流行病學方法論及實驗
(The Methods of Epidemiology and Practices)
柯南護理流行病學

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I 臨床推理

檢驗及診斷工具的正確性

Accuracy of Test and Diagnosis

怕麻煩又怕痛 乳癌篩檢率不到4成

記者吳欣恬、羅碧 / 台北報導

乳癌是國內女性發生率最高的癌症，國健署也有條件提供婦女免費篩檢服務，但乳癌防治基金會的調查卻赫然發現，高達93%的受訪者明知有此項免費篩檢，卻有近半數（45%）的人不願接受篩檢，最主要原因是「怕痛」（29%）。

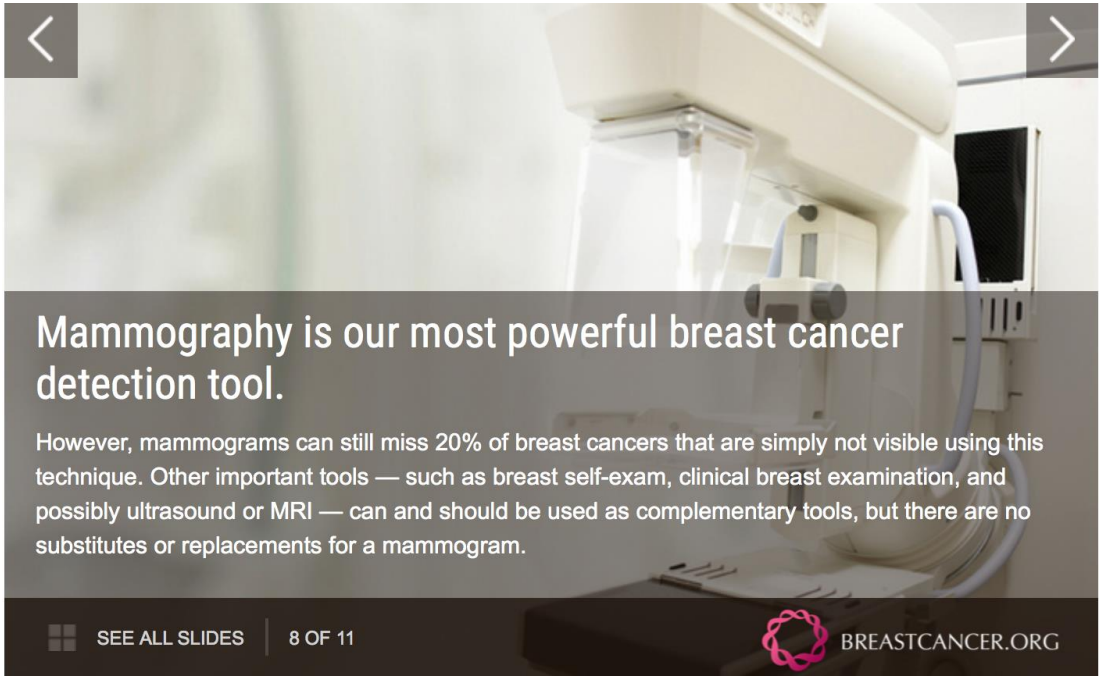
逾40歲年長族群不願做乳癌篩檢的原因依序。（記者叢昌瑾攝）

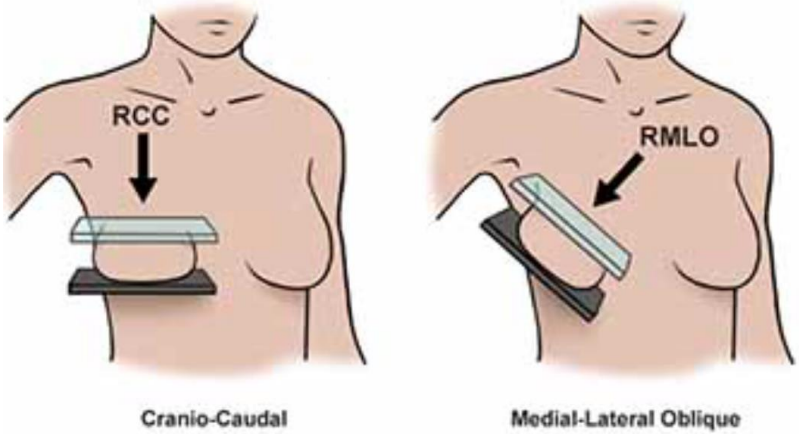
乳癌防治基金會董事長張金堅表示，10月是國際乳癌防治月，因此該會在昨天公布針對全台近千名20-70歲女性所做調查，有效問卷為981份，其中40歲-70歲者佔55%，另外45%是20-39歲的年輕女性。

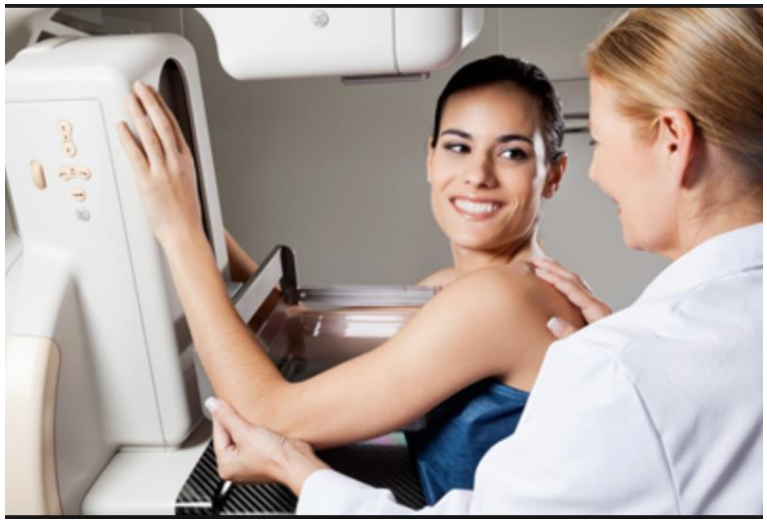
調查發現，超過40歲以上女性不願意做乳癌篩檢的前四大原因是「因為很麻煩（31%）」、「因為很痛（27%）」、「因為太忙（14%）」以及「害羞（12%）」。（見圖）

自由時報 Liberty Times Net

http://news.ltn.com.tw/news/life/paper/918269

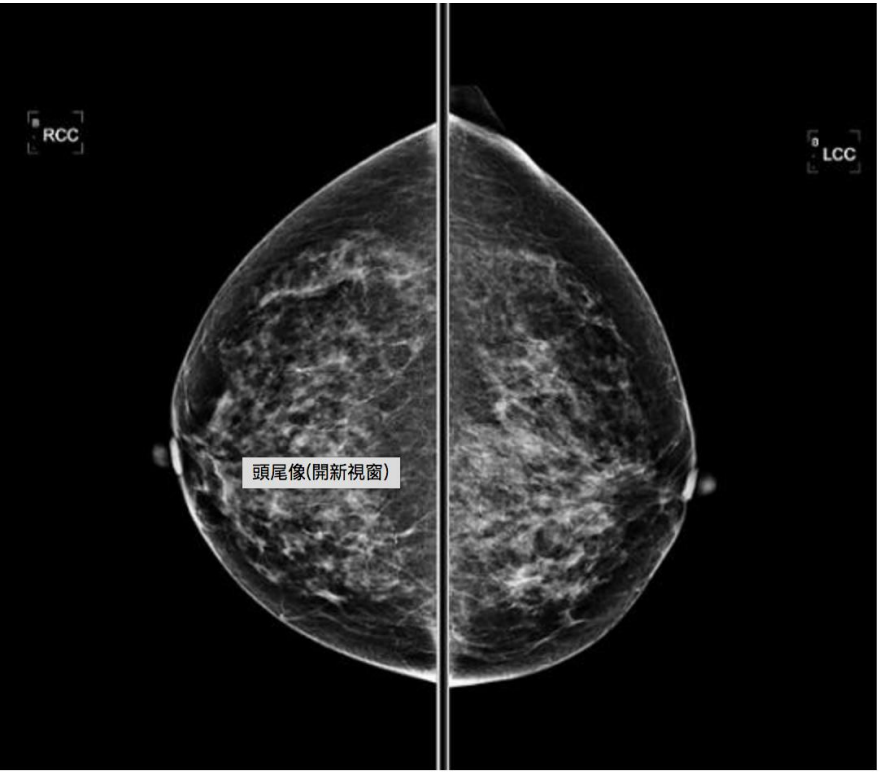




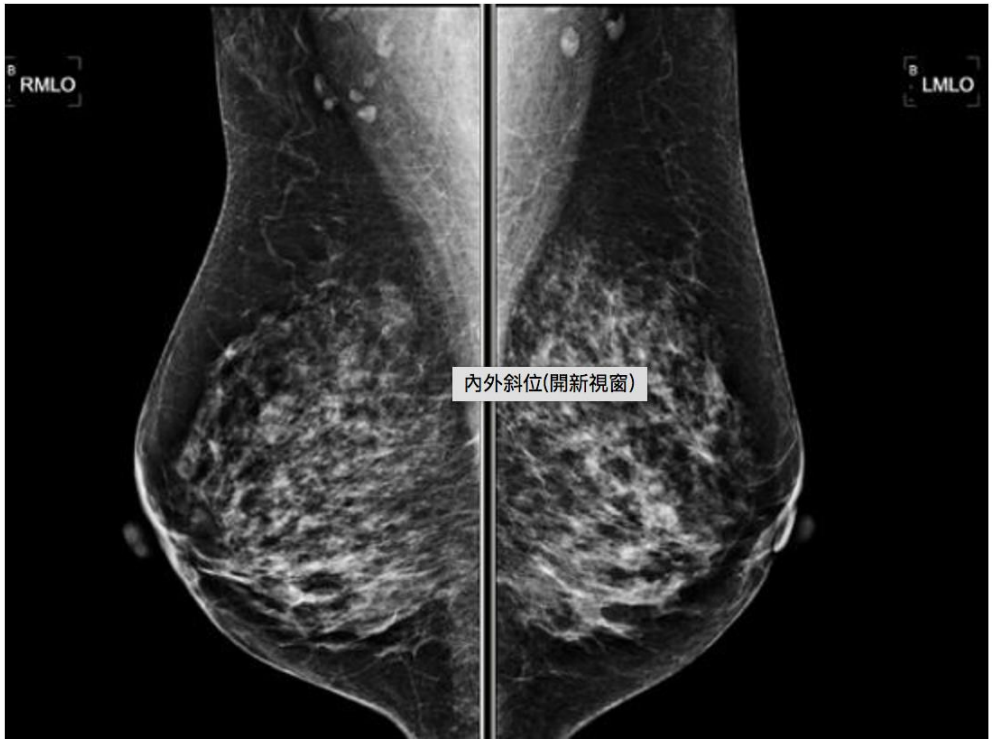


http://breastcancer.org

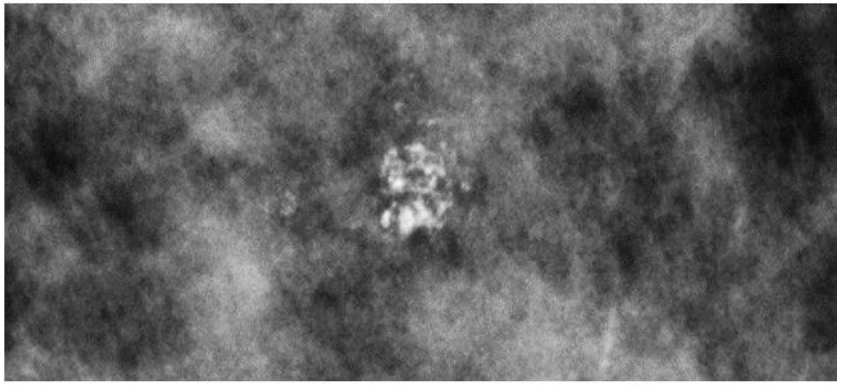
Current mammography

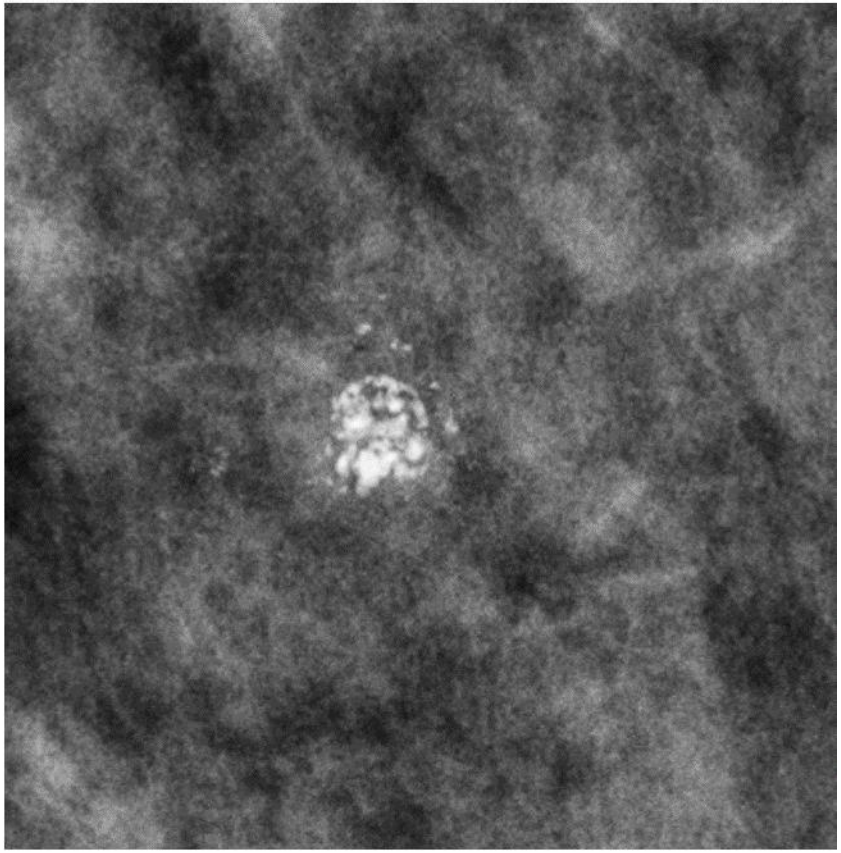


頭尾向(Craniocaudal, CC)

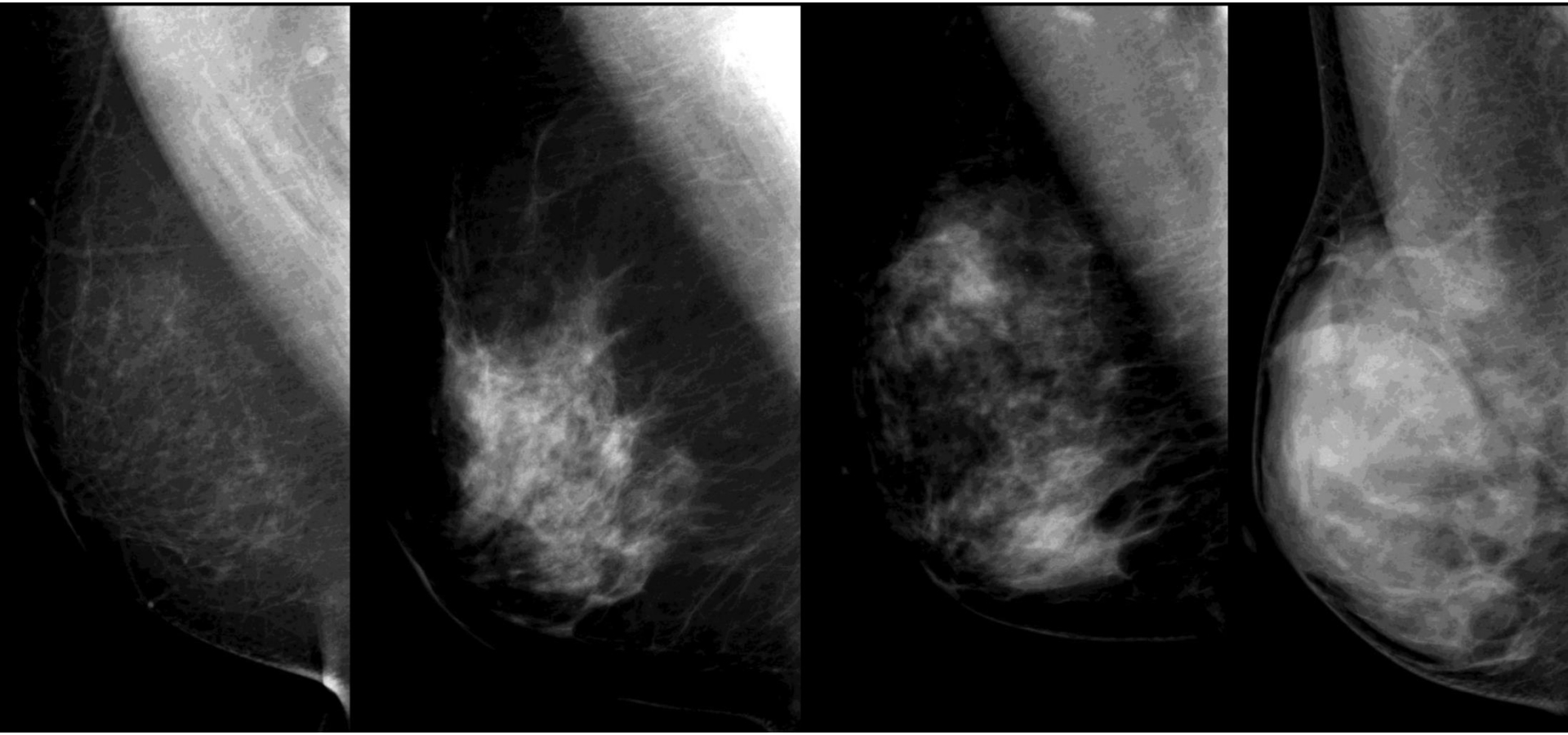


斜位向
(mediolateral oblique; MLO)





F/50 Screening DCIS



<25% Glandular 25-50% Glandular 51-75% Glandular >75% Glandular

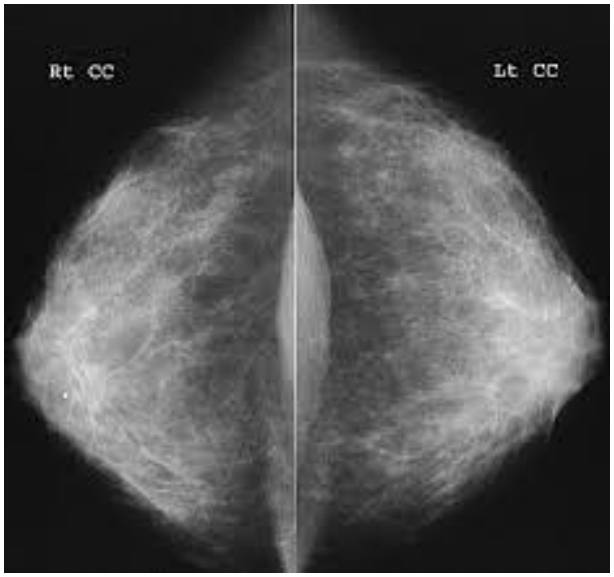
乳房的緻密度 (Breast Density)

Breast Ultrasound
乳房超音波

臨床實例(1) 乳癌篩檢工具比較:
乳房攝影合併超音波 vs 乳房攝影

ORIGINAL CONTRIBUTION

Combined Screening With Ultrasound and Mammography vs Mammography Alone in Women at Elevated Risk of Breast Cancer



JAMA. 2008;299(18):2151-2163

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Karan Boparai, RT
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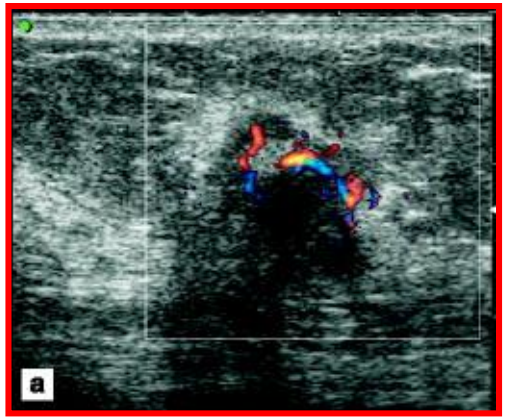
Ultrasound Screening 乳房超音波篩檢

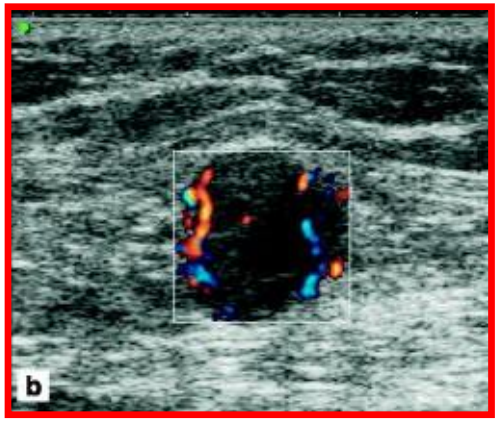
Relevance of technological innovations

拜科技進步之賜…



Infiltrating ductal carcinoma, 8mm in size, irregular margins

外緣不規則狀，8釐米的浸潤管癌

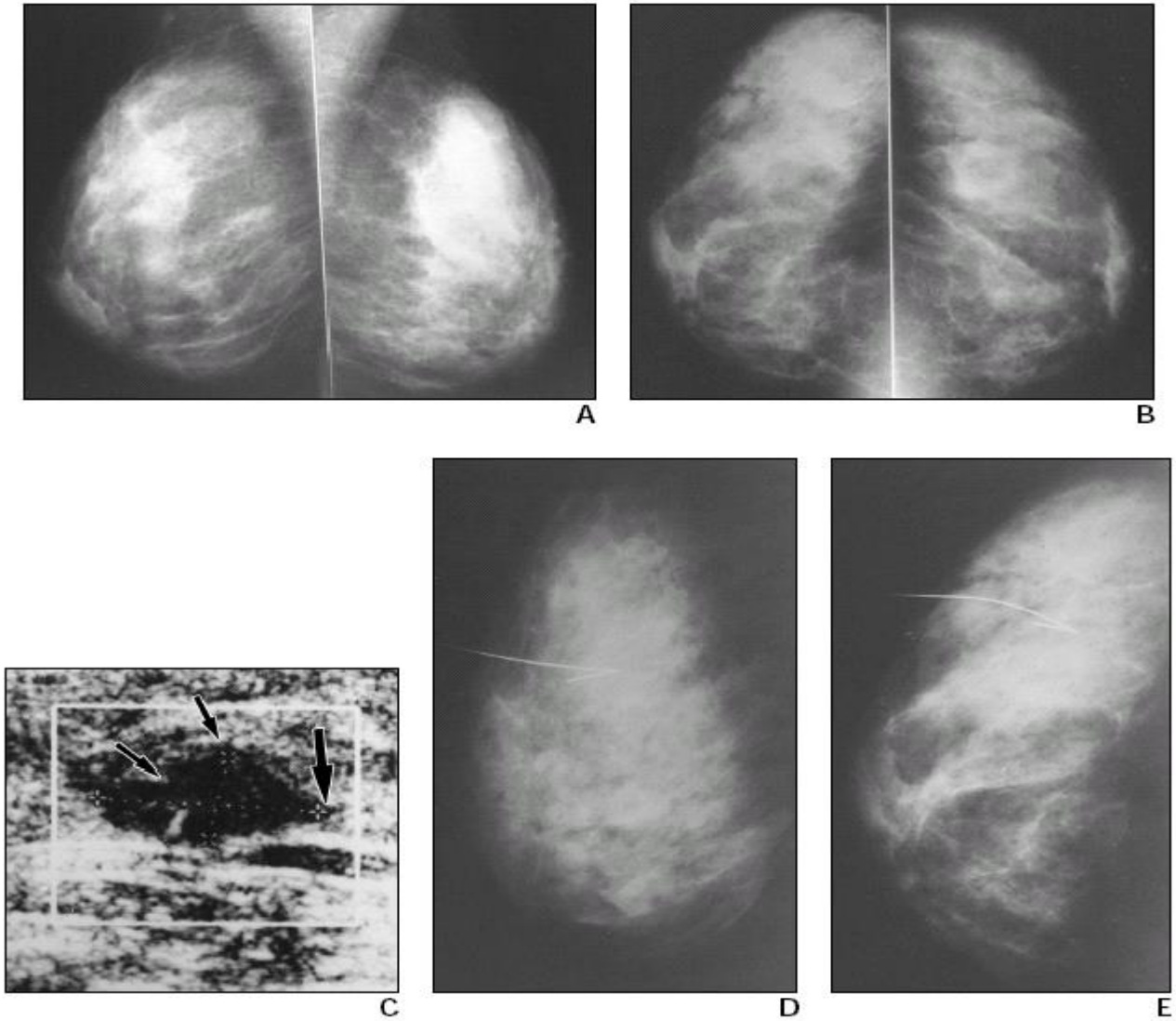


Medullary arcinoma, 7mm in size, regular margins

外緣呈規則狀，7釐米髓狀弓形瘤

Using Sonography to Screen Women with Mammographically Dense Breasts

以乳房超音波篩檢緻密性乳房



1.敏感度(Sensitivity),特異度 (Specificity),
陽性預測值 (positive predictive value (PPV))
陰性預測值 (negative predictive value (NPV))

2×2 Table (列聯表)

關鍵字

Sensitivity (敏感度), Specificity (特異度),

Positive predictive value(PPV) (陽性預測值),

Negative predictive value (NPV) (陰性預測值)

		乳癌個案(Y)		
		是 (Y=1)	否 (Y=0)	
乳房攝影加超音波檢查(X)	陽性 (X=1)	a (31)	b (275)	a+b (306)
	陰性(X=0)	c (9)	d (2322)	c+d (2331)
		a+c (40)	b+d (2597)	

臨床診斷工具的效度評估
敏感度(Sensitivity) 與特異度 (Specificity)

Test Results	True status (Disease)	
	Yes	*No*
Positive	a	b
Negative	c	d

$$Sen\ (\text{Sensitivity}) = \frac{a}{a+c} \qquad FN(False\ negative) = \frac{c}{a+c}$$

$$Spe\ (\text{Specificity}) = \frac{d}{b+d} \qquad FP(False\ posotive) = \frac{b}{b+d}$$

$$PPV(\text{PositivePredictiveValue}) = \frac{a}{a+b}$$

$$NPV(Negative\ \text{Predictive Value}) = \frac{d}{c+d}$$

Indicators

2×2 Table

		乳癌個案(Y) 是 (Y=1)	否 (Y=0)	
乳房攝影加超音波檢查 (X)	陽性 (X=1)	a (31)	b (275)	a+b (306)
	陰性(X=0)	c (9)	d (2322)	c+d (2331)
		a+c (40)	b+d (2597)	

$$Sen\ (\text{Sensitivity}) = \frac{a}{a+c} = \frac{31}{31+9} = 77.5\%$$

$$Spe\ (\text{Specificity}) = \frac{d}{b+d} = \frac{2322}{275+2322} = 89.4\%$$

$$PPV(\text{PositivePredictiveValue}) = \frac{a}{a+b} = \frac{31}{31+275} = 10.1\%$$

$$NPV(Negative\ \text{Predictive Value}) = \frac{d}{c+d} = \frac{2322}{2322+9} = 99.6\%$$

$$FN(False\ negative) = \frac{c}{a+c} = \frac{9}{31+9} = 22.5\%$$

$$FP(False\ posotive) = \frac{b}{b+d} = \frac{275}{275+2322} = 10.9\%$$

乳癌篩檢實例：
乳房攝影 vs 乳房攝影+超音波

Estimate (95% CI)	乳房攝影+超音波	乳房攝影
敏感度 (%)	77.5	50.0
特異度 (%)	89.4	95.5
Area under ROC curve (%)	90	68
陽性預測值 (%)	10.1	14.7
陰性預測值 (%)	99.6	99.2

Predictive Validity of the Braden Scale for Pressure Sore Risk in a Nursing Home Population

Barbara J. Braden and Nancy Bergstrom

Volume 17, Issue 6
December 1994
Pages 459–470

預測長照病患褥瘡風險:
Braden Scale

Table 2. Definitions of Measures of Validity for Screening Tools to Predict Who Will and Will Not Develop Pressure Sores (PS+/PS−)

	PS+	PS−
Positive test	TP (true positive)	FP (false positive)
Negative test	FN (false negative)	TN (true negative)

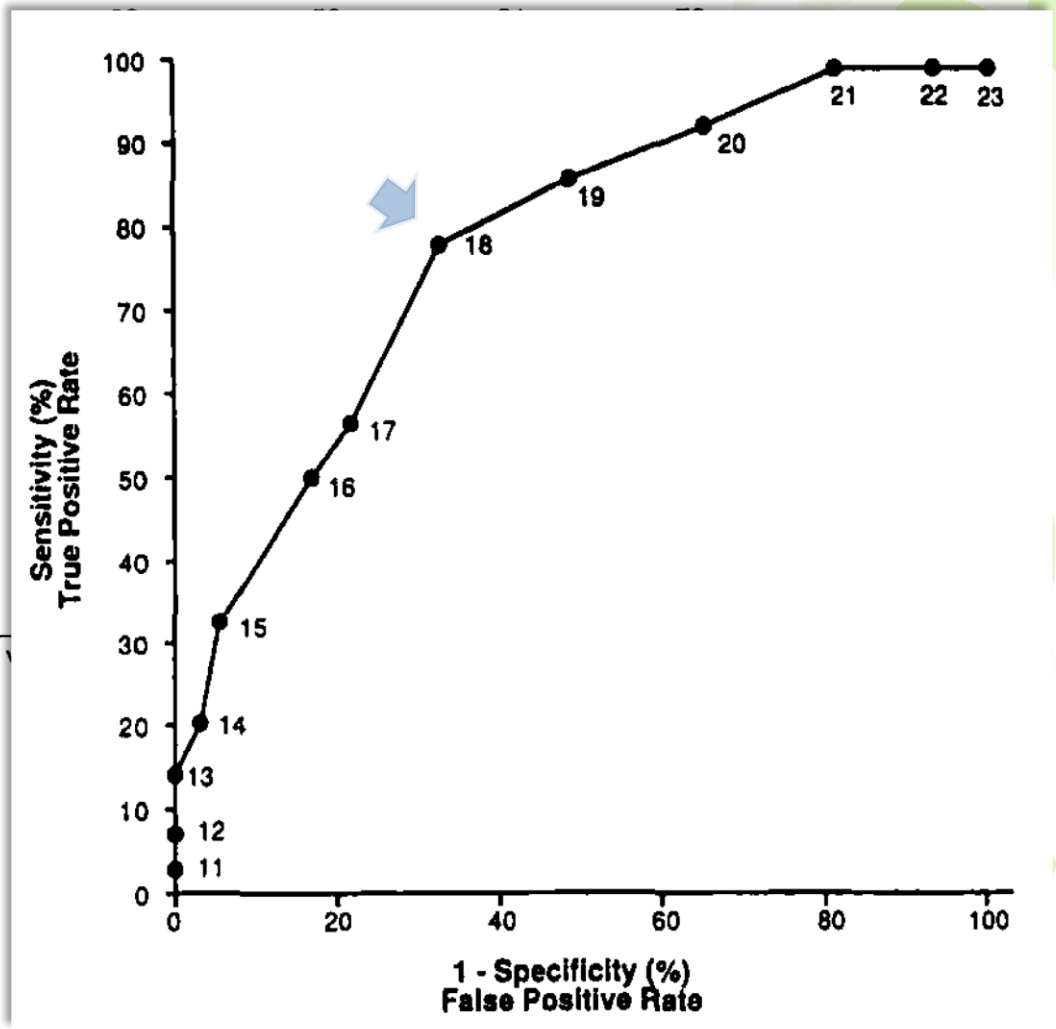
Sensitivity: Those with pressure sore whose scores are equal to or less than cut-off	$\frac{TP}{TP + FN} \times 100$
Specificity: Those without pressure sores whose scores are greater than the cut-off	$\frac{TN}{TN + FP} \times 100$
Predictive value of a positive test Those with scores equal to or less than cut-off with pressure sores	$\frac{TP}{TP + FP} \times 100$
Predictive value of a negative test Those with scores higher than the cut-off who do not have pressure sores	$\frac{TN}{FN + TN} \times 100$

The predictive validity of the Braden Scale and the timing of assessment for optimal prediction of pressure sore development (PS) were studied in a nursing home population. Subjects (N = 102) over age 19, free of PS and admitted within the previous 72 hr, were randomly selected from consecutive admissions to a skilled nursing facility. Subjects were assessed for risk and skin condition every 48 to 72 hr for 4 weeks. Twenty-eight subjects (27.5%) developed a PS. A cut score of 18 used at the observation prior to the first recorded PS maximized prediction, producing a sensitivity of 79%, a specificity of 74%, a 54% predictive value of a positive test, 90% predictive value of a negative test, and 75% correct classification rate. © 1994 John Wiley & Sons, Inc.

Table 5. Estimates of Predictive Validity at Each Score on the Braden Scale

	Braden Score	% Sensitive	% Specific	% PVP	% PNP	% CC
Time 1	14	29	99	89	78	79
	15	36	96	77	80	79
	16	46				
	17	61				
	18	75				
	19	89				
	20	96				
Time 2	14	29				
	15	43				
	16	46				
	17	61				
	18	79				
	19	93				
	20	96				
Observation preceding first PS	14	21				
	15	32				
	16	50				
	17	57				
	18	79				
	19	86				
	20	93				

Note. PVP = predictive value of a positive test; PNP = predictive



Braden Scale 對於長照病患發生褥瘡之預測可達
79%之敏感度，
74%之特異度。
整體預測準確度達75%

盛行率與陽性預測值的關係

- 高盛行率情境: Prevalence=25%
- Sensitivity=80%, Specificity=80%, PPV=57.1%

		疾病狀態 (Y)		
		Disease (Y=1)	Non-disease (Y=0)	Total
檢測結果 (X)	Positive (X=1)	400	300	700
	Negative (X=0)	100	1200	1300
	Total	500	1500	2000

- 低盛行率情境: Prevalence=5%
- Sensitivity=80%, Specificity=80%, PPV=17.4%

		疾病狀態 status (Y)		
		Disease (Y=1)	Non-disease (Y=0)	Total
檢測結果 (X)	Positive (X=1)	80	380	460
	Negative (X=0)	20	1520	1540
	Total	100	1900	2000

- A test with high specificity will yield a high PPV in a given population. When disease prevalence in the population increases the PPV will increase.
- A test with high sensitivity will yield a high NPV in a given population. As disease prevalence in the population decreases the NPV will also increase.

盛行率與陽性預測值的關係

- Prior probability (Prevalence) ↑ ➔ PPV ↑, NPV ↓
- Prior probability (Prevalence) ↓ ➔ PPV ↓, NPV ↑

- Specificity ↑ ➔ PPV ↑ → Rule in (Sp-In)
- Sensitivity ↑ ➔ NPV ↑ → Rule out (Sen-Out)

2. 貝氏觀點與臨床診斷學

Y ：真實疾病狀態 (Y=1: Disease Y=0: non-disease)

X ：工具檢測結果 (X=1: positive; X=0:negative)

陽性預測值 **(PPV)** :

$$\mathbf{P(Y=1|X=1)} = \mathbf{P(Y=1)} \times \mathbf{P(X=1|Y=1)} / \boxed{\mathbf{P(X=1)}}$$

Normalizing constant.
A marginal distribution

$= P(Y=1) \times \mathrm{P}(X=1|Y=1) + \quad P(Y =$

Epidemiological viewpoint: PPV α Prevalence × Sensitivity

Bayesian viewpoint: Posterior α Prior × Likelihood

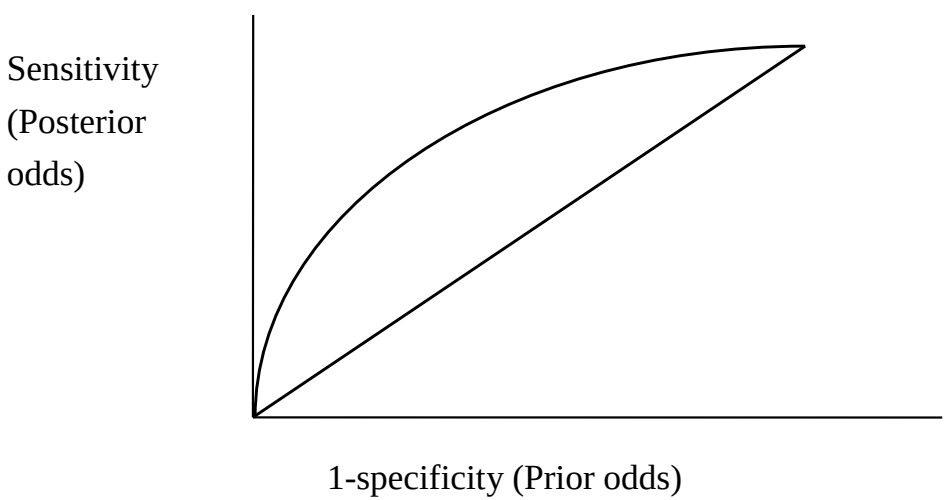
陽性預測值之貝氏觀點

Remind that PPV

$$\mathrm{P}(Y=1|X=1) = {}^{P(Y=1)\times \mathrm{P}(X=1|Y=1)}\big/_{P(X=1)}$$

$$\rightarrow \quad \frac{\mathrm{P}(Y=1|X=1)}{\mathrm{P}(Y=0|X=1)} = \frac{P(Y=1)}{P(Y=0)} \times \frac{\mathrm{P}(X=1|Y=1)}{\mathrm{P}(X=1|Y=0)}$$

$$\{\text{Posterior Odds}\} = \{\text{Prior Odds}\} \times \left\{\boldsymbol{Likelihood\ Ratio}\left(=\frac{\boldsymbol{Sensitivity}}{\boldsymbol{1-Specificity}}\right)\right\}$$



盛行率與陽性預測值的關係: HIV 診斷

Prevalence and HIV test

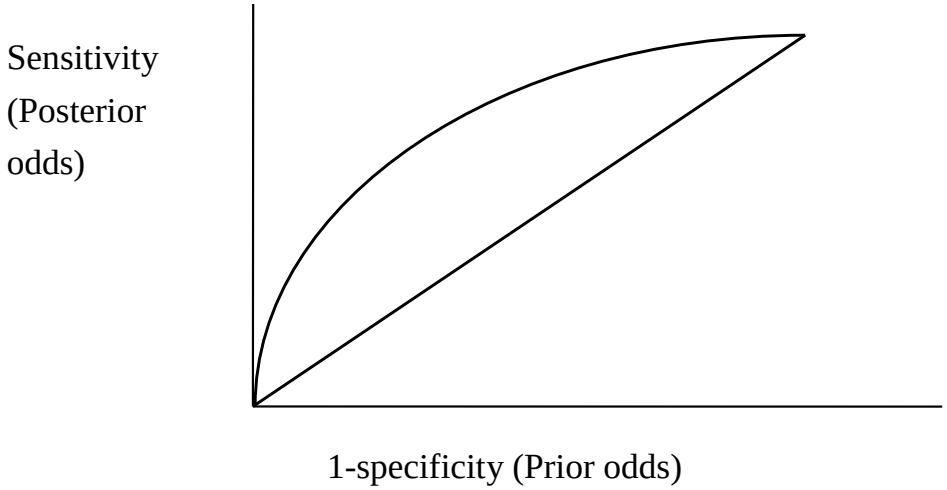
In a population with an HIV prevalence of 0.001 (prior odds: 0.001)

		HIV +	HIV –	
Test	+	95	1998	2093
Test	-	5	97902	97909
		100	99900	100,000

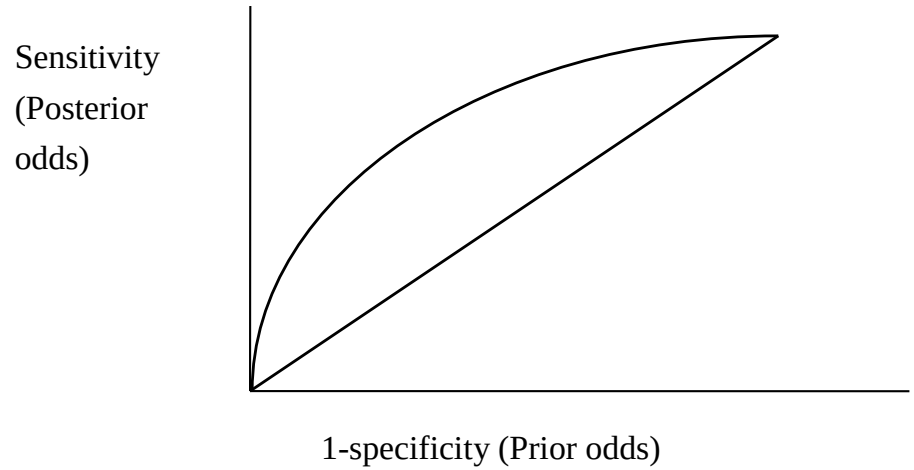
Sen=0.95
Spe=0.98
LR=47.5 (sen/1-spe=0.95/0.02)
PPV=0.0454
Posterior odds =0.048

3. Receiver operating characteristics (ROC)

- 評估診斷工具之指標
- 曲線下面積越大，工具精準度越高.



ROC 之貝氏理論詮釋



P(Y=1)↑ => P(Y=1|X=1)↑.

事前機率 事後機率

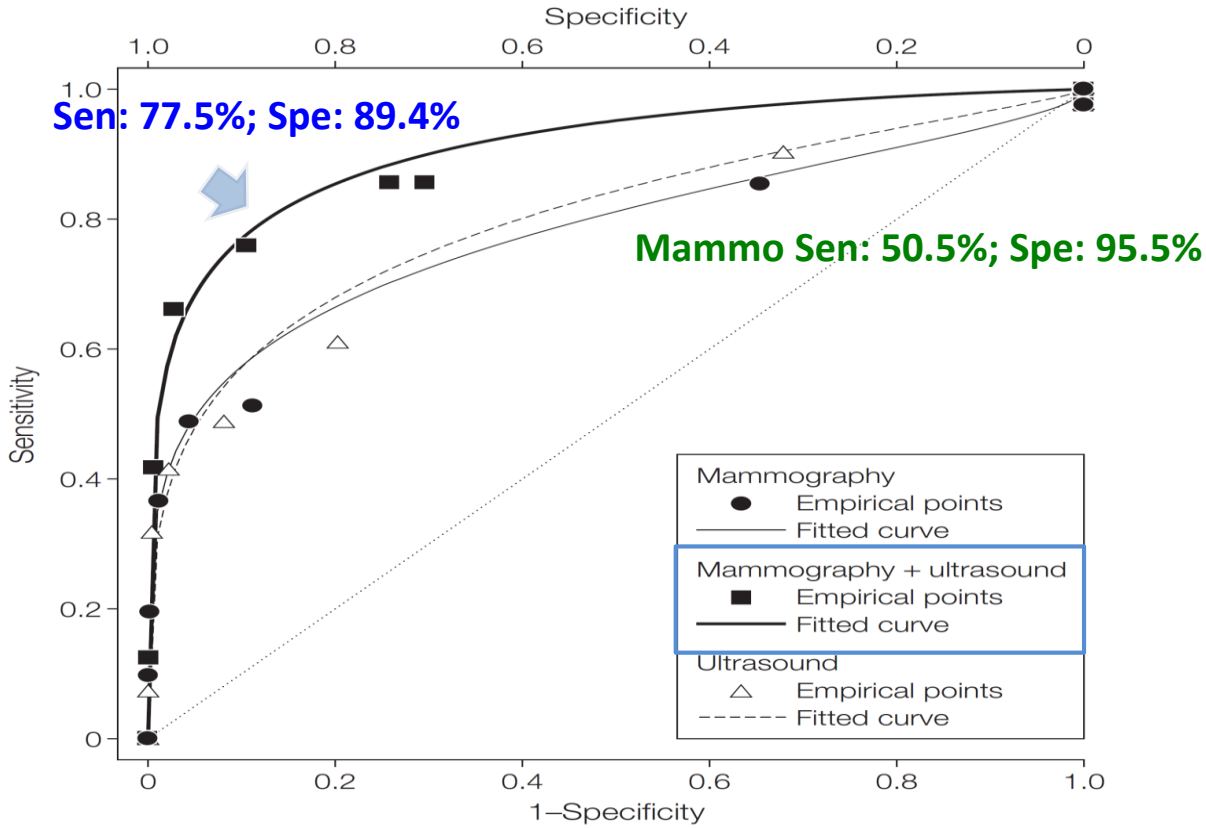
- When P(Y=1|X=1) = P(Y=1),

  對角線代表工具無法提升疾病檢出機率 (事後機率=事前機率)

- 可用於決定連續檢測數值之最佳切點值

臨床實例(1) 乳癌篩檢工具比較

Berg et al, JAMA 2008



- 乳房攝影+超音波優於乳房攝影

臨床實例(2) 褥瘡風險預測分數

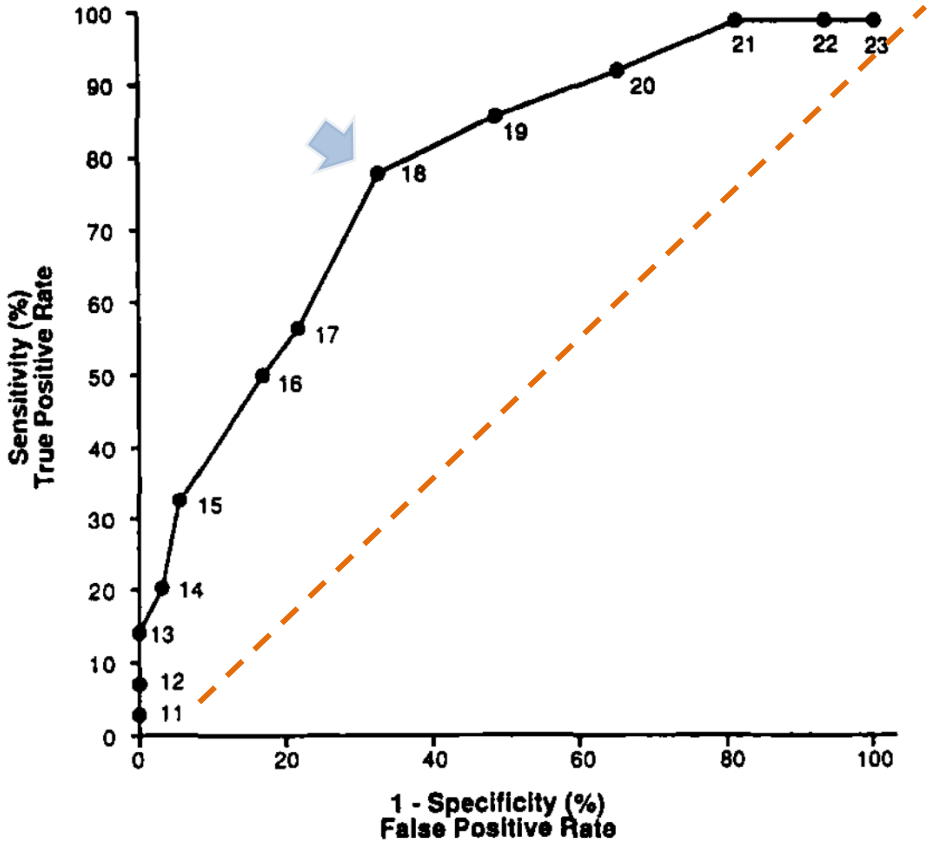


FIGURE 1. Receiver Operator Curve (ROC) plotting the true positive rate (sensitivity) against the false positive rate (1-specificity) over a range of Braden Scale scores using data collected at the observation point preceding the first recorded pressure sore.

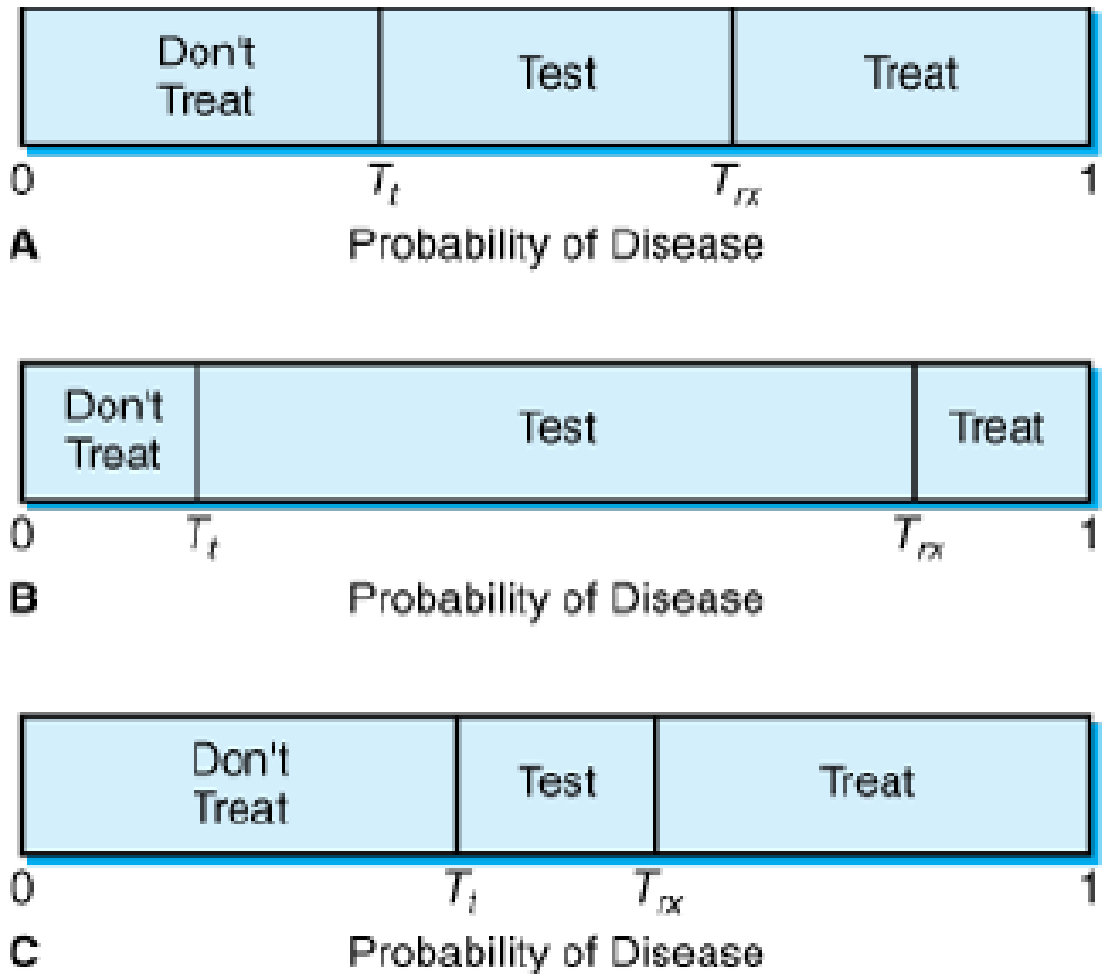
Table 5. Estimates of Predictive Validity at Each Score on the Braden Scale

	Braden Score	% Sensitive	% Specific	% PVP	% PNP	% CC
Time 1	14	29	99	89	78	79
	15	36	96	77	80	79
	16	46	88	59	81	76
	17	61	76	49	84	72
	18	75	59	41	86	64
	19	89	39	36	91	53
	20	96	28	34	95	47
Time 2	14	29	97	80	78	78
	15	43	95	75	81	80
	16	46	84	52	81	74
	17	61	78	52	84	74
	18	79	68	48	89	71
	19	93	51	42	95	63
	20	96	35	36	96	52
Observation preceding first PS	14	21	96	67	76	75
	15	32	95	69	79	77
	16	50	89	64	83	78
	17	57	85	59	84	77
	18	79	74	54	90	75
	19	86	59	44	92	67
	20	93	43	38	94	57

Note. PVP = predictive value of a positive test; PNP = predictive value of negative results; CC = correctly classified.

II 臨床決策分析

1. 決策閾值模式 (Threshold model)



臨界點

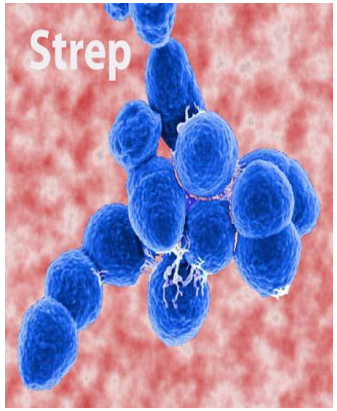
T_t: 選取**檢查**與**不治療**沒有差別

T_{trx}: 選擇**檢驗**和**直接治療病人但不接受檢驗**沒有差別

決定因素：

- 檢查之危險性 (the risk of diagnostic test)
- 治療有病之病人之益處 (the benefit of treatment to patients who have the disease)
- 治療有病及無病病人之危險性 (the risk of the treatment to patients with and without disease)
- 檢查之準確性 (accuracy of test)

臨床實例 (3)
鏈球菌感染咽峽炎
(streptococcal pharyngitis)



Shilpa Nimshikavi: Streptococcus pharyngitis. NEJM 2005:352:e10

臨床實例(3)
鏈球菌感染咽峽炎
(streptococcal pharyngitis)

- 臨床案例

一個8歲左右男孩向他的醫師主訴他三天來的症狀包括喉嚨痛、流鼻水、及發燒。他目前扁桃腺有紅斑及淋巴結腫大。他的父親十分擔心他為咽峽炎。主要的診斷應為鏈球菌性咽峽炎，如果延誤治療，疾病會更趨嚴重，潛在的併發症包含咽喉膿腫、風濕熱、腎絲球腎炎。

臨床實例(3)
鏈球菌感染咽峽炎
(streptococcal pharyngitis)

- 檢驗及治療方案
  - 鏈球菌性咽峽炎快速檢測法 (Rapid streptococcal test)
    - 敏感度 (Sensitivity) 90%
    - 特異度 (Specificity) 95%
  - 抗生素治療
    - 療效好，但有少部份副作用，例如過度使用會對社區有不良的嚴重後果。
    - 不使用抗生素治療，將會增加副作用及死亡的風險。
    - 醫師必需在抗生素治療對病人效益與可能的社區損害間取得平衡。

臨床實例(3)
鏈球菌感染咽峽炎
(streptococcal pharyngitis)

- 事前機率
  - 來自小兒科醫師的臨床經驗。
  - 鏈球菌性咽峽炎較其他常見病毒性感染而言是較為罕見，較少出現流鼻水，也可能有淋巴結滲出液。
  - 鏈球菌感染常伴隨喉嚨痛、發燒及扁桃腺腫，但這些症狀並未在這個男孩上看見。
  - 綜合這些情形，此男孩罹患鏈球菌性咽峽炎的事前機率約為**10%**。

2x2聯列表(Contingency table)

		鏈球菌感染咽峽炎 (streptococcal pharyngitis)		
		是	否	合計
快速檢驗 (Rapid streptococcal test)	陽性	90	45	135
	陰性	10	855	865
	合計	100	900	1,000

PPV=67% →以抗生素治療 (檢測結果為陽性)
NPV=99% →不治療繼續追蹤 (檢測結果為陰性)

快速鏈球菌檢查為陽性結果下 (Given a positive rapid strep test)

- 陽性概似度比值 (Likelihood ratio positive)

$$= \frac{\text{Sen}}{1-\text{Sp}} = \frac{0.90}{0.05} = 18$$

- 陽性事後勝算比 (Posterior odds (given test is positive)) (當P(D)=0.1)

$$= \frac{P(D|+)}{P(\bar{D}|+)} = \frac{P(D)}{P(\bar{D})} \times \frac{\text{Sen}}{1-\text{Spe}} = \frac{1}{9} \text{ X18} = 2$$

- 事後機率

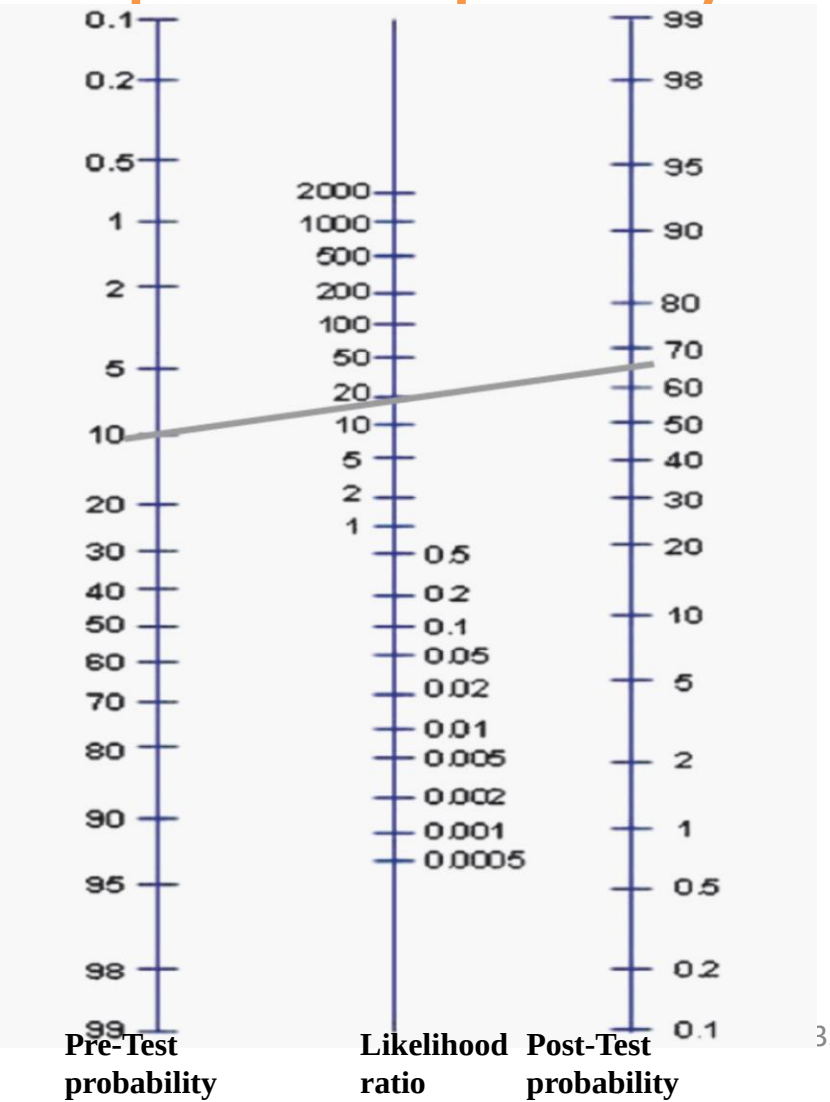
$$= \frac{2}{1+2} = \frac{2}{3} = 0.67 \longrightarrow$$ 選擇使用抗生素!!

參考 *Fagan TJ. Nomogram for Bayes' theorem. (Letter.) N Engl J Med 1975;293:257.*

快速鏈球菌檢查為陽性結果下 (Given a positive rapid strep test)

貝氏諾謨圖 (Bayesian nomogram)

Given a positive rapid strep test, the post-test probability of disease is about 67%
在快速鏈球菌檢查為陽性結果下，檢查後得病機率約67%



快速鏈球菌檢查為陰性結果下 (Given a negative rapid strep test)

- 陰性概似度比值 (Likelihood ratio negative)
- $\frac{1-\mathrm{Sen}}{\mathrm{Sp}}$
- 陰性事後勝算比 (Posterior odds (given test is negative)) (當P(D)=0.1)

$$= \frac{P(D|-)}{P(\bar{D}|-)} = \frac{P(D)}{P(\bar{D})} \text{ X } \frac{P(-|D)}{P(-|\bar{D})} \left(= \frac{1-\mathrm{Sen}}{\mathrm{Sp}} \right) = \frac{1}{9} \times \frac{0.1}{0.95} = 0.012$$

- 事後機率

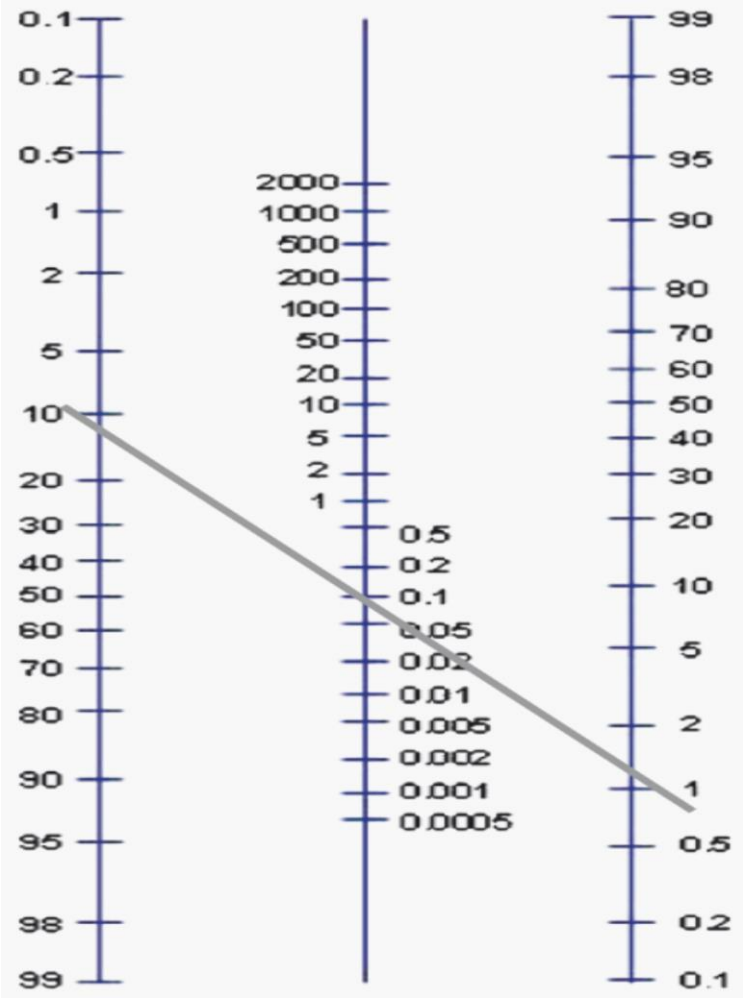
$$P(D|-) = \frac{0.012}{1+0.012} = 0.012 \longrightarrow$$ 繼續觀察

參考 *Fagan TJ. Nomogram for Bayes' theorem. (Letter.) N Engl J Med 1975;293:257.*

快速鏈球菌檢查為陰性結果下 (Given a negative rapid strep test)

貝氏諾謨圖 (Bayesian nomogram)

Given a negative test result, the post-test probability of disease is about 1%
在快速鏈球菌檢查為陰性結果下，檢查後得病機率約1%



Pre-Test probability **Likelihood ratio** **Post-Test probability**

Table 2. Useful Findings in the Evaluation of Abdominal Pain

			5% pretest probability (%)		*25% pretest probability (%)*	
Finding	*LR+*	*LR–*	*Finding present*	*Finding absent*	*Finding present*	*Finding absent*
Appendicitis[3]						
Right lower quadrant pain	8.4	0.2	31	1	74	6
Migration of pain from the periumbilical area to the right lower quadrant of the abdomen	3.6	0.4	16	2	54	13
Fever	3.2	0.4	14	2	51	12
Psoas sign	3.2	0.88	14	4	52	23
Rebound tenderness	2.03	0.54	10	3	40	15
Rigidity	1.59	0.88	9	5	38	23
Anorexia	1.1	0.9	5	5	26	23
Bowel obstruction[4]						
Constipation	8.8	0.6	32	3	75	16
Abdominal distention	5.7	0.4	23	2	66	12
Pain decreases after vomiting	4.5	0.8	19	4	60	21
Colic	2.8	0.8	13	4	48	21
Previous abdominal surgery	2.7	0.4	12	2	47	12
Cholecystitis[5]						
Murphy's sign	5.0	0.4	21	2	62	12
Right upper quadrant pain	2.5	0.3	11	2	45	9
Fever	1.8	0.8	8	4	37	21
Jaundice[6]	1.0	1.0	5	5	25	25

LR+ = positive likelihood ratio; LR– = negative likelihood ratio.

Information from references 3 through 6.

PSA 是否適合用於早期偵測攝護腺癌?

ABSTRACT

Objective To evaluate if prostate specific antigen test attains validity standards required for screening in view of recent prostate cancer screening trial results.

Design Case-control study nested in longitudinal cohort.

Setting Västerbotten Intervention Project cohort, Umeå, Sweden.

Participants 540 cases and 1034 controls matched for age and date of blood draw.

Main outcome measure Validity of prostate specific antigen for prediction of subsequent prostate cancer diagnosis by record linkage to cancer registry.

Results Blood samples were drawn on average 7.1 (SD 3.7) years before diagnosis. The area under the curve for prostate specific antigen was 0.84 (95% confidence interval 0.82 to 0.86). At prostate specific antigen cut-off values of 3, 4, and 5 ng/ml, sensitivity estimates were 59%, 44%, and 33%, and specificity estimates were 87%, 92%, and 95%. The positive likelihood ratio commonly considered to "rule in disease" is 10; in this study the positive likelihood ratios were 4.5, 5.5, and 6.4 for prostate specific antigen cut-off values of 3, 4, and 5 ng/ml. The negative likelihood ratio commonly considered to "rule out disease" is 0.1; in this study the negative likelihood ratios were 0.47, 0.61, and 0.70 for prostate specific antigen cut-off values of 3, 4, and 5 ng/ml. For a cut-off of 1.0 ng/ml, the negative likelihood ratio was 0.08.

Conclusions No single cut-off value for prostate specific antigen concentration attained likelihood ratios formally required for a screening test. Prostate specific antigen concentrations below 1.0 ng/ml virtually ruled out a prostate cancer diagnosis during the follow-up. Additional biomarkers for early detection of prostate cancer are needed before population based screening for prostate cancer should be introduced.

Benny H et al. Prostate specific antigen for early detection of prostate cancer: longitudinal study. BMJ 2009;339:b3573

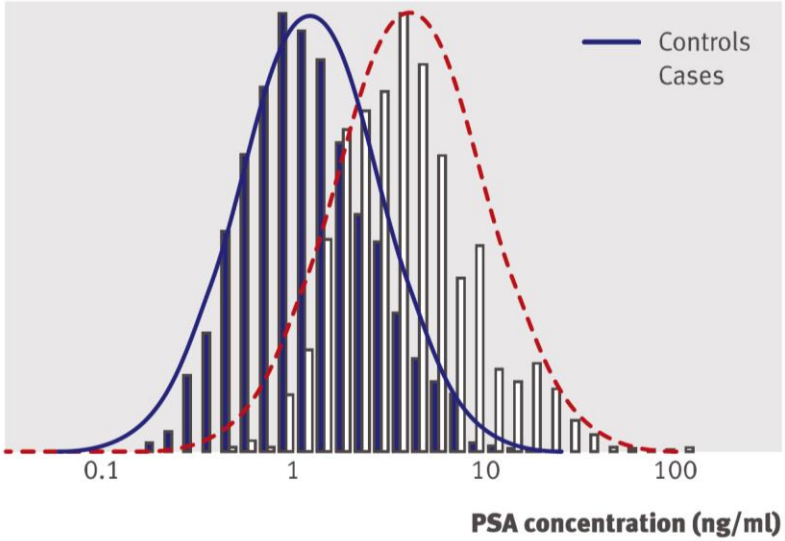
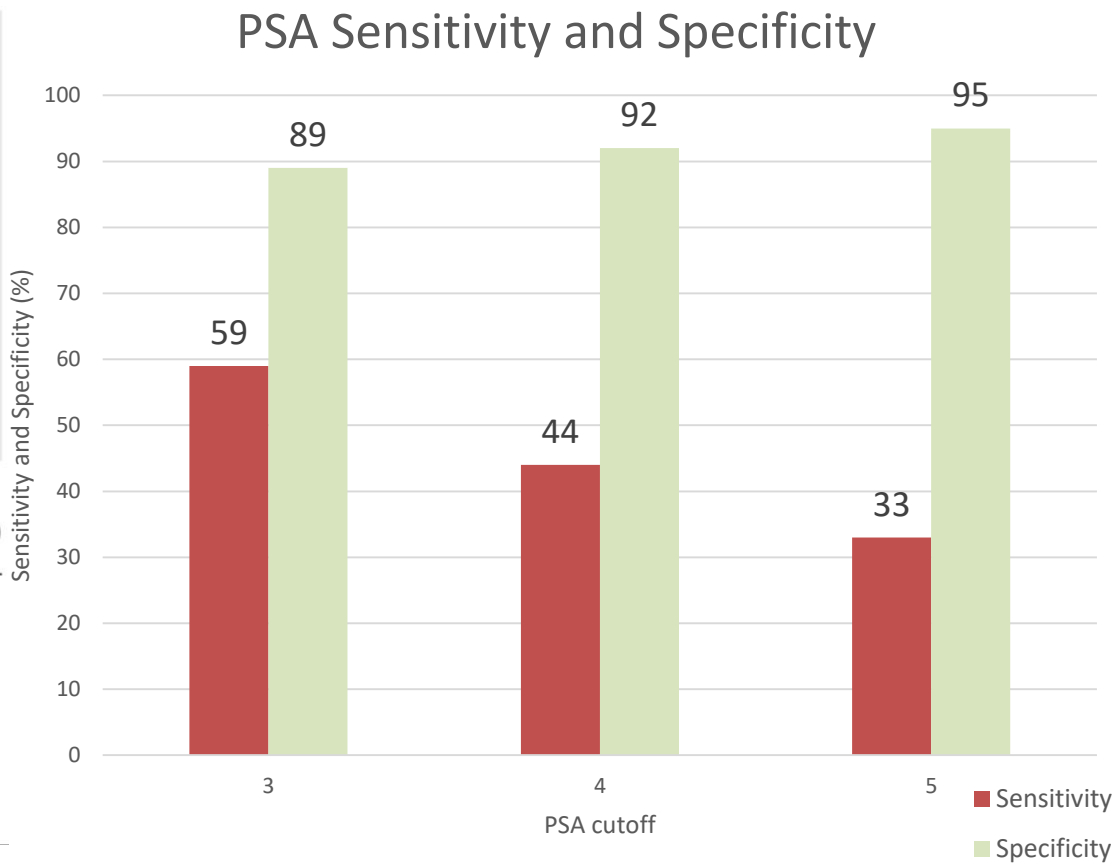
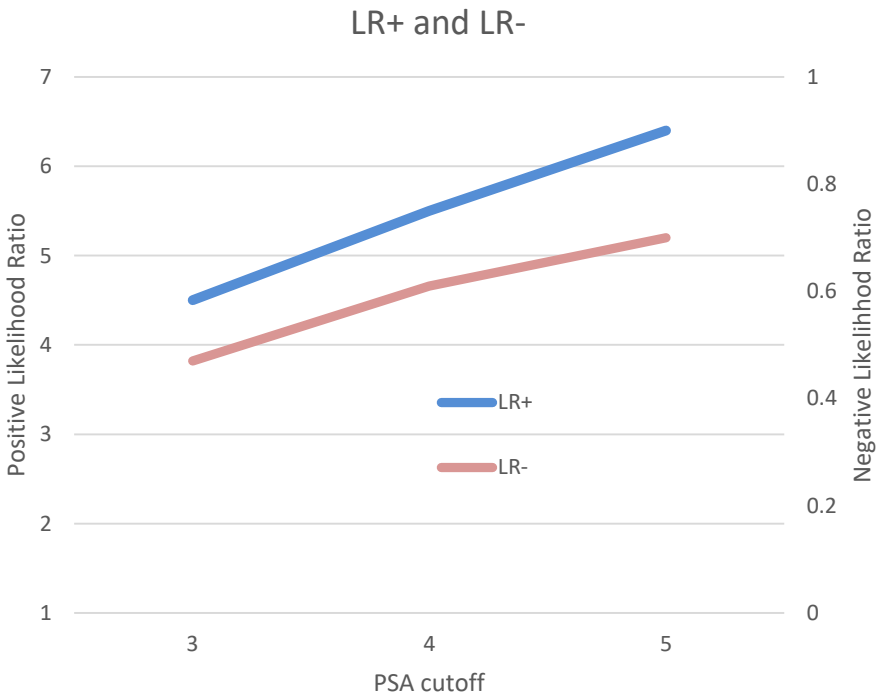


Fig 1 | Distribution of plasma prostate specific antigen (PSA) concentrations in cases and controls. Curves indicate frequency functions of calculated normal distribution of logarithm of PSA concentrations according to mean and standard deviation in cases and controls. Histogram shows observed distribution of logarithm of PSA concentrations in cases and controls



利用PSA數值作為預測工具



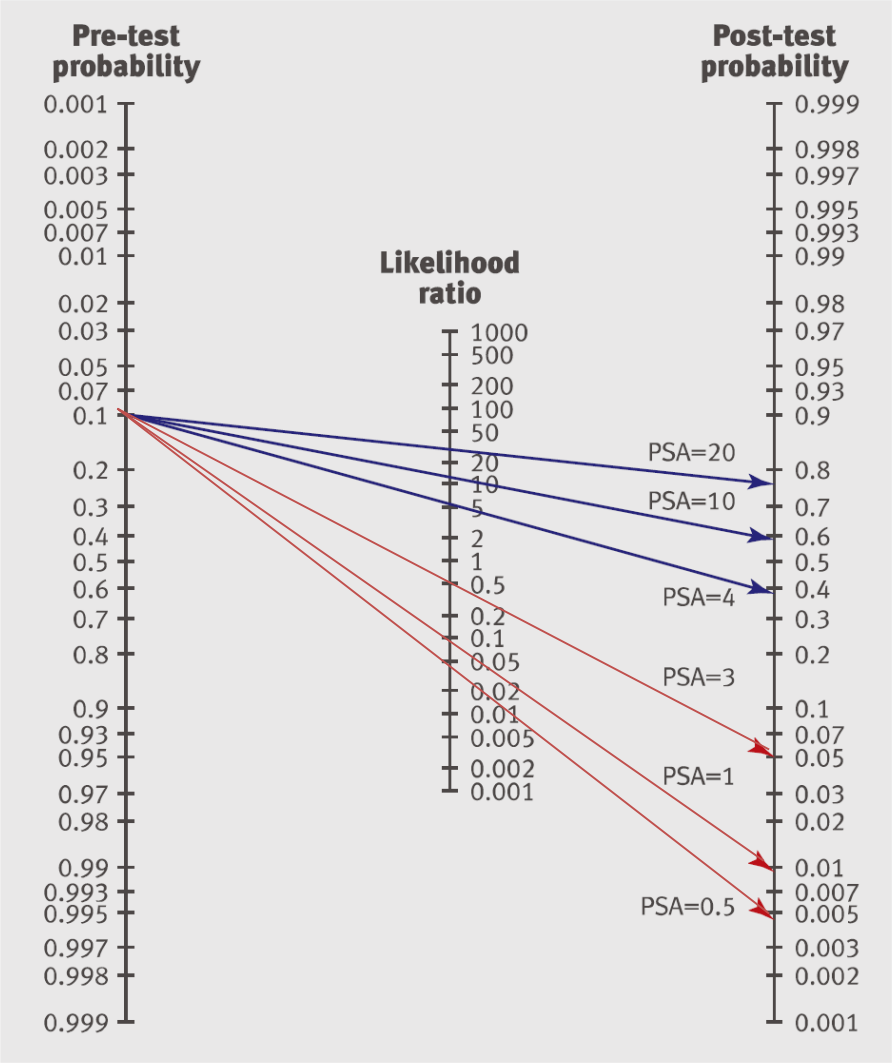


Fig 2 | Fagan's nomogram for calculation of post-test probabilities. Blue (solid) arrows indicate post-test probability of diagnosis during follow-up for men with prostate specific antigen (PSA) concentrations above given cut-offs. Red (broken) arrows indicate post-test probability of diagnosis during follow-up for men with PSA concentrations below given cut-offs