EBM~Journal Reading

張惠敏

970415

Diagnostic Procedure: Threshold Model
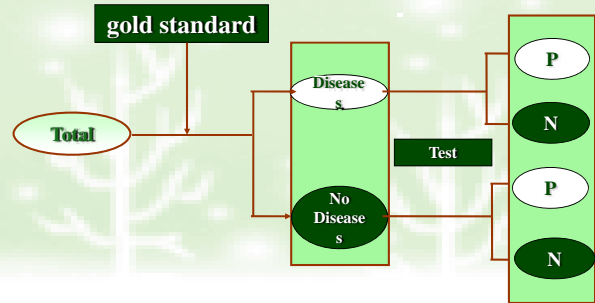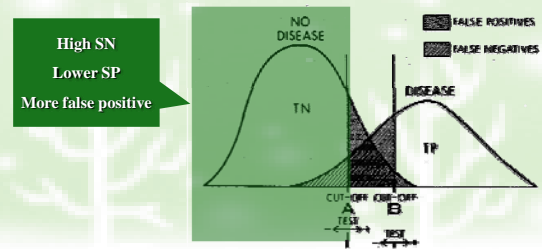

Test – Disease 2×2 set up table

	Disease （＋）	Disease （－）	合計
Test （＋）	真陽性(a)	假陽性(b)	a＋b
Test （－）	假陰性(c)	真陰性(d)	c＋d
合計	a＋c	b＋d	a＋b＋c＋d

ROC Curve
Receive Operating Characteristic Curve(1)

High SN
Lower SP
More false positive

ROC Curve
Receive Operating Characteristic Curve(2)

Lower SN
Higher SP
More false negatives
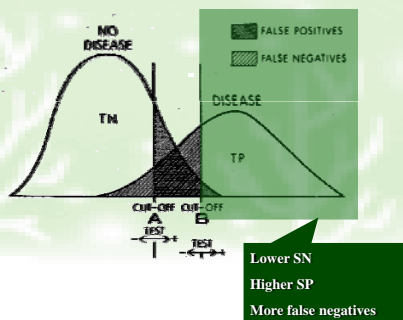
ROC Curve : A Graphic Method for Comparing Two or More Diagnostic Tests

High SN
Lower SP
More false positive

Lower SN
Higher SP
More false negatives
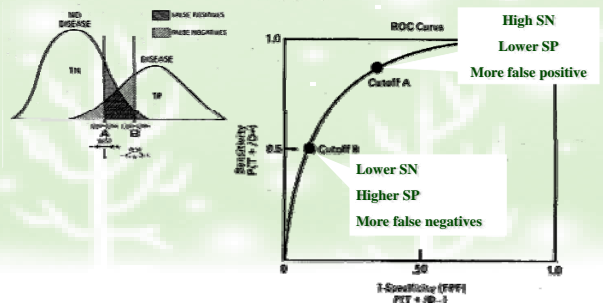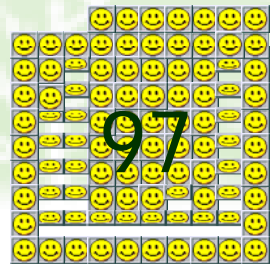
For a prevalence of 3% - in every 100 patients

3 will have the disease

Prevalence=(a+c)/(a+b+c+d)

	Disease（＋）	Disease（－）	合計
Test（＋）	真陽性	假陽性	a＋b
Test（－）	假陰性	真陰性	c＋d
合計	a＋c（3）	b＋d（97）	a＋b＋c＋d（100）

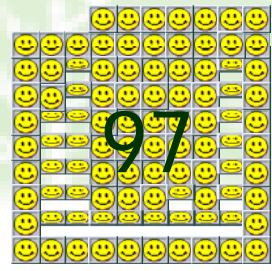97

Will not have the disease

For a test with a sensitivity of 50%

For every 100 patients with the disease 1-2 will test positive

How many will not have the disease?

97

	Disease（＋）	Disease（－）	合計
Test（＋）	真陽性(1.5)	假陽性	a＋b
Test（－）	假陰性(1.5)	真陰性	c＋d
合計	a＋c（3）	b＋d（97）	a＋b＋c＋d（100）
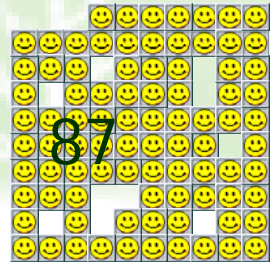
For a test with a specificity of 90%

	Disease（＋）	Disease（－）	合計
Test（＋）	真陽性(1.5)	假陽性(10)	a＋b(11.5)
Test（－）	假陰性(1.5)	真陰性(87)	c＋d(88.5)
合計	a＋c（3）	b＋d（97）	a＋b＋c＋d（100）

False positive rate

= 1-Specificity   (10%)

87

For those who don't have the disease 10 patients will go on to test positive

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Given a positive test what are my chances of disease doc?
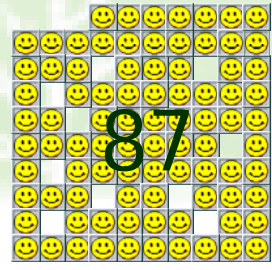
	Disease（＋）	Disease（－）	合計
Test（＋）	真陽性(1.5)	假陽性(10)	a＋b(11.5)
Test（－）	假陰性(1.5)	真陰性(87)	c＋d(88.5)
合計	a＋c（3）	b＋d（97）	a＋b＋c＋d（100）

11 ½ people have a positive test
Of which 1 ½ have will have the disease

87

13% chance of having the disease given a positive test
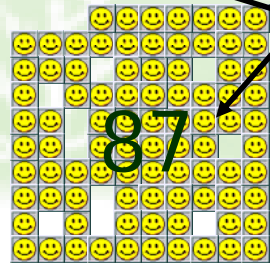
Given a negative test what are my chances of not having the disease doc?

	Disease（＋）	Disease（－）	合計
Test（＋）	真陽性(1.5)	假陽性(10)	a＋b(11.5)
Test（－）	假陰性(1.5)	真陰性(87)	c＋d(88.5)
合計	a＋c（3）	b＋d（97）	a＋b＋c＋d（100）

88 ½ people

will have a negative test of which 1 ½ will have the disease

False reassurance rate of 1.7%

87

Describe the result to your patient

Positive predictive vale

For every 100 people who have a positive test 13 will have the disease

Slide 1

What happens if I have an negative test
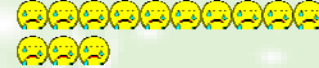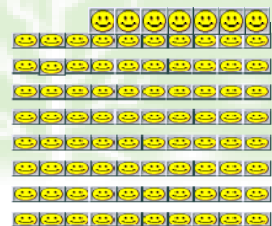
Negative test pretty much rules out the disease but a small number 1-2 people in every 100 will still have the disease

評價指標的計算

- 敏感度＝a/(a+c)
- 特異度＝d/(b+d)
- 陽性預測值＝a/(a+b)
- 陰性預測值＝d/(b+d)
- 診斷指數＝敏感度＋特異度
- 診斷效率(準確度)＝(a+d)/(a+b+c+d)
- 陽性概似比＝敏感度/(1－特異度)
- 陰性概似比＝(1－敏感度)/特異度

Slide 3

- 靈敏度(sensitivity)： 真陽性率(真患者) 試驗檢出已被gold standard確定為患者的能力 a/(a+c)
- 特異性(specificity)，真陰性率(非患者) 試驗排除已被gold standard確定為非患者的能力 d/(b+d)
- 陽性預測值(positive predictive value) 陽性試驗的事後機率，某檢驗為陽性時被檢者患病的機率 a/(a+b)。
- 準確性(accuracy) 陰性試驗的事後機率，某檢驗為陰性時被檢者未患病的機率 d/(c+d)。

陽性試驗概似比

- 陽性試驗似然比(positive likelihood ratio, +LR) 患者試驗真陽性比例與非患者試驗假陽性比例的比值，表明試驗陽性時，患病與不患病機會的比值。比值越大(如≧10)，患病機率越大，試驗越好。
- +LR=靈敏度/（1-特異性）=[a/(a+c)]/[1-d/(b+d)]

陰性試驗似然比

- 陰性試驗似然比(negative likelihood ratio, -LR) 患者試驗假陰性比例與非患者試驗真陰性比例的比值，表明試驗陰性時，患病與不患病機會的比值。比值越小(如≦0.1)，不患病的機率越大，試驗越好。
- -LR= (1-靈敏度)/特異性
- =[1-a/(a+c)]/[d/(b+d)]

Slide 6

HbA1c as a screening tool for detection of Type 2 diabetes: a systematic review
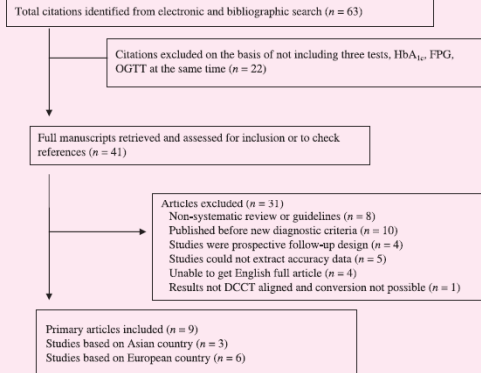
Diabet. Med. 24, 333–343 (2007)

Slide 1: Methods

Methods

- Databases:MEDLINE,PUBMED and EMBASE electron databases (1994–September 2004)
- Keywords:'diabetes mellitus','screening', 'diagnosis', 'HbA1c', 'fasting plasma glucose test'and 'OGTT'.

Slide 2: Criteria

Criteria

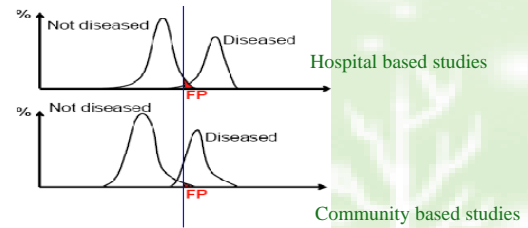Total citations identified from electronic and bibliographic search (n = 63)

Citations excluded on the basis of not including three tests, HbA1c, FPG, OGTT at the same time (n = 22)

Full manuscripts retrieved and assessed for inclusion or to check references (n = 41)

Articles excluded (n = 31)
Non-systematic review or guidelines (n = 8)
Published before new diagnostic criteria (n = 10)
Studies were prospective follow-up design (n = 4)
Studies could not extract accuracy data (n = 5)
Unable to get English full article (n = 4)
Results not DCCT aligned and conversion not possible (n = 1)

Primary articles included (n = 9)
Studies based on Asian country (n = 3)
Studies based on European country (n = 6)

Slide 3: Table

Slide 4: Effects of patient spectrum: Specificity

Effects of patient spectrum: Specificity

Hospital based studies

Community based studies

Slide 5: Table

Slide 6: Table

高雄榮總藥劑部

4

Slide 1

Macrovascular Risk and Diagnostic Criteria for Type 2 Diabetes

Diabetes Care 26:485–490, 2003

Slide 2

HPLC: *HbA1c ≥ 5.7% (SN= 80.0% SP=86.3%)*. HbA1c levels< 4.7 and ≥ 6.2% have almost 100% accuracy for predicting the absence and presence of type 2 diabetes

DCA2000: *HbA1c ≥ 6.2% (SN= 72.2%, SP=94.7%)*, and HbA1c< 5.0 and ≥ 6.8% predict the absence or presence of diabetes, respectively, with almost 100% certainty

FPG, the area under the ROC curve was 0.9065. *FPG ≥ 6.0mmol/l (SN= 74.1%, SP=94.5%)* .FPG levels<4.7 and ≥ 6.4 mmol/l had almost 100% accuracy for detecting the absence or presence of type 2 diabetes.

HbA1c as measured by HPLC and DCA2000 for detecting type 2 diabetes, compared with OGTT, were 0.893 and 0.911, respectively (*P*= 0.77)

Diabetes Care 26:485–490, 2003

Slide 3

Fasting plasma glucose and HbA1c to predict diabetes

Diabetes care, volume 21, number 8, august 1998

Slide 4

Fasting plasma glucose and HbA1c to predict diabetes

- N=2,877 Hong Kong Chinese subjects
- These subjects *had known risk factors* for glucose intolerance and were referred to the Diabetes and Endocrine Center of the Prince of Wales Hospital for diabetes screening.
  - The risk factors for glucose intolerance included a family history of diabetes
  - history of gestational diabetes
  - Obesity
  - history of impaired glucose tolerance.

Slide 5

Fasting plasma glucose and HbA1c to predict diabetes

- The test was performed after 3 days of normal carbohydrate intake and physical activity and after an 8-h fast.
- No smoking was allowed during the test.
- FPG and 2-h PG were measured together with HbA1 c and fructosamine.
- Both the WHO and ADA criteria were used for the diagnosis of glucose intolerance

Slide 6

Fasting plasma glucose and HbA1c to predict diabetes

FPG (mmol/l)	HbA1c (%)	Number of subjects	75-g OGTT		
			Normal	IGT	Diabetes
≥5.6	≥5.5	880	132	221	527
≥5.6	<5.5	143	64	52	27
<5.6	≥5.5	965	683	234	48
<5.6	<5.5	889	714	150	25
	Total	2,877	1,593 (55.4%)	657 (22.8%)	627 (21.8%)

高雄榮總藥劑部

Slide 1

Fasting plasma glucose and HbA1c to predict diabetes

FPG (mmol/l)	Fructosamine (μmol/l)	Number of subjects	75-g OGTT		
			Normal	IGT	Diabetes
≥5.4	≥235	695	154	164	377
≥5.4	<235	254	142	69	43
<5.4	≥235	684	546	102	36
<5.4	<235	775	660	108	7
	Total	2,408	1,502 (62.4%)	443 (18.4%)	463 (19.2%)

Slide 2

Fasting plasma glucose and HbA1c to predict diabetes

WHO and ADA criteria

2877

Diseases

No Diseases

FPG or Hba1c

P
N
P
N

Slide 3

Fasting plasma glucose and HbA1c to predict diabetes

FPG (mmol/l)	HbA1c (%)	Number of subjects	75-g OGTT		
			Normal	IGT	Diabetes
≥5.6	≥5.5	880	132	221	527
≥5.6	<5.5	143	64	52	27
<5.6	≥5.5	965	683	234	48
<5.6	<5.5	889	714	150	25
	Total	2,877	1,593 (55.4%)	657 (22.8%)	627 (21.8%)

	D(+)	D(-)
Test (+)	575	1270
Test (-)	52	980

527+48=575

132+221+683+234=1270

27+25=52

64+52+714+150=980

Slide 4

Fasting plasma glucose and HbA1c to predict diabetes

FPG (mmol/l)	HbA1c (%)	Number of subjects	75-g OGTT		
			Normal	IGT	Diabetes
≥5.6	≥5.5	880	132	221	527
≥5.6	<5.5	143	64	52	27
<5.6	≥5.5	965	683	234	48
<5.6	<5.5	889	714	150	25
	Total	2,877	1,593 (55.4%)	657 (22.8%)	627 (21.8%)

	D(+)	D(-)
Test (+)	575	1270
Test (-)	52	980

DM

SN(%)=575/(575+52) ×100%=91.7%

SP(%)=980/(1270+980) ×100%=43.6%

PLR=0.917/(1-0.436)=1.63

NLR=(1-0.917)/0.436=0.19

Slide 5

Fasting plasma glucose and HbA1c to predict diabetes

FPG (mmol/l)	HbA1c (%)	Number of subjects	75-g OGTT		
			Normal	IGT	Diabetes
≥5.6	≥5.5	880	132	221	527
≥5.6	<5.5	143	64	52	27
<5.6	≥5.5	965	683	234	48
<5.6	<5.5	889	714	150	25
	Total	2,877	1,593 (55.4%)	657 (22.8%)	627 (21.8%)

	D(+)	D(-)
Test (+)	1030	815
Test (-)	254	778

221+234+527+48=1030

132+683=815

52+150+27+25=254

64+714=778

Slide 6

Fasting plasma glucose and HbA1c to predict diabetes

FPG (mmol/l)	HbA1c (%)	Number of subjects	75-g OGTT		
			Normal	IGT	Diabetes
≥5.6	≥5.5	880	132	221	527
≥5.6	<5.5	143	64	52	27
<5.6	≥5.5	965	683	234	48
<5.6	<5.5	889	714	150	25
	Total	2,877	1,593 (55.4%)	657 (22.8%)	627 (21.8%)

	D(+)	D(-)
Test (+)	1030	815
Test (-)	254	778

IGT

SN(%)=1030/(1030+254) ×100%=80.2%

SP(%)=778/(815+778) ×100%=48.8%

PLR=0.802/(1-0.488)=1.57

NLR=(1-0.802)/0.488=0.41

Slide 1

Fasting plasma glucose and HbA1c to predict diabetes

FPG (mmol/l)	HbA1c (%)	Number of subjects	75-g OGTT Normal	IGT	Diabetes
≥5.6	≥5.5	880	132	221	527
≥5.6	<5.5	143	64	52	27
<5.6	≥5.5	965	683	234	48
<5.6	<5.5	889	714	150	25
	Total	2,877	1,593 (55.4%)	657 (22.8%)	627 (21.8%)

	D(+)	D(-)
Test (+)	554	469
Test (-)	73	1781

527+27=554
48+25=73
132+221+64+52=469
683+234+714+150=1781

DIABETES CARE, VOLUME 21, NUMBER 8, AUGUST 1998

Slide 2

Fasting plasma glucose and HbA1c to predict diabetes

FPG (mmol/l)	HbA1c (%)	Number of subjects	75-g OGTT Normal	IGT	Diabetes
≥5.6	≥5.5	880	132	221	527
≥5.6	<5.5	143	64	52	27
<5.6	≥5.5	965	683	234	48
<5.6	<5.5	889	714	150	25
	Total	2,877	1,593 (55.4%)	657 (22.8%)	627 (21.8%)

	D(+)	D(-)
Test (+)	554	469
Test (-)	73	1781

DIABETES CARE, VOLUME 21, NUMBER 8, AUGUST 1998

DM

SN(%)=554/(554+73) ×100%=88.4%

SP(%)=1781/(469+1781) ×100%=79.2%

PLR=0.884/(1-0.792)=4.25

NLR=(1-0.884)/0.792=0.15

Slide 3

Fasting plasma glucose and HbA1c to predict diabetes

FPG (mmol/l)	HbA1c (%)	Number of subjects	75-g OGTT Normal	IGT	Diabetes	Likelihood ratio Abnormal	Diabetes
≥5.6	≥5.5	880	132	221	527	7.03	5.36
≥5.6	<5.5	143	64	52	27	1.53	0.84
<5.6	≥5.5	965	683	234	48	0.51	0.19
<5.6	<5.5	889	714	150	25	0.30	0.10
	Total	2,877	1,593 (55.4%)	657 (22.8%)	627 (21.8%)		

	D(+)	D(-)
Test (+)	827	196
Test (-)	457	1397

221+52+527+27=827
132+64=196
234+150+48+25=457
683+714=1397

DIABETES CARE, VOLUME 21, NUMBER 8, AUGUST 1998

Slide 4

Fasting plasma glucose and HbA1c to predict diabetes

FPG (mmol/l)	HbA1c (%)	Number of subjects	75-g OGTT Normal	IGT	Diabetes
≥5.6	≥5.5	880	132	221	527
≥5.6	<5.5	143	64	52	27
<5.6	≥5.5	965	683	234	48
<5.6	<5.5	889	714	150	25
	Total	2,877	1,593 (55.4%)	657 (22.8%)	627 (21.8%)

	D(+)	D(-)
Test (+)	827	196
Test (-)	457	1397

DIABETES CARE, VOLUME 21, NUMBER 8, AUGUST 1998

IGT

SN(%)=827/(827+457) ×100%=64.4%

SP(%)=1397/(196+1397) ×100%=87.7%

PLR=0.644/(1-0.877)=5.24

NLR=(1-0.644)/0.877=0.41

Slide 5

Criterion	Colagiuri et al.	
Age (year)	> 25 years summary statistics not reported	
No. and gender (M/F)	10 447 Not stated	
Ethnicity	Australia national population	
Baseline data	No	
Prevalence of diabetes (%)	7.4	
Results of tests		
HbA1c		
Cut-off point (%)	≥ 5.3	
Items	DM	IGT
Sn (%)	78.7	42.0
Sp (%)	82.8	88.2
Likelihood ratio		
PLR	4.58	3.56
NLR	0.26	0.66
FPG		
Cut-off point (mmol/l)	≥ 5.5	≥6.1
Items	DM	
	IGT	
Sn (%)	79.9	63.6
	51.9	34.6
Sp (%)	79.9	93.9
Likelihood ratio		
PLR	3.98	10.4
	3.9	∞
NLR	0.25	0.39
	0.55	0.65
ROC curve available	No	
Diagnose criteria	WHO (1999)	

IGT: HBA1C had a lower sensitivity,but higher specificity

IGT: FPG had a lower sensitivity

Diabet. Med. 24, 333–343 (2007)

Slide 6

Criterion	Mannucci et al*	
Age (year)	52.2 ± 18.5 (30–70)	
No. and gender (M/F)	1213 567/648	
Ethnicity	Italian	
Baseline data	Yes	
Prevalence of diabetes (%)	6.6	
Results of tests		
HbA1c		
Cut-off point (%)	>6.6	
Items	DM	IGT
Sn (%)	M 98	M 59
	F 100	F 55
Sp (%)	M 30	M 19
	F 21	F 9
Likelihood ratio		
PLR	M 1.30	M 0.73
	F 1.28	F 0.60
NLR	M 0.31	M 2.12
	F 0	F 4.86
FPG		
Cut-off point (mmol/l)	≥7.0	≥6.1
Items	DM	IGT
Sn (%)	M 91	M 59
	F 100	F 55
Sp (%)	M 30.0	M 19.3
	F 21.6	F 9.3
Likelihood ratio		
PLR	1.30	0.73
	1.28	3.60
NLR	0	2.12
		4.86
ROC curve available	Yes (for IGT)	
Diagnose criteria	WHO 1999	

IGT: HBA1C had a lower sensitivity and specificity

Diabet. Med. 24, 333–343 (2007)

HbA1c had a lower sensitivity, but higher specificity

higher specificity of HbA1c

higher sensitivity of FPG

HbA1c had higher sensitivity but lower specificity than FPG to diagnose diabetes at different cut-off points

Results by cut-off point

Cut-off point	HbA1c			FPG	
	≧5.9	≧6.1	≧6.2	≧6.1	≧5.6
SN（%）	76-95	78-81	43-81	48-64	80-88
SP （%）	67-86	79-84	88-99	94-98	79.2-85.8

Conclusions

- HbA1c and FPG are both *equally effective as screening tools in early detection of Type 2 diabetes, but neither of the tests is effective in detecting IGT*
- OGTT is therefore still required to diagnose IGT.
- need for the standardization of HbA1c measurements worldwide to allow meaningful comparison of results across laboratories.

Review: glycated haemoglobin A1c and fasting plasma glucose screening tests have similar sensitivities and specificities for early detection of type 2 diabetes

EBM Volume 12 October 2007

Review: glycated haemoglobin A1c and fasting plasma glucose
screening tests have similar sensitivities and specificities
for early detection of type 2 diabetes

Operating characteristics of the HbA1c and FPG tests for early detection of type 2 diabetes*

Diagnostic tests	Number of trials (n)	Cut-point	Sensitivity	Specificity	+LR	-LR
Hb1Ac	1 (866)	≥5.9%	76%	86%	5.4	0.28
	1 (111)		95%	67%	2.9	0.07
	1 (2877)	≥6.1%	76%	79%	3.7	0.29
	1 (111)		81%	84%	5.1	0.23
	1 (505)	≥6.2%	43%	99%	107	0.58
	1 (111)		81%	88%	6.8	0.22
FPG	1 (2877)	≥5.6 mmol/l	88%	79%	4.3	0.15
	1 (505)		80%	86%	5.6	0.24
	1 (111)	≥6.1 mmol/l	48%	98%	24	0.53
	1 (10 447)		64%	94%	10	0.39

Conclusions

- The HBA1c and FPG screening tests have similar sensitivities and specificities for early detection of type 2 diabetes.
- The HbA1c and FPG tests have lower sensitivities for detecting impaired glucose tolerance.

Commentary

- Any single HbA1c cut-point to rule in or rule out diabetes would lead to significant misdiagnosis. Hence, separate HbA1c values may be needed:
  - one that clearly rules out diabetes mellitus and a higher HbA1c value that clearly rules it in.
  - Patients with values between these thresholds would need to proceed to an OGTT.
  - At this time, clinicians should continue to use the current approach of screening high risk patients with an FPG test and recommending an OGTT if the value is >5.6 mmol/l.

高雄榮總藥劑部