

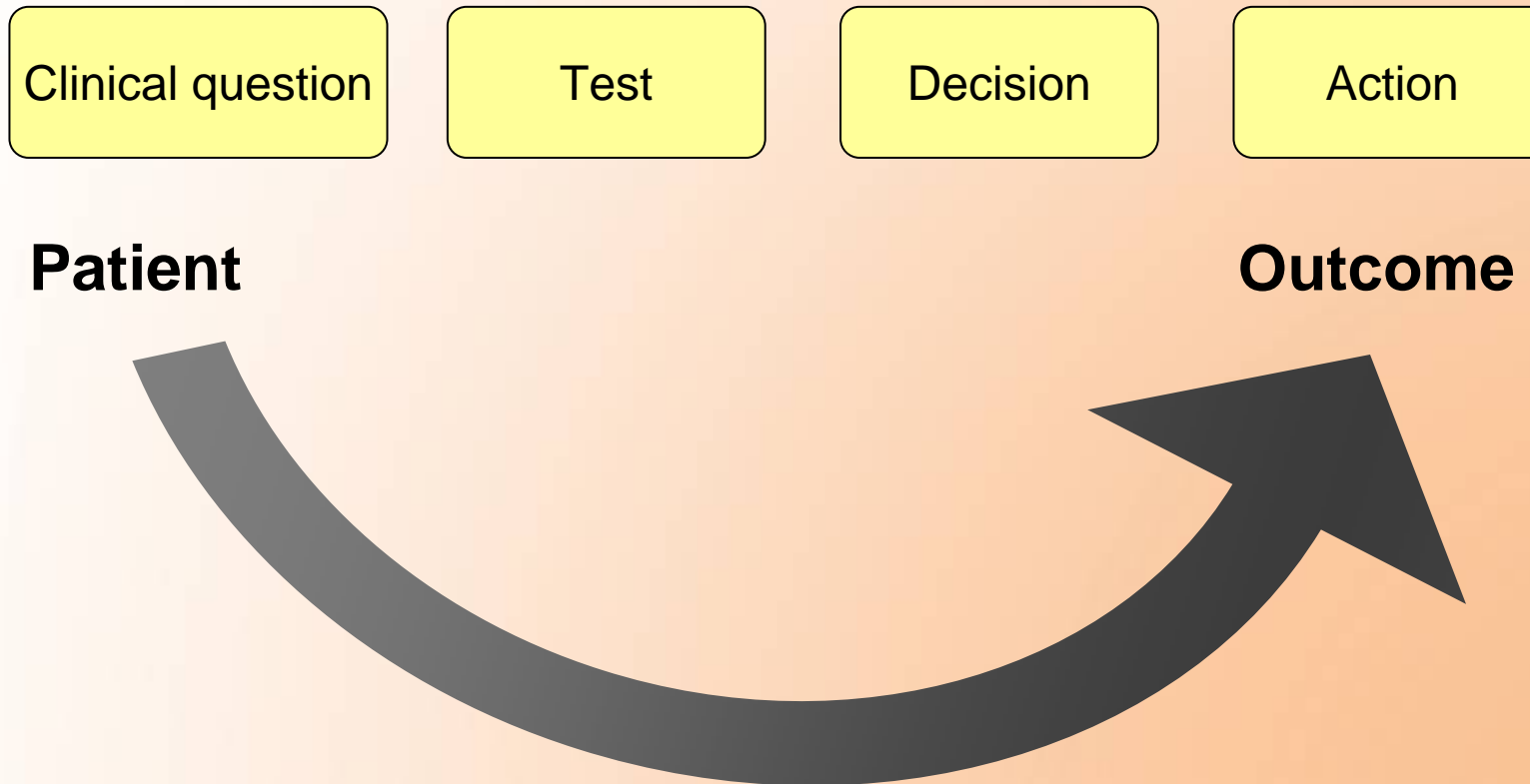


# 實證醫學月會報告

檢驗醫學部 住院醫師  
林宜靜



# The Relationship between The Clinical Question and The Outcome





# 臨床情境 (Clinical Scenario)

- 呂先生，50歲男性，因懷疑自己患有糖尿病而至內科夜間門診求診。
- 他是一位工廠大門保全警衛，每天早上6點上班，傍晚6點下班，生活大致規律。呂先生過去沒有任何重大內科疾病，也非常自豪自己除了在診所看過兩次感冒外，從來沒使用過健保卡。
- 呂先生的雙親很早就過世，是否患有糖尿病、高血壓等疾病則不得而知。呂先生唯一的一位哥哥則在一年前被診斷出患有糖尿病，目前有規律追蹤治療。
- 最近，呂先生自覺身體容易疲勞，精神不好。但體重沒有明顯的變化，也沒有多喝、多渴及食量改變的情形。在偶然與哥哥聊天時，聽到自己家人患有糖尿病，心中大為震驚。因此趁下班時間到內科夜間門診就診。



# 臨床情境 (Clinical Scenario)

- 門診醫師在問診後建議呂先生接受空腹血糖檢驗，但呂先生表示有困難。因為工作的關係，他必須很早就吃飯以維持體力。而要請假也有困難，因人力的關係，要安排不容易。呂先生說他的哥哥每三個月都會檢驗一種名叫醣化血色素的檢查來看看糖尿病的情形，而且醫師說不用空腹就可以檢查。呂先生希望可以當下做一下這個名叫醣化血色素的檢查來看看自己是否有糖尿病。

# Patient's Concerns (words to the doctor)

1. 我家人患有糖尿病，我想知道我有沒有糖尿病？
2. 我最近比較容易累，但沒有典型的三多症狀。
3. 因為工作的關係，我不能找另外的時間空腹做檢查。
4. 糖化血色素的檢查好像可以知道糖尿病的情形，而且別的醫師說不用空腹就可以檢查。
5. 我可不可以做這個糖化血色素的檢查來看看自己是否有糖尿病？



# What We Ask for Our Patient and Ourselves

Our questions	In respond to patient's concerns
What is diabetes mellitus?	1
Is the man in the "high-risk" groups of diabetes mellitus?	1
How to make a diagnosis of diabetes mellitus?	2,4,5
What test is standard and most common used to detect diabetes mellitus?	5
If the test is not available, is there any other alternative test we can choice, such like HbA1c?	3,4,5



# Clinical Question

- Can HbA1c be used as an alternative test to make a diagnosis of diabetes mellitus?

# EBM的五大步驟 (5A)

- **Asking**
  - 將病人的問題寫成PICO
- **Acquire**
  - 找資料來回答問題
- **Appraisal**
  - 嚴格評讀文獻
- **Apply**
  - 是否可應用到病人身上
- **Audit**
  - 自我評估



# EBM的五大步驟 (5A)

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# PICO

<b>P</b> Patient/Problem	A 50 year-old man with family history of diabetes mellitus. No any symptom was complained except easy fatigue.
<b>I</b> Intervention	Hb A1c
<b>C</b> comparison	Fasting plasma glucose
<b>O</b> Outcome	Diagnostic power for diabetes mellitus



# EBM的五大步驟 (5A)

- Asking
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# Searching Strategy 1 : Finding out The Correct Keywords

Keywords from questions



Use MeSH to help identify terms

The screenshot shows the MeSH (Medical Subject Headings) search interface. The search term 'gastric ulcer' is entered in the search box. The results page displays a list of suggestions: Gastric ulcer, Gastric ulcers, Ulcer, gastric, Ulcers, gastric, Peptic ulcer, Peptic ulcers, Gastric cancer, Carotid ulcer, Gastric acid, Varicose ulcer, and More... The first result is 'Stomach Ulcer', which is highlighted. The description for 'Stomach Ulcer' is: 'Ulceration of the GASTRIC MUCOSA due to contact with GASTRIC JUICE. It is often associated with HELICOBACTER PYLORI infection or consumption of nonsteroidal anti-inflammatory drugs (NSAIDS).'



The correct keyword for search



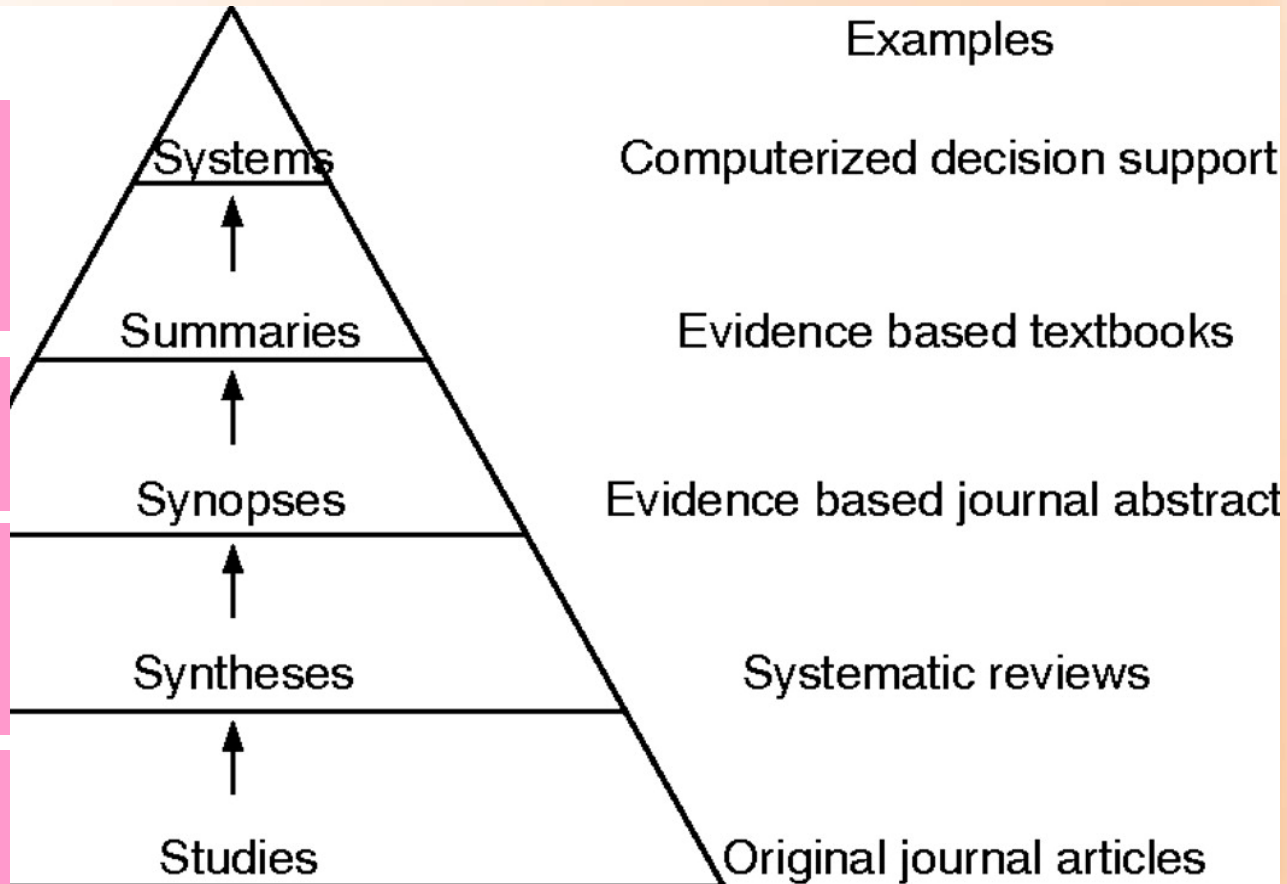
# Search Strategy 2 : "The 5S" Levels

The "5S" levels of organisation of evidence from healthcare research

Brian Haynes, R Evid Based Med 2006;11:162-164



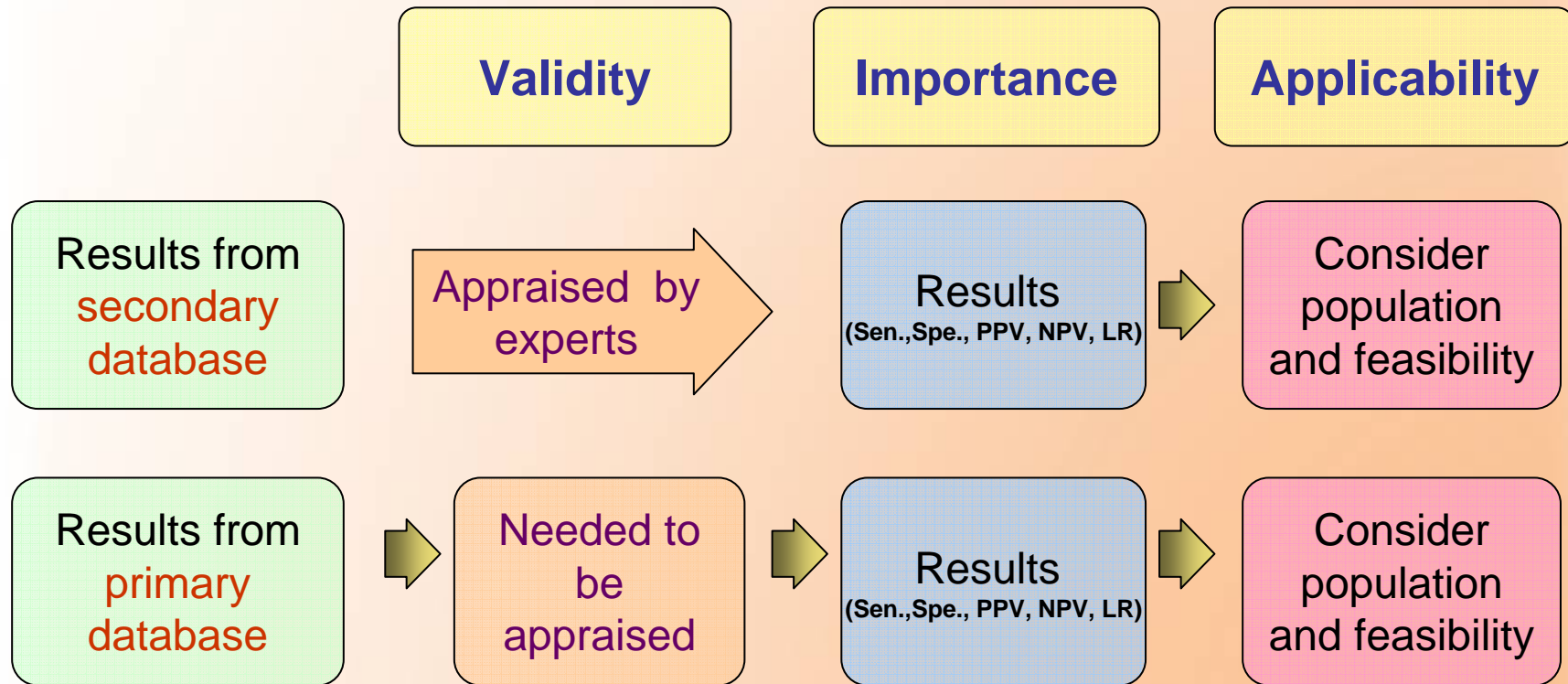
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  - TRIP
  - Google



Jeanne Yiching Lin

# Search Strategy 3 : Trust Something You Can Trust

According to “Sharon E. Straus et al, Evidence-based medicine: how to practice and teach EBM, Elsevier, 2005: 33-7. “





# PubMed MeSH Definition

- **HbA1c (Hemoglobin A, Glycosylated):**
  - Minor hemoglobin components of human erythrocytes designated A1a, A1b, and A1c.
  - Hemoglobin A1c is most important since its sugar moiety is glucose covalently bound to the terminal amino acid of the beta chain.
  - Since normal glycohemoglobin concentrations exclude marked blood glucose fluctuations over the preceding three to four weeks, the concentration of glycosylated hemoglobin A is a more reliable index of the blood sugar average over a long period of time.





# Search for Answers





# Results from Searching: Summaries

Database	UpToDate
Title of article	<b>Diagnosis of diabetes mellitus</b>
Content	<ol style="list-style-type: none"><li>1. The term diabetes mellitus describes several diseases of <u>abnormal carbohydrate metabolism that are characterized by hyperglycemia.</u></li><li>2. It is associated with a relative or absolute impairment in insulin secretion, along with varying degrees of peripheral resistance to the action of insulin.</li><li>3. The diagnosis is based on one of three abnormalities: <u>fasting plasma glucose (FPG), random elevated glucose with symptoms, or abnormal oral glucose tolerance test (OGTT).</u></li></ol>



## Results from Searching: Summaries

### Criteria for the diagnosis of diabetes mellitus

1. Symptoms of diabetes and a casual plasma glucose 200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

or

2. FPG 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 hours.

or

3. 2-h plasma glucose 200mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. Third measure (OGTT) is not recommended for routine clinical use.

FPG: Fasting plasma glucose; OGTT: Oral glucose tolerance test

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American Diabetes Association (ADA; 1997)

Results from Searching: Summaries

Database	UpToDate
Title of article	<b>Diagnosis of diabetes mellitus</b>
Content	<p><b>HEMOGLOBIN A1C (A1C) —</b></p> <ol style="list-style-type: none"> <li>In the 1999 to 2004 National Health and Nutrition Examination Survey (NHANES) population, an A1C of 5.8 percent had the highest sensitivity (86 percent) and specificity (92 percent) for diagnosing diabetes (fasting plasma glucose &gt;126 mg/dl [7 mmol/L])<sup>*</sup>.</li> <li>A1C and FPG were found to be similarly effective in diagnosing diabetes<sup>**</sup>.</li> <li>Using an A1C cut-off point of &gt;6.1 percent to diagnose diabetes, sensitivity ranged from 78 to 81 percent and specificity 79 to 84 percent.</li> </ol>

A systematic review

<sup>\*</sup>Buell, C, Kermah, D, Davidson, MB. Utility of A1C for diabetes screening in the 1999-2004 NHANES population. *Diabetes Care* 2007;30:233.

<sup>\*\*</sup>Bennett, CM, Guo, M, Dharmage, SC. HbA(1c) as a screening tool for detection of Type 2 diabetes: a systematic review. *Diabet Med* 2007;24:333.



## Results from Searching: Summaries

Database	UpToDate
Title of article	<b>Diagnosis of diabetes mellitus</b>
Content	<p>4. The practical advantages of using A1C over FPG or OGTT include ability to collect a sample regardless of prandial status and to provide a two to three month average blood glucose concentration, which is a better predictor than fasting glucose of micro and macrovascular complications.</p> <p>5. However, A1C is a more expensive test and may be <u>influenced by the presence of renal failure and hemoglobinopathies</u>, depending on the method used. Thus, A1C measurements are <u>not currently recommended to diagnose diabetes</u>.</p>



# The Reference in



DIABETICMedicine

DOI: 10.1111/j.1464-5491.2007.02106.x

## HbA<sub>1c</sub> as a screening tool for detection of Type 2 diabetes: a systematic review

C. M. Bennett, M. Guo and S. C. Dharmage

Department of Public Health, School of Population Health, The University of Melbourne, Australia

Accepted 20 September 2006

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**Conclusions** HbA<sub>1c</sub> and FPG are equally effective screening tools for the detection of Type 2 diabetes. The HbA<sub>1c</sub> cut-off point of  $> 6.1\%$  was the recommended optimum cut-off point for HbA<sub>1c</sub> in most reviewed studies; however, there is an argument for population-specific cut-off points as optimum cut-offs vary by ethnic group, age, gender and population prevalence of diabetes. Previous studies have demonstrated that HbA<sub>1c</sub> has less intra-individual variation and better predicts both micro- and macrovascular complications. Although the current cost of HbA<sub>1c</sub> is higher than FPG, the additional benefits in predicting costly preventable clinical complications may make this a cost-effective choice.

Diabet. Med. 24, 333–343 (2007)

# Evidence-based Medicine Levels of Evidence

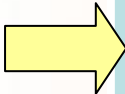
## Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)

Level	Diagnosis
1a	SR (with homogeneity*) of Level 1 diagnostic studies; CDR <sup>†</sup> with 1b studies from different clinical centres
1b	Validating** cohort study with good <sup>†††</sup> reference standards; or CDR <sup>†</sup> tested within one clinical centre
1c	Absolute SpPins and SnNouts <sup>††</sup>
2a	SR (with homogeneity*) of Level >2 diagnostic studies
2b	Exploratory** cohort study with good <sup>†††</sup> reference standards; CDR <sup>†</sup> after derivation, or validated only on split-sample\$\$\$ or databases
2c	
3a	SR (with homogeneity*) of 3b and better studies
3b	Non-consecutive study; or without consistently applied reference standards
4	Case-control study, poor or non-independent reference standard
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

CDR: Clinical Decision Rule; An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.



# Grades of Recommendation

 <b>A</b>	consistent level 1 studies
<b>B</b>	consistent level 2 or 3 studies <b>or</b> extrapolations from level 1 studies
<b>C</b>	level 4 studies <b>or</b> extrapolations from level 2 or 3 studies
<b>D</b>	level 5 evidence <b>or</b> troublingly inconsistent or inconclusive studies of any level



# Results from Searching: Synopses



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3. 1996 - Meta-analysis: Glycosylated hemoglobin levels are useful for diagnosing diabetes

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<input type="checkbox"/> <b>Hormonal versus non-hormonal contraceptives in women with diabetes mellitus type 1 and 2</b> J Visser, M Snel, HAAM Van Vliet Year: 2005 <a href="#">Record</a> <a href="#">Review</a>	
<input type="checkbox"/> <b>Alpha-glucosidase inhibitors for type 2 diabetes mellitus</b> FA Van de Laar, PLBJ Lucassen, RP Akkermans, EH Van de Lisdonk, GEHM Rutten, C Van Weel Year: 2005 <a href="#">Record</a> <a href="#">Review</a>	
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[Validation of the German Diabetes Risk Score with metabolic risk factors for type 2 diabetes]  
Dtsch Med Wochenschr. 2008 Apr;133(17):878-83. German.  
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Combined use of fasting plasma glucose and glycated hemoglobin A1c in a stepwise fashion to detect undiagnosed diabetes mellitus.



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**Comment in:**  
[Evid Based Med.](#) 2007 Oct;12(5):152.

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Department of Public Health, School of Population Health, The University of Melbourne, Australia. c.bennett@unimelb.edu.au

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**Methods** Systematic review of primary cross-sectional studies of the accuracy of HbA<sub>1c</sub> for the detection of Type 2 diabetes using the oral glucose tolerance test as the reference standard and fasting plasma glucose as a comparison.

**Results** Nine studies met the inclusion criteria. At certain cut-off points, HbA<sub>1c</sub> has slightly lower sensitivity than fasting plasma glucose (FPG) in detecting diabetes, but slightly higher specificity. For HbA<sub>1c</sub> at a Diabetes Control and Complications Trial and UK Prospective Diabetes Study comparable cut-off point of  $\geq 6.1\%$ , the sensitivity ranged from 78 to 81% and specificity 79 to 84%. For FPG at a cut-off point of  $\geq 6.1$  mmol/l, the sensitivity ranged from 48 to 64% and specificity from 94 to 98%. Both HbA<sub>1c</sub> and FPG have low sensitivity for the detection of impaired glucose tolerance (around 50%).

**Conclusions** HbA<sub>1c</sub> and FPG are equally effective screening tools for the detection of Type 2 diabetes. The HbA<sub>1c</sub> cut-off point of  $> 6.1\%$  was the recommended optimum cut-off point for HbA<sub>1c</sub> in most reviewed studies; however, there is an argument for population-specific cut-off points as optimum cut-offs vary by ethnic group, age, gender and population prevalence of diabetes. Previous studies have demonstrated that HbA<sub>1c</sub> has less intra-individual variation and better predicts both micro- and macrovascular complications. Although the current cost of HbA<sub>1c</sub> is higher than FPG, the additional benefits in predicting costly preventable clinical complications may make this a cost-effective choice.

Diabet. Med. 24, 333–343 (2007)



EBM journal也對這篇paper做了 appraisal




# Review: glycated haemoglobin A<sub>1c</sub> and fasting plasma glucose screening tests have similar sensitivities and specificities for early detection of type 2 diabetes


Bennett CM, Guo M, Dharmage SC. HbA<sub>1c</sub> as a screening tool for detection of type 2 diabetes: a systematic review. *Diabet Med* 2007;24:333-43.


Clinical impact ratings GP/FP/Primary care ★★★★★☆ IM/Ambulatory care ★★★★★☆ Endocrine ★★★★★☆

Q How do the glycated haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) and fasting plasma glucose (FPG) tests compare as screening tools for early detection of type 2 diabetes?

### METHODS

 **Data sources:** Medline, EMBASE/Excerpta Medica (1994 to September 2004), and bibliographies of relevant articles.

 **Study selection and assessment:** English language cross-sectional studies that compared the HbA<sub>1c</sub> test with the FPG test as screening tools for detecting type 2 diabetes, reported sensitivities and specificities using the 75 g oral glucose tolerance test (OGTT) as the reference standard, and reported HbA<sub>1c</sub> test results in a format compatible with that of the Diabetes Control and Complications Trial. 9 studies (n = 19 500, 13-92 y) published in 1998-2004 met the selection criteria; 4 studies were community-based, and 5 were hospital-based. Quality assessment of individual studies was based on the sampling frame and size, measurements of HbA<sub>1c</sub> and FPG, adequacy of test descriptions, and 80% verification with OGTT.

 **Outcomes:** sensitivity, specificity, and likelihood ratios (LRs).

### Commentary

The systematic review by Bennett *et al* compared HbA<sub>1c</sub>, a measure commonly used to assess diabetes control, with FPG, using OGTT as the gold standard in screening for type 2 diabetes. Currently, the American Diabetes Association (ADA) recommends 2 tests to screen for diabetes among asymptomatic individuals: plasma glucose obtained after 8 hours of fasting or an OGTT given according to the World Health Organization protocol.<sup>1</sup> Both screening tests require patient preparation, which may promote missed opportunities for screening, and because of burden, OGTT is not usually done except in pregnant women. A third test, random plasma glucose, is recommended for diagnostic testing in symptomatic patients. Unless there is clear evidence of hyperglycaemia, it is recommended that each of these tests be repeated.

HbA<sub>1c</sub> testing is an attractive alternative as it reflects average plasma glucose concentrations over 60-90 days and does not require additional burden from patients other than phlebotomy. However, although the



# EBM的五大步驟 (5A)

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# Critical Appraisal

**Valid:** systematic review worksheet

**Importance:** test characteristics

**Applicability:** population and feasibility



## What question did the systematic review addressed (PICO) 想要回答什麼問題？

是

否

不清楚

評論：

● How do the glycated haemoglobin A1c (HbA1c) [I] and fasting plasma glucose (FPG) tests [C] compare as screening tools [P] for early detection of type 2 diabetes [O]?

● To assess the validity of HbA1c as a screening tool and determine the most appropriate cut-off point for the diagnosis of diabetes.

Is it unlikely that important, relevant studies were missed 沒有遺漏重要的文獻？

是

否

不清楚

評論：

**Search Strategy:**

●MEDLINE, PUBMED and EMBASE electron databases (1994–September 2004) were searched.

●Keywords: ‘*diabetes mellitus*’, ‘*screening*’, ‘*diagnosis*’, ‘*HbA1c*’, ‘*fasting plasma glucose test*’ and ‘*OGTT*’.

-- Search engines, such as ‘Google’ and ‘Medscape’, were also used to search for related articles.

-- Reference lists of all publications including original studies, letters, commentaries, guidelines, and reviews were manually checked to identify studies not found through electronic searching.

## Were the criteria used to select articles for inclusion appropriate 選擇文獻的準則適當?

是

否

不清楚

評論：

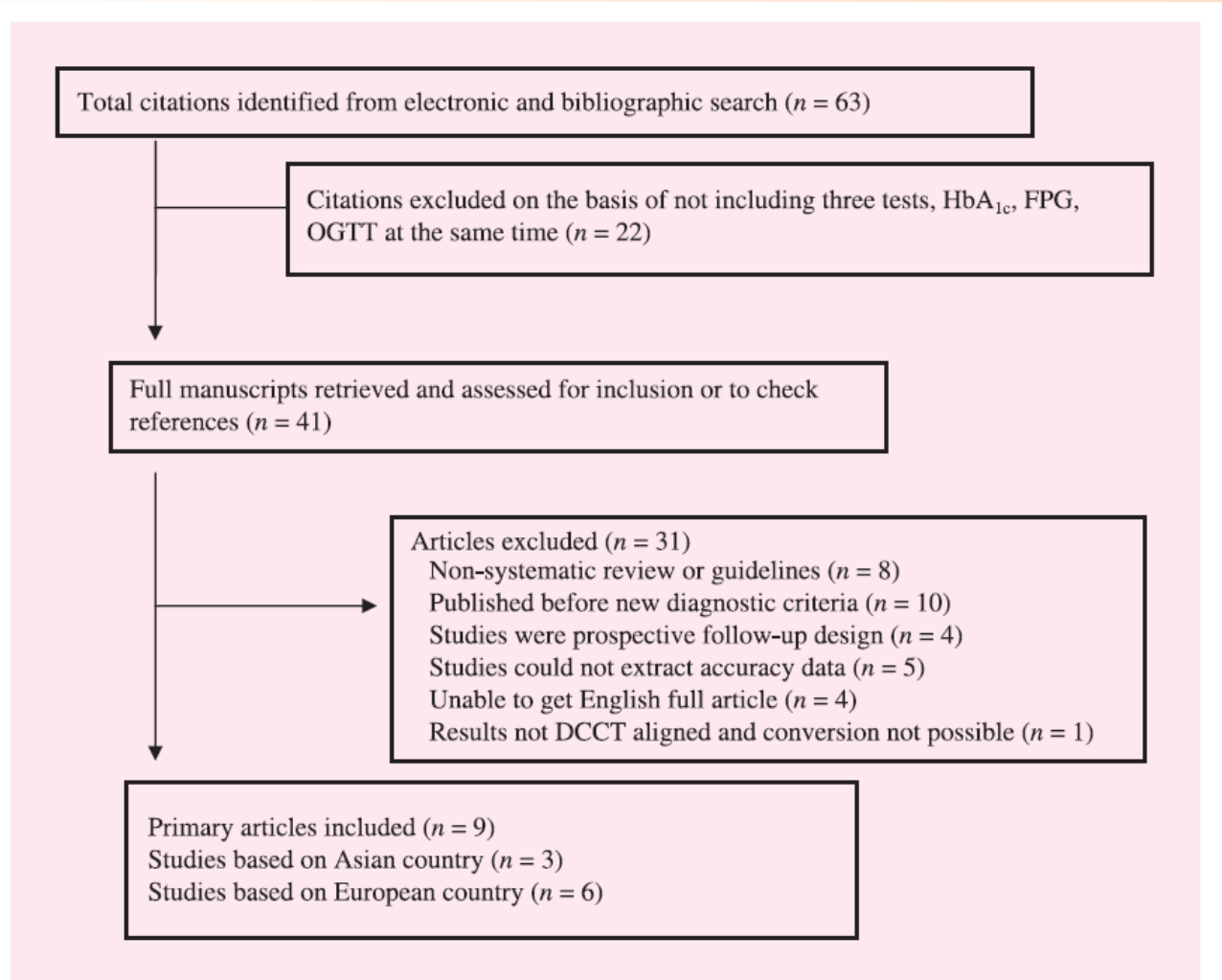
● English language cross sectional studies that **compared the HbA1C test with the FPG test as screening tools for detecting type 2 diabetes, reported sensitivities and specificities** using the 75 g oral glucose tolerance test (OGTT) as the reference standard, and reported HbA1c test results in a format compatible with that of the Diabetes Control and Complications Trial.

● **9 studies (n = 19,500, 13–92 y) published in 1998–2004** met the selection criteria; 4 studies were community-based, and 5 were hospital-based. **3 studies on Asian country**, and 6 studies on European country.

-- The diagnosis of diabetes must have been based on the diagnostic criteria according to American Diabetes Association (ADA; 1997) or World Health Organization (WHO; 1999) guidelines. .



# Were the criteria used to select articles for inclusion appropriate 選擇文獻的準則適當?





Were the included studies sufficiently valid for the type of question asked

選擇的文獻有效回答所問的問題?

是

否

不清楚

評論：

**Conclusions:**

● The sensitivities, specificities, and LRs for the HbA1c and FPG tests were similar for detecting diabetes.

● At equivalent cut-points, both the HbA1c and FGP tests had generally lower sensitivities (about 50%) for detecting impaired glucose tolerance.

● The cut-off for HbA1c is recommended as either  $\geq 6.1\%$  ( $\geq 2$  SD above the normal mean) or  $\geq 6.2\%$ , as found to be the optimum cut-off point in most studies. (The current advisable method is ion-exchange HPLC or immunological assay based on the DCCT/UKPDS where the normal range is approximately 4.0–6.1%.)



## Were the results similar from study to study 各研究的結果相似?

是

否

不清楚

評論：

- This systematic review did not find clear evidence to suggest that one test, HbA1c or FPG, was superior to the other in screening for diabetes or IGT.
- On the whole, HbA1c had slightly lower sensitivity but higher specificity than the FPG in detection of diabetes, but neither was effective in detecting IGT. This is not surprising as neither FPG or HbA1c involve a glucose challenge.



# Are test characteristics presented 呈現指標診斷工具的特性？

- Sensitivity:
  - 有病者檢驗呈陽性的機率
- Specificity:
  - 無病者檢驗呈陰性的機率
- Likelihood ratio (positive likelihood ratio):
  - 有病者/無病者 檢驗呈陽性的比率  $LR+ = \text{sens}/(1-\text{spec})$
- Likelihood ratio (negative likelihood ratio):
  - 有病者/無病者 檢驗呈陰性的比率  $LR- = (1-\text{sens})/\text{spec}$
- Positive predictive value (PPV):
  - 測驗陽性者有病的機率  $PPV. = P * \text{Sen.} / \{P * \text{Sen.} + (1 - p)(1 - \text{Spe.})\}$
- Negative predictive value (NPV):
  - 測驗陰性者無病的機率  $NPV. = (1 - P)\text{Spe.} / \{P(1-\text{Sen.}) + (1 - P)\text{Spe.}\}$

Importance: test characteristics



# Are test characteristics presented 呈現指標診斷工具的特性？

Operating characteristics of the HbA<sub>1c</sub> 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%	78%	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

110 mg/dl

\*HbA<sub>1c</sub> = glycated haemoglobin A<sub>1c</sub>; FPG = fasting plasma glucose; LR = likelihood ratio. Diagnostic terms defined in glossary.

**Hb1Ac** Positive predictive value : 13.4-17.4 %  
Negative predictive value : 98.8-99.0 %

Importance: test characteristics



## Are test characteristics presented 呈現指標診斷工具的特性？

- 以  $\text{HbA1c} \geq 6.1\%$  做為 cut-off point:
  - Sensitivity: 78-81%
  - Specificity: 79-84%
  - Positive likelihood ratio: 3.7-5.1 ( $\geq 4$  is valuable)
  - Negative likelihood ratio: 0.23-0.29 ( $\leq 0.6$  is useful)
  - Positive predictive value: 13.4-17.4%
  - Negative predictive value: 98.8-99% (是很好的 screening tool)

Importance: test characteristics



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# Apply The Result to Our Patient

<b>P</b> Patient/Problem	A 50 year-old man with family history of diabetes mellitus. No any symptom was complained. It is inconvenient for obtaining timed (fasting) blood samples.
<b>I</b> Intervention	HbA1C
<b>C</b> comparison	Fasting plasma glucose
<b>O</b> Outcome	The sensitivities, specificities, and LRs for the HbA1c and FPG tests were similar for detecting diabetes.

如果真的無法空腹，可以先做醣化血色素檢查。



# EBM的五大步驟 (5A)

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## 在「提出臨床問題」方面的自我評估

- 我提出的問題是否具有臨床重要性？
  - 有，因為可決定在非空腹情形下是否可用HbA1c代替fasting plasma glucose檢驗
- 我是否明確的陳述了我的問題？
  - 我的foreground question 是否可以清楚的寫成PICO？可以
  - 我的background question是否包括what, when, how, who等字根？有，但未全能概括
- 我是否清楚的知道自己問題的定位？（亦即可以定位自己的問題是屬於診斷上的、治療上的、預後上的或流行病學上的），並據以提出問題？
  - 知道，屬於診斷範疇
- 對於無法立刻回答的問題，我是否有任何方式將問題紀錄起來以備將來有空時再找答案？
  - 有



# Thank You for Your Attention