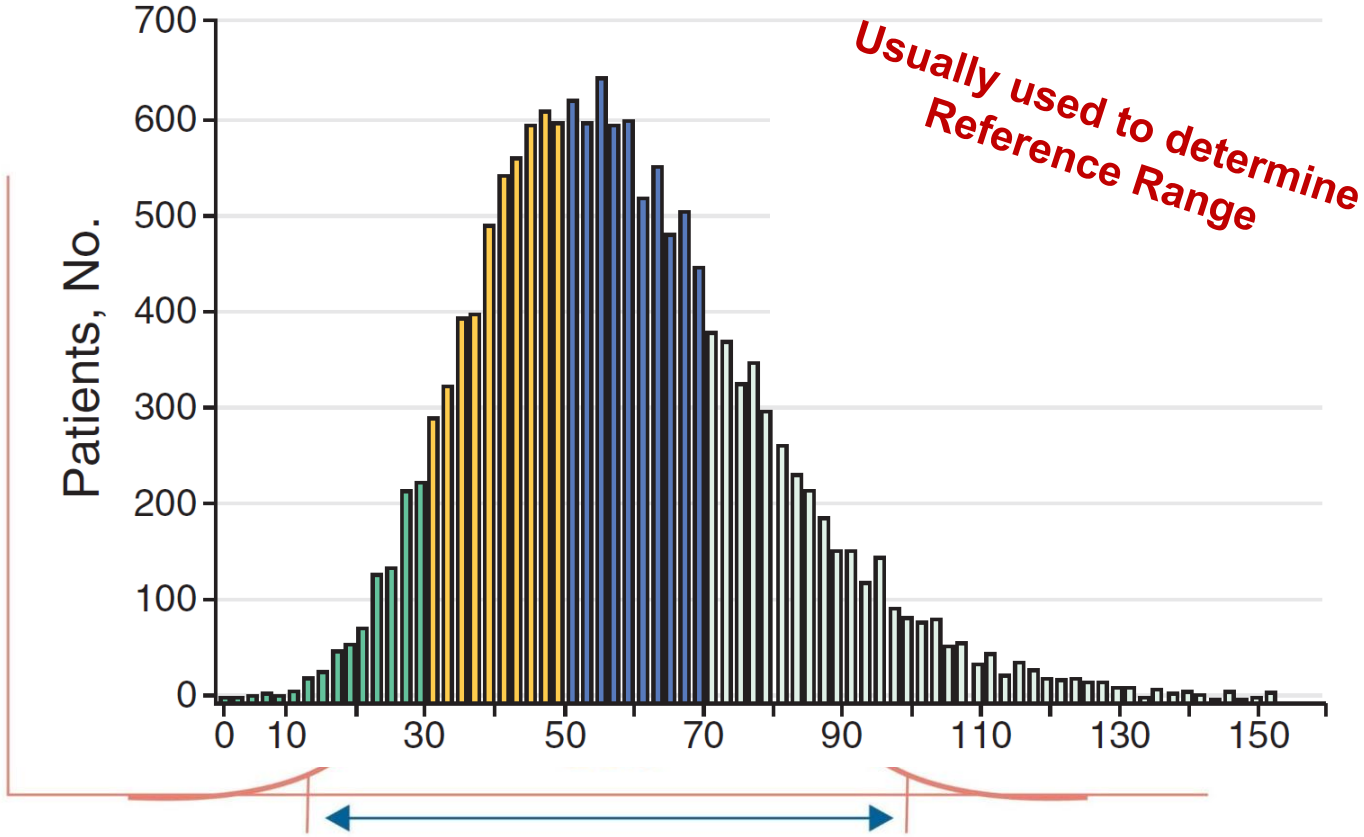

NUMBER OF PEOPLE
0
5
10
15
20
25
30
35
40
45
6
12
21
38
44
25
34
17
5
8
4
2 2 2
Distribution of blood sugar levels
in persons without diabetes
0
5
Distribution of blood sugar levels in persons with diabetes
40
80
120
160
200
240
280
320
360
BLOOD SUGAR (mg/dL)

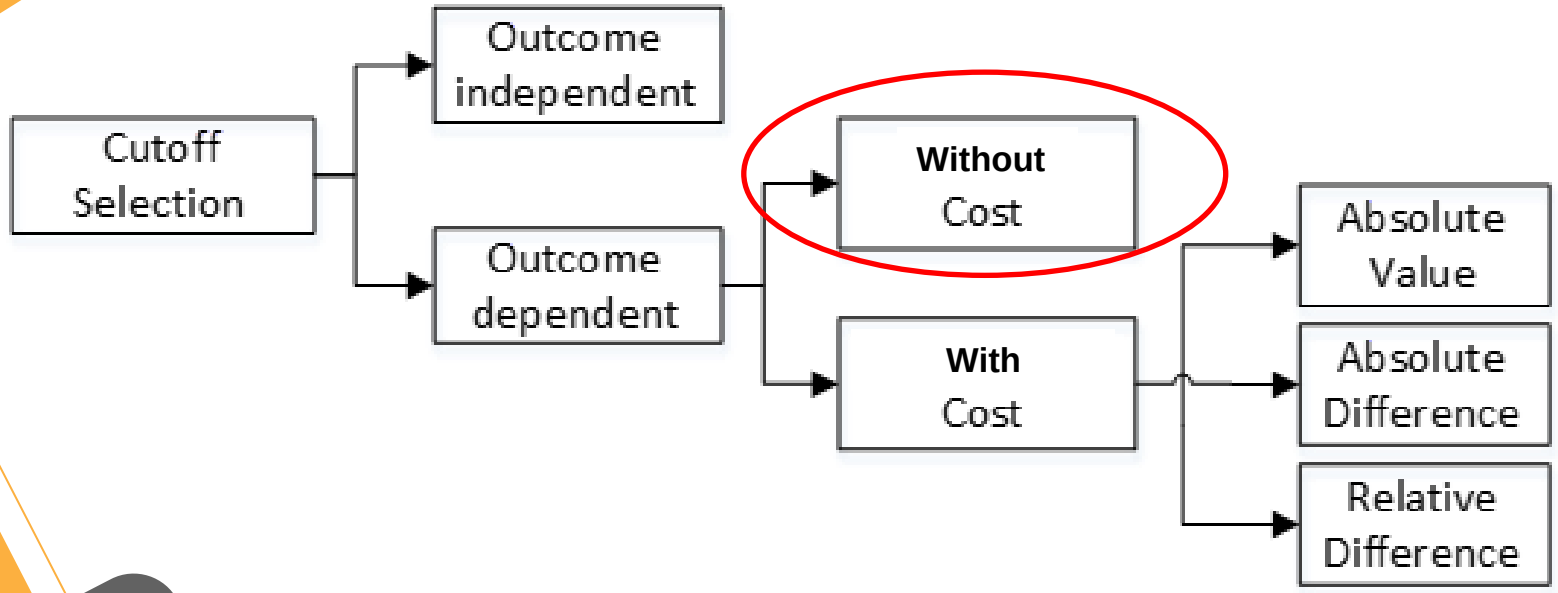
Gordis 2019

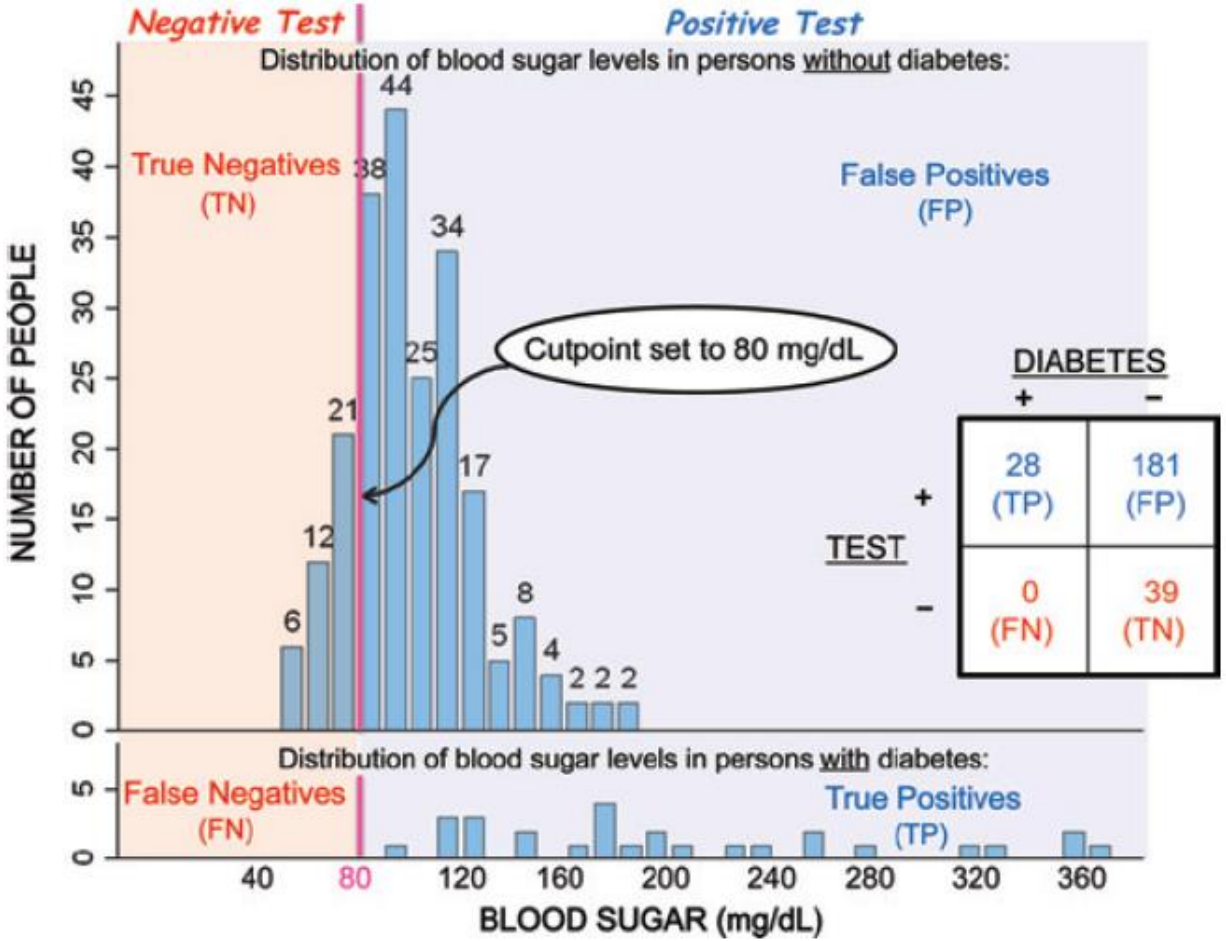

Cutoff Selection
Outcome independent
Outcome dependent
Without Cost
With Cost
Absolute Value
Absolute Difference
Relative Difference


Cutoff Selection
Outcome independent
Outcome dependent
Without Cost
With Cost
Absolute Value
Absolute Difference
Relative Difference

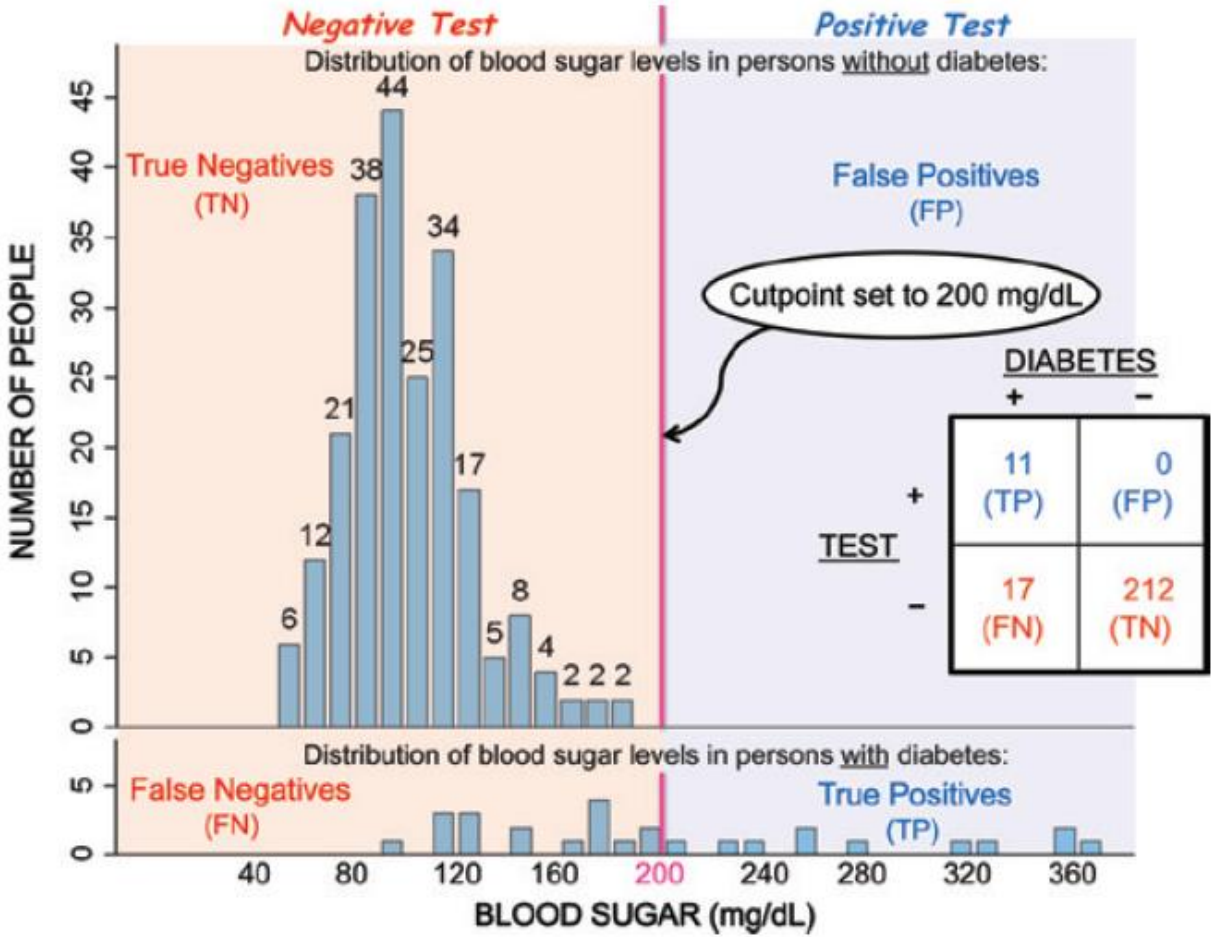
Outcome Independent




Cutoff Selection
Outcome independent
Outcome dependent
Without Cost
With Cost
Absolute Value
Absolute Difference
Relative Difference

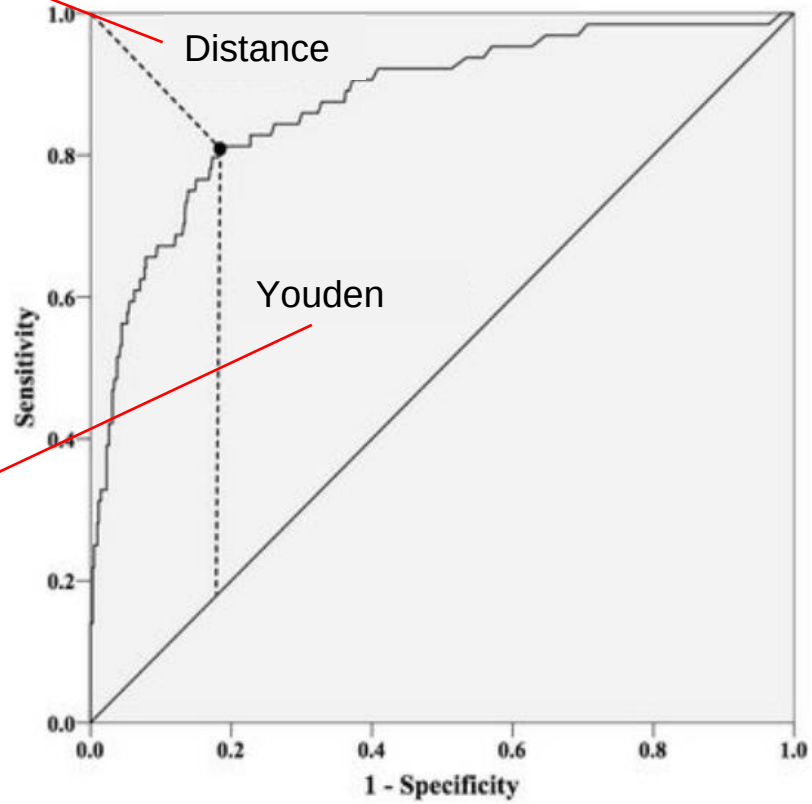

Negative Test
Positive Test
Distribution of blood sugar levels in persons without diabetes:
True Negatives
(TN)
False Positives
(FP)
Cutpoint set to 80 mg/dL
NUMBER OF PEOPLE
0
5
10
15
20
25
30
35
40
45
6
12
21
38
44
34
25
17
8
5
4
2 2 2
DIABETES
+
–
TEST
+
–
28
(TP)
181
(FP)
0
(FN)
39
(TN)
Distribution of blood sugar levels in persons with diabetes:
False Negatives
(FN)
True Positives
(TP)
0
5
40
80
120
160
200
240
280
320
360
BLOOD SUGAR (mg/dL)

Outcome Dependent



$$(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$$

Should be Minimum



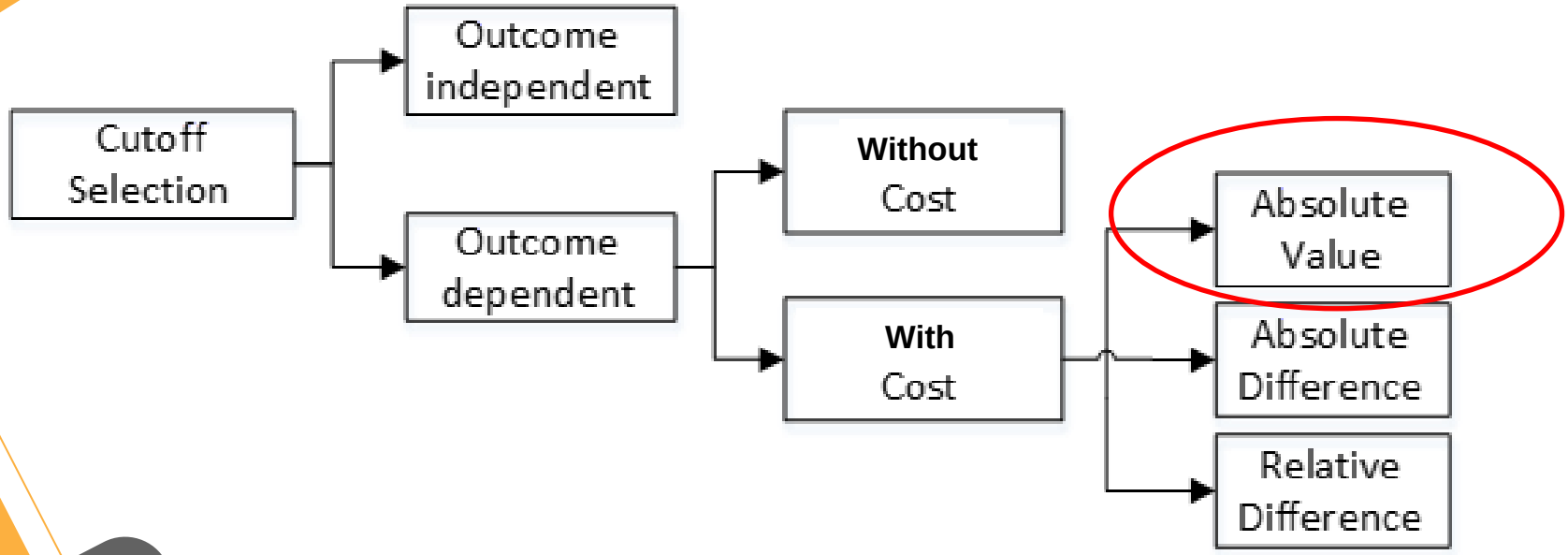
$$\text{Sensitivity} + \text{Specificity} - 1$$

Should be Maximum

$$(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$$

$$\text{Sensitivity} + \text{Specificity} - 1$$

Same values !!

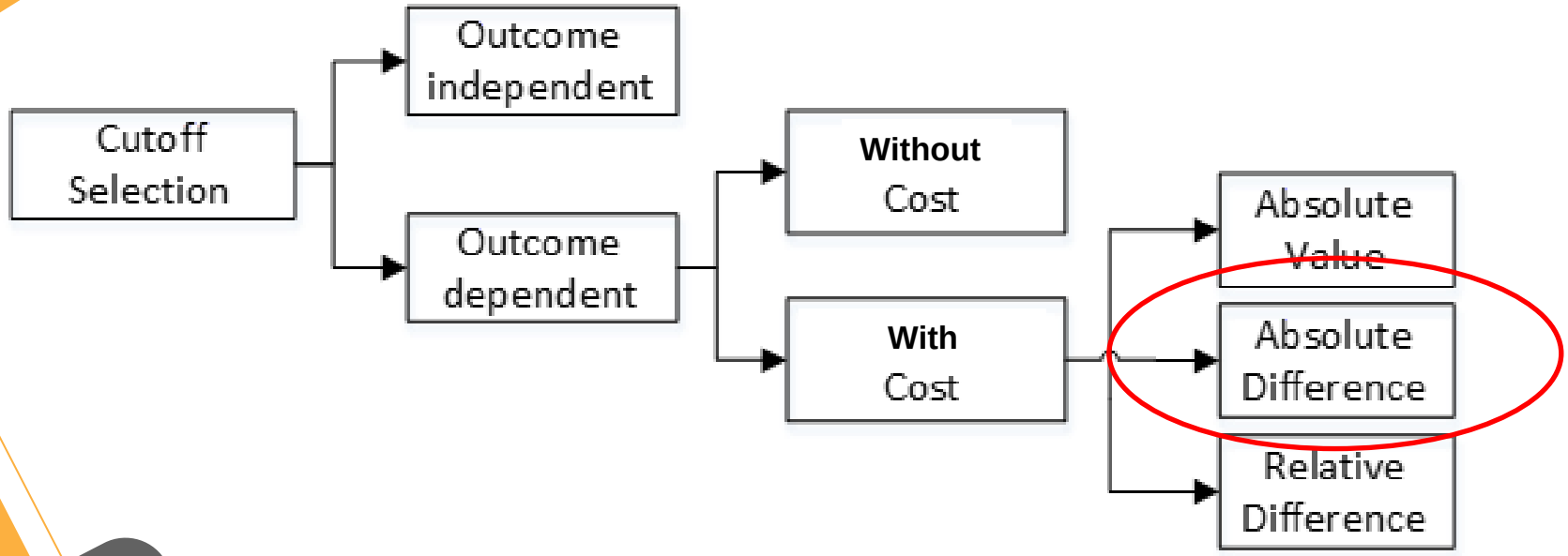

Cutoff Selection
Outcome independent
Outcome dependent
Without Cost
With Cost
Absolute Value
Absolute Difference
Relative Difference

So difficult !

		Predicted class: P	Predicted class: N
Actual Class	P	True Positives (TP)	False Negatives (FN)
	N	False Positives (FP)	True Negatives (TN)

For each cutoff:

EC = C0 + TPC×p(TP) + TNC×p(TN) + FPC×p(FP) + FNC×p(FN)

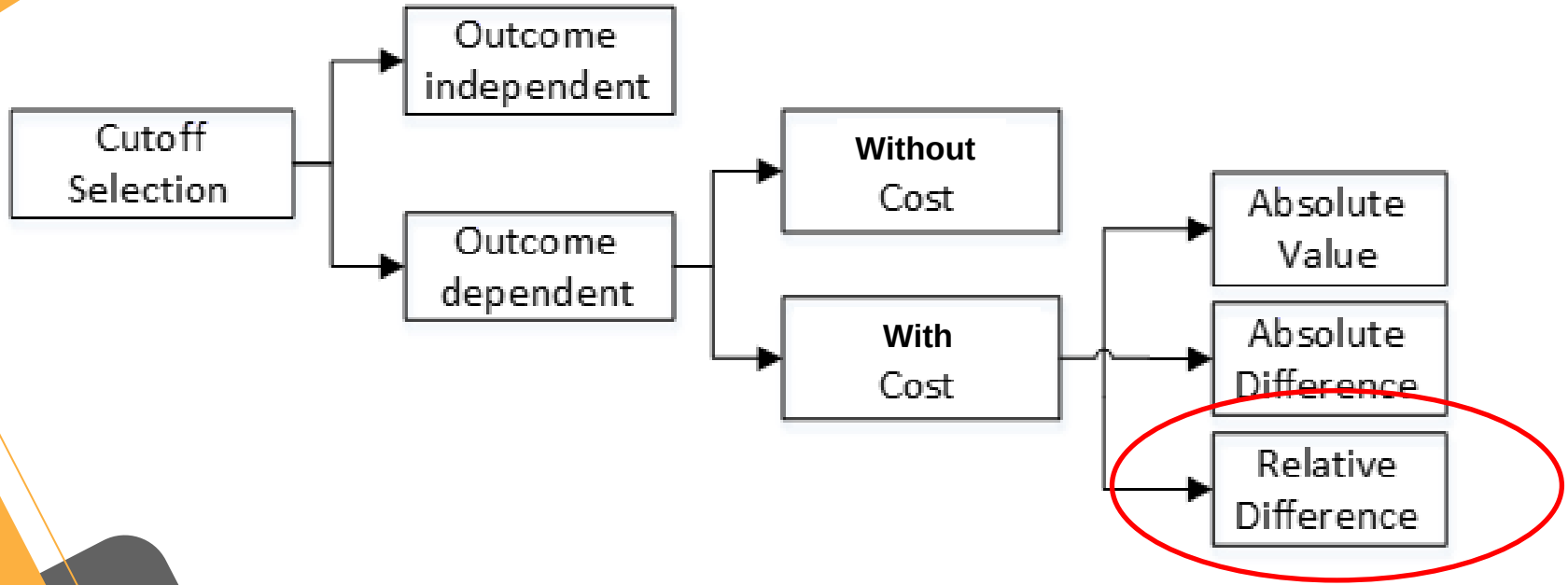

Cutoff Selection
Outcome independent
Outcome dependent
Without Cost
With Cost
Absolute Value
Absolute Difference
Relative Difference

For each cutoff:

$$\text{Net Benefit} = b \times TP/N - h \times FP/N$$

b: Benefit from predicting a true positive

h: Harm from every false positive


Cutoff Selection
Outcome independent
Outcome dependent
Without Cost
With Cost
Absolute Value
Absolute Difference
Relative Difference

For each cutoff:

Net Benefit = TP/N − (h/b) × FP/N

b: Benefit from predicting a true positive

h: Harm from every false positive

h/b means the harm-to-benefit ratio of the intervention for positive cases
It equals to:

$$\frac{PT}{1 - PT}$$

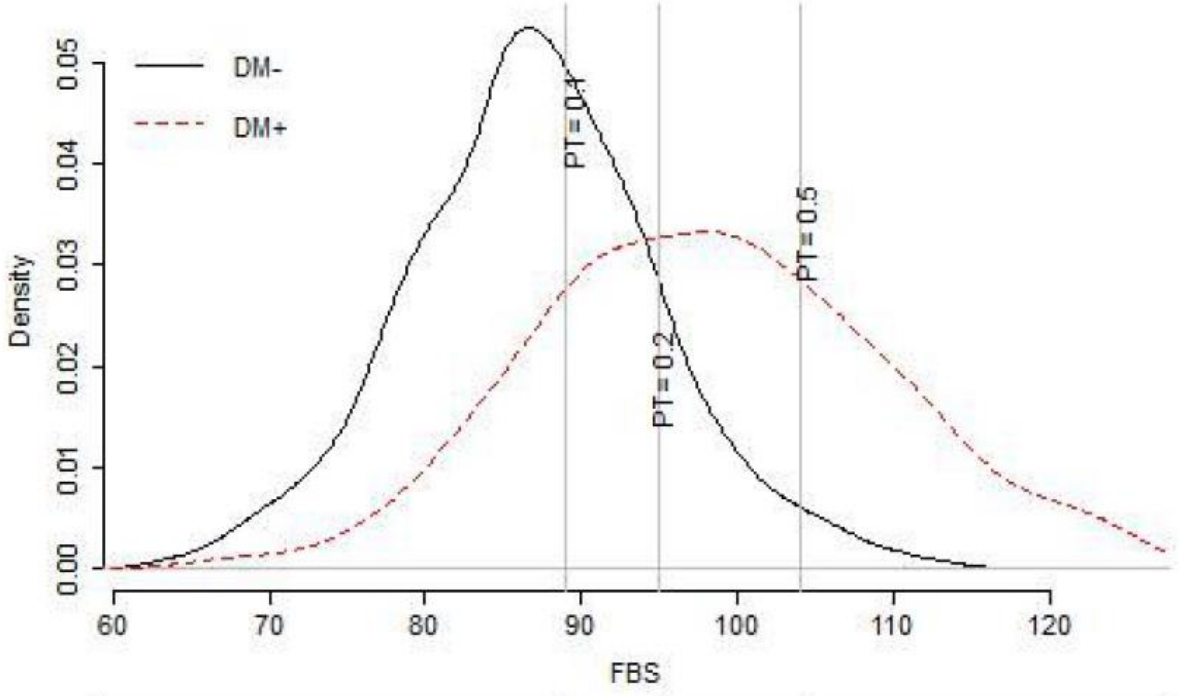
PT is the probability threshold desired for intervention

Generalized Youden = Se + r×Sp − 1

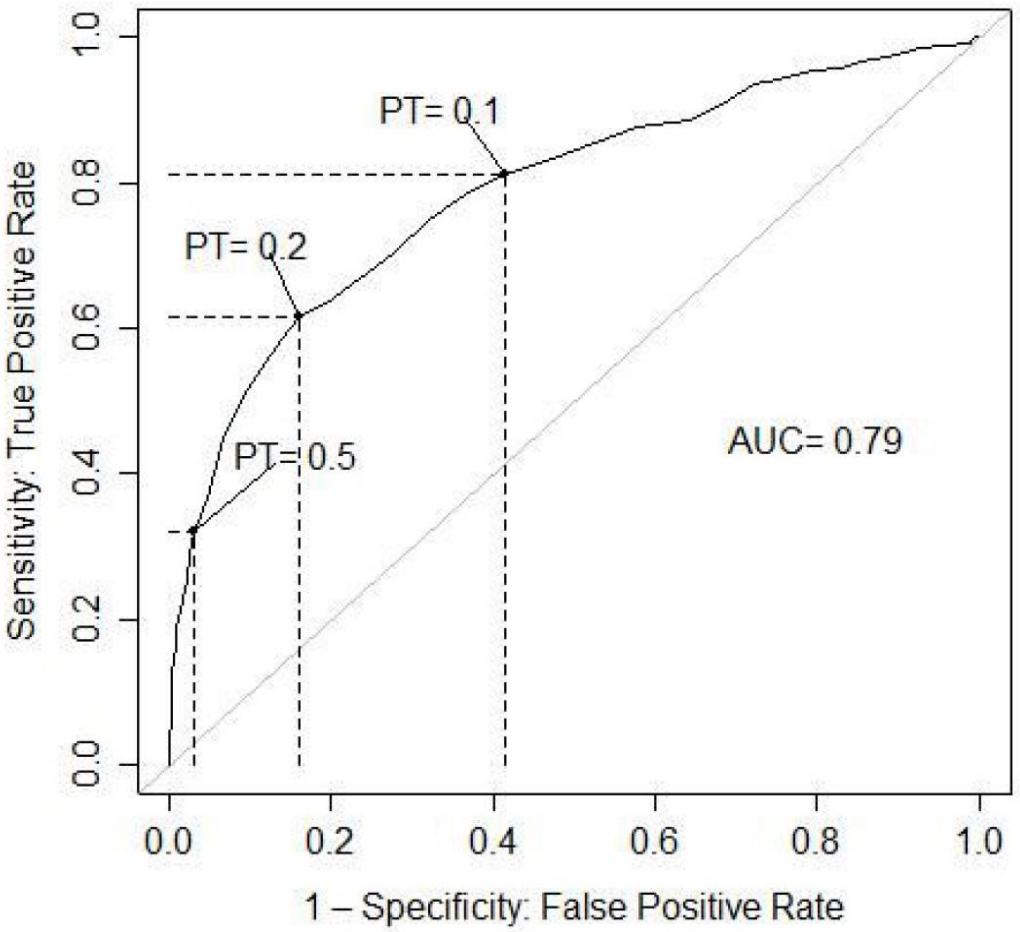
$r = [(1-pp)/pp] \times (FPC/FNC)$

Misclassification Cost Term = $(1-pp)\times(1-Sp) + (FNC/FPC)\times pp\times(1-Se)$

Probability density plot of FBS for nondiabetic and diabetic women: TLGS



ROC curve of FBS for the prediction of diabetes in Women: TLGS



					PT=0.1			PT=0.2		
Cut	Se	Sp	PPV	NPV	GY	MCT	NBF	GY	MCT	NBF
85	0.89	0.36	0.22	0.94	0.09	0.7	0.53	0.34	0.61	0.09
86	0.88	0.42	0.23	0.95	0.11	0.66	0.56	0.4	0.56	0.16
87	0.85	0.48	0.25	0.94	0.12	0.66	0.56	0.45	0.53	0.2
88	0.83	0.53	0.26	0.94	0.13	0.64	0.57	0.49	0.51	0.24
89	0.81	0.58	0.28	0.94	0.14	0.63	0.58	0.54	0.47	0.3
90	0.78	0.63	0.3	0.94	0.13	0.63	0.58	0.57	0.45	0.33
91	0.75	0.68	0.32	0.93	0.12	0.65	0.57	0.59	0.44	0.35
92	0.7	0.72	0.34	0.92	0.1	0.68	0.55	0.6	0.43	0.36
93	0.67	0.76	0.36	0.92	0.09	0.69	0.54	0.62	0.42	0.38
94	0.64	0.8	0.39	0.92	0.08	0.71	0.53	0.63	0.41	0.39
95	0.62	0.84	0.43	0.92	0.08	0.71	0.53	0.66	0.39	0.41
96	0.59	0.86	0.46	0.91	0.06	0.74	0.51	0.66	0.39	0.41
97	0.54	0.89	0.49	0.91	0.03	0.78	0.48	0.65	0.4	0.4
98	0.52	0.9	0.52	0.9	0.02	0.81	0.46	0.64	0.4	0.4
99	0.48	0.92	0.55	0.9	-0.01	0.85	0.44	0.63	0.41	0.38
100	0.45	0.93	0.58	0.89	-0.03	0.88	0.41	0.61	0.42	0.37
101	0.4	0.95	0.6	0.89	-0.08	0.95	0.37	0.58	0.45	0.33
102	0.37	0.95	0.61	0.88	-0.11	0.99	0.34	0.55	0.46	0.31
103	0.34	0.96	0.64	0.88	-0.12	1.02	0.32	0.54	0.47	0.3
104	0.32	0.97	0.67	0.88	-0.14	1.05	0.3	0.53	0.48	0.28
105	0.29	0.97	0.69	0.87	-0.17	1.09	0.27	0.5	0.5	0.26

Conclusion:

- Using Youden's Index considers the same weight for sensitivity and specificity.
- The probability threshold for treatment is suggested as a tangible cost index for patients/physicians and Net Benefit as an understandable and practical tool for cut-off selection.
- But H/B ratio should be based on a trial or consensus!!!

Thanks!