

實證醫學概論

光田綜合醫院 家醫科

健康檢查中心

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學習目標

- 瞭解實證醫學的意義與臨床應用
- 知道如何使用資料庫快速而準確的搜尋出有價值的文獻
- 可以評讀不同類型的研究文獻，並能了解統計學上的意義

診治病人的依據：過去vs.現在

- 演繹推理法(過去的舊思維)
 - 了解疾病的病理生理學並且有治療方法，便認為治療方法可以改善疾病
- 實證推理法
 - 如果有一群優勢的資料被合在一起檢視，支持疾病的某種治療方法，那麼這種治療將可以被安全有效的使用

什麼是實證醫學？

- 實證醫學(evidence-base medicine, EBM)是從龐大醫學資料庫中，篩選出值得信賴的資料，進行嚴格的評析，獲得最佳文獻和證據，並與醫護人員的專業、病人的價值和偏好以及病人的個別情況相結合，應用於臨床工作中，做出最適當的醫療決策

實證醫學的歷史發展

- 1972:英國臨床流行病學者Archie Cochrane出版 *Effectiveness and Efficiency-- “that health services should be evaluated on the basis of scientific evidence rather than on clinical impression, anecdotal experience, ‘expert’ opinion or tradition”*，並強調randomized controlled trials的重要性
- 1980's:美國腎臟科醫師David L. Sackett在加拿大McMaster大學成立臨床流行病學與統計學碩士學門，推行實證醫療(Evidence-based clinical practice)

實證醫學的歷史發展

- 1992: Evidence-based Medicine 一詞由加拿大 McMaster 大學 Gordon Guyatt 所領導的學術組織正式命名，英國國家衛生部成立實證醫學中心，以 Archie Cochrane 之名命名，並由 David L. Sackett 擔任實證醫學中心主任
- 1993: Cochrane Collaboration 設立，英國的 National Health Service Research and Development Program 組織設置研究發展部，並在牛津大學設立研究中心，開始與全世界專家對各醫學領域的隨機對照研究進行系統性文獻回顧評論，目前世界各地有 13 個國家、15 個實證醫學中心 (Cochrane Center) 在積極推動這個工作

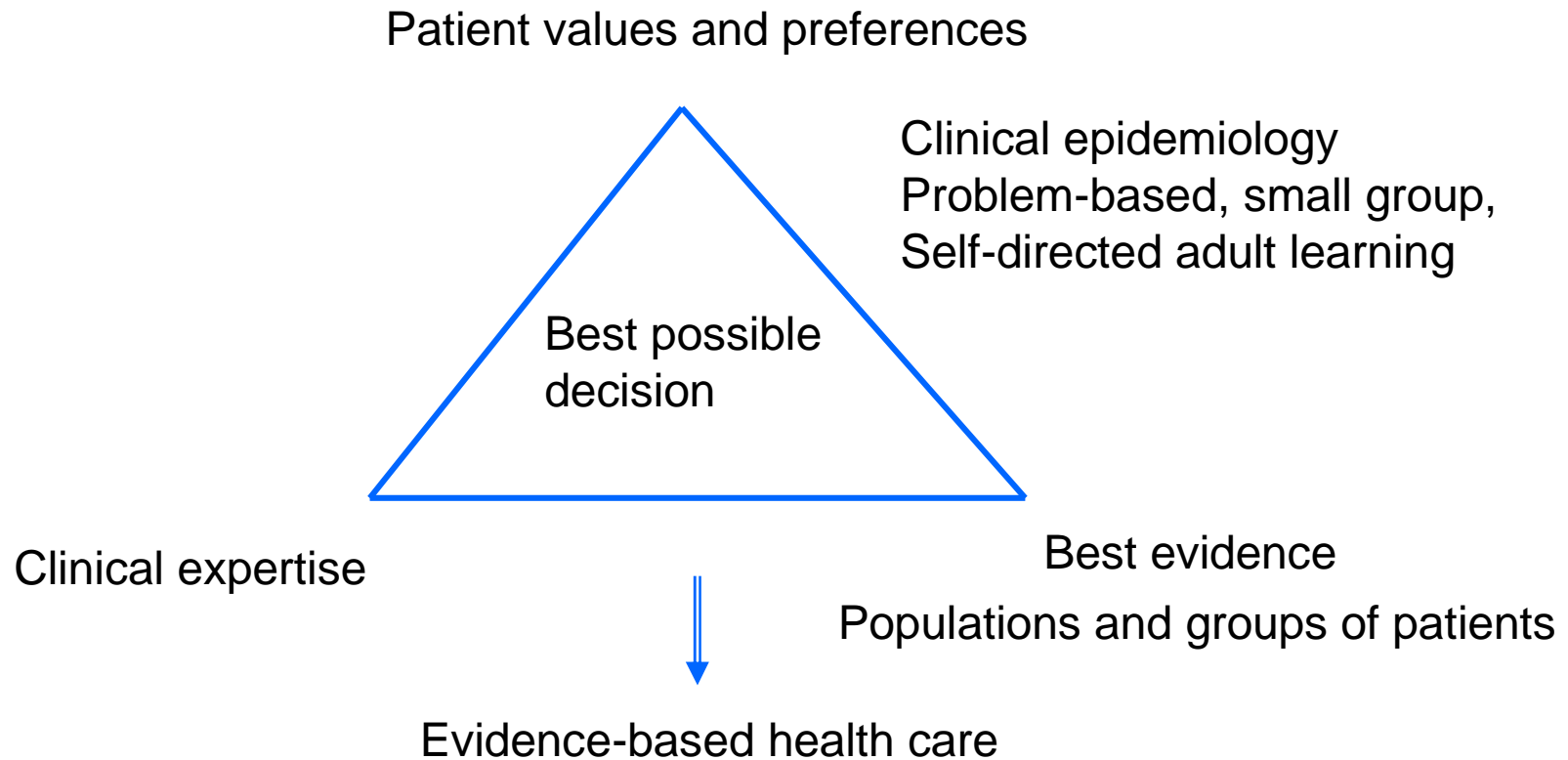
實證醫學的歷史發展

Cochrane Collaboration Logo
(meta-analysis of seven trials)



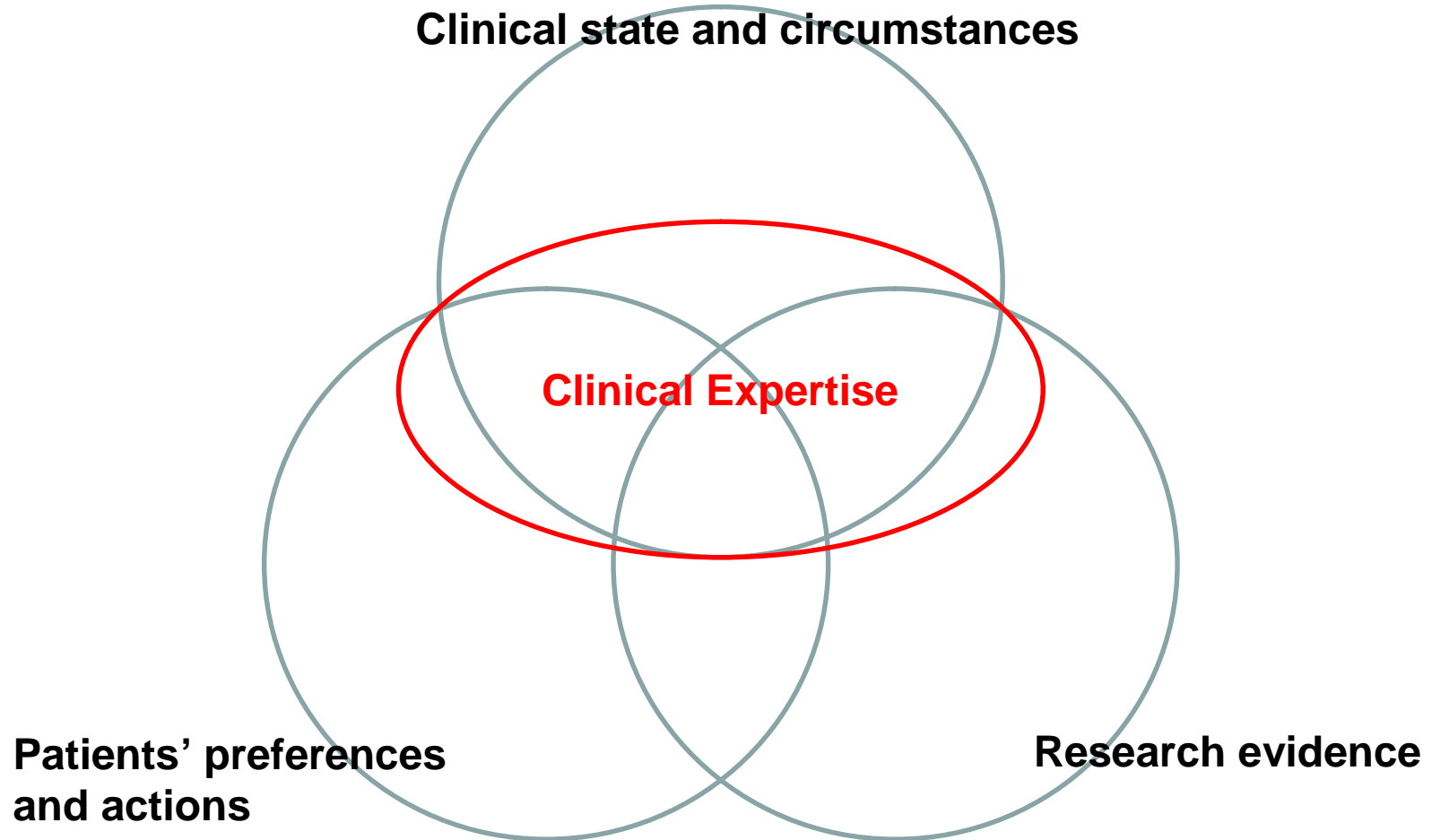
實證醫學的涵義

David L. Sackett, Oxford University



An Updated Model of EBM

Haynes RB, McMaster University



The reason of interest: 4 realizations

- Daily need for valid clinical information
- Inadequacy of traditional sources of information
- Disparity between experience and up-to-date knowledge & performance
- Inability to afford time for finding and assimilating the evidence

The reason of interest: 5 developments

- Strategies for tracking down and appraising evidence
- Systematic review (Cochrane Collaboration)
- Secondary journals
- Information technology eg. internet
- Strategies for lifelong learning and improving clinical performance

EBM的五個步驟(5 steps)

- Step 1: Ask an answerable question
- Step 2: Search the best evidence
- Step 3: Critical appraisal
- Step 4: Apply to our patients(extrapolation)
- Step 5: Self evaluation(audit)

步驟一：形成一個可以回答的問題

- 不包含「無法回答」或「已經有答案」的問題
- 要想：怎樣才算是對病人有幫助的問題？
問題的重點為何？
- 從臨床情境(clinical scenario)到background vs. foreground questions

Background Questions

- Ask for general knowledge about a disorder
- Two components
 - A question root (who, what, where, when, how, why)
 - A disorder, or an aspect of a disorder
- Ex: What causes babesiosis? When do complications of acute pancreatitis usually occur?
- Background resources: textbooks, narrative reviews in journals (Online Harrison, UpToDate)
 - Answering only background questions is insufficient to help getting the best available care to our patients

Foreground questions

- Ask for specific knowledge about managing patients with a disorder
- 4 components(PICO)
 - **P**atient and/or problem
 - **I**ntervention (or exposure, test)
 - **C**omparison
 - **O**utcomes
- Ex: In older patients with isolated diastolic dysfunction, does adding digoxin to standard diuretic and ACEI treatment yield enough reduction in morbidity and/or mortality to be worth its adverse effects?

Determining question type

- Therapy
 - Determining the effect of different treatments on improving patient function or avoiding adverse events
- Harm
 - Ascertaining the effects of potentially harmful agents (including the vary therapies we would be interested) on patient function, morbidity, and mortality
- Diagnosis
 - Establishing the power of an intervention to differentiate between those with and without a target condition of disease
- Prognosis
 - Estimating the future course of a patient's disease

步驟二：搜尋最佳證據

- 利用**PICO**結構式問題，設定搜尋策略
- 找出關鍵字，可用**MeSH**詞彙搜尋效率更高
- 一次單就一個**PICO**元素如**Intervention**開始
- 需聯集(**OR**)所有同義詞
- 可使用截斷字(**truncation**)並加上*，如**child***取代**children**來搜尋

從PICO問題找尋關鍵字

- Scenario: you are interested in whether statin is effective in reducing CV risk and mortality rate in DM patients
- Question
 - Population: In DM patients does
 - Intervention: statin therapy
 - Comparison: placebo
 - Outcome: reduce CV event risk and mortality rate?

搜尋策略設計表

原始關鍵字	同義字1	同義字2
P(Diabetes mellitus	OR	OR)AND
I (HMG-CoA Reductase Inhibitors	OR statin	OR)AND
C(OR	OR)AND
O(Cardiovascular disease	OR mortality	OR)

資料庫的選擇

- 可從次級資料庫如Cochrane Library開始
- 建議利用PubMed的Clinical Queries→選擇在某種question type的文獻下搜尋



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As a policy maker or healthcare manager you are a generalist in search of high-quality information across a broad range of issues. [More](#)

What's New in Issue 4, 2008?

[Highlights of new and updated Reviews \(PDF\)](#)
[What's New in Issue 4 - Important Changes to The Cochrane Library \(PDF\)](#)

Cochrane Reviews of Diagnostic Test Accuracy

- [LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women](#)
- [St John's wort for major depression](#)
- [Nebulized hypertonic saline solution for acute bronchiolitis in infants](#)
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Release Notes

8 October: Changes with Issue 4, 2008... [More](#)

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步驟三：

嚴格評讀證據的效度與重要性

- 效度(Validity)：各種形式的問題都包含以下三個共同項目(RAM-bo)
 - 研究族群是否具有代表性(Representative)？隨機選擇(random selection)/隨機分派(random allocation)
 - 是否有足夠的確認與追蹤(Ascertainment)？反應率/追蹤/確認>80%
 - 結果的估計值(Measurement)是否公正？盲法(blinded)或客觀的(objective)估計

步驟三：

嚴格評讀證據的效度與重要性

- 效度(Validity)
 - 通常在文章中的方法學(method)部分和結果(result)的第一、二段中找到

步驟三：

嚴格評讀證據的效度與重要性

- 重要性—效益大小(Impact size)
 - 效果的相對估計值：相對危險(relative risk)、相對危險性降低度(relative risk reduction)、勝算比(odds ratio)，代表生物學上的影響
 - 效果的絕對估計值：絕對危險性降低度(absolute risk reduction)、益一需治數(number needed to treat, NNT)，代表臨床上對病人的影響(會隨population不同而改變)

步驟三：

嚴格評讀證據的效度與重要性

- 重要性—效益大小(**Impact size**)
 - 請看結果段(**result section**)中所描述的主要結果：效果有多大？多重要？統計意義要看信賴區間(**confidence interval**)和p值，臨床意義要看效果的估計值

Treatment Study

Occurrence of diabetic neuropathy at 5 years among insulin-dependent diabetics in the DCCT trial		Relative risk reduction (RRR)	Absolute risk reduction (ARR)	Number needed to treat (NNT)
Usual insulin regimen control event rate (CER)	Intensive insulin regimen experimental event rate (EER)	$\frac{\text{CER} - \text{EER}}{\text{CER}}$	CER-EER	$\frac{1}{(\text{RRR} \times \text{CER})} = \frac{1}{\text{ARR}}$
9.6%	2.8%	$\frac{9.6\% - 2.8\%}{9.6\%} = 71\%$	9.6% - 2.8% = 6.8%	$\frac{1}{6.8\%} = 15$ patients
		95% CI *\Rightarrow	4.4% to 9.2%	11 to 23

Confidence Interval(CI)

- 95% CI on an NNT = 1/(limits on the CI of its ARR)
- Limits on the CI of ARR

$$= ARR \pm 1.96 \sqrt{\left(\frac{CER \times (1 - CER)}{\#ofControlPts} \right) + \left(\frac{EER \times (1 - EER)}{\#ofExperPts} \right)}$$
$$= 6.8\% \pm 1.96 \sqrt{\left(\frac{0.96 \times 0.904}{730} \right) + \left(\frac{0.028 \times 0.972}{711} \right)} = 6.8\% \pm 2.4\%$$

Diagnosis Study

		Target disorder (iron deficiency anemia)		
		Present	Absent	Totals
Diagnostic test result (serum ferritin)	Positive (< 65 mmol/L)	731 a	270 b	1001 a+b
	Negative (≥ 65 mmol/L)	78 c	1500 d	1578 c+d
Totals		809 a+c	1770 b+d	2579 a+b+c+d

“Constant” Parameters of A Diagnostic Test

- **Sensitivity, $S_n = a/(a+c) = 731/809 = 90\%$**
- **Specificity, $S_p = d/(b+d) = 1500/1770 = 85\%$**
- **Likelihood ratio for a positive test result, $LR+ = S_n/(1-S_p) = 90\%/15\% = 6$**
- **Likelihood ratio for a negative test result, $LR- = (1-S_n)/S_p = 10\%/85\% = 0.12$**

Independent Variables

- **Pre-test probability (prevalence, p) = $(a'+c')/(a'+b'+c'+d')$**
 - $p = (a+c)/(a+b+c+d) = 809/2579 = 31\%$
- **Pre-test odds = $p/(1-p) = 31\%/69\% = 0.45$**
 - **Pre-test odds = $(a+c)/(b+d) = 809/1770 = 0.45$**

Predictive Values

- **Positive Predictive Value, $PPV = p \times Sn / \{p \times Sn + (1-p) \times (1-Sp)\} = 0.31 \times 0.9 / \{0.31 \times 0.9 + (1-0.31) \times (1-0.85)\} = 73\%$**
 - $PPV = a / (a+b) = 731 / 1001 = 73\%$
- **Negative Predictive Value, $NPV = (1-p) \times Sp / \{p \times (1-Sn) + (1-p) \times Sp\} = (1-0.31) \times 0.85 / \{0.31 \times (1-0.9) + (1-0.31) \times 0.85\} = 95\%$**
 - $NPV = d / (c+d) = 1500 / 1578 = 95\%$
- **PPV NPV: p $1-p$; Sn Sp**

Post-test Odds

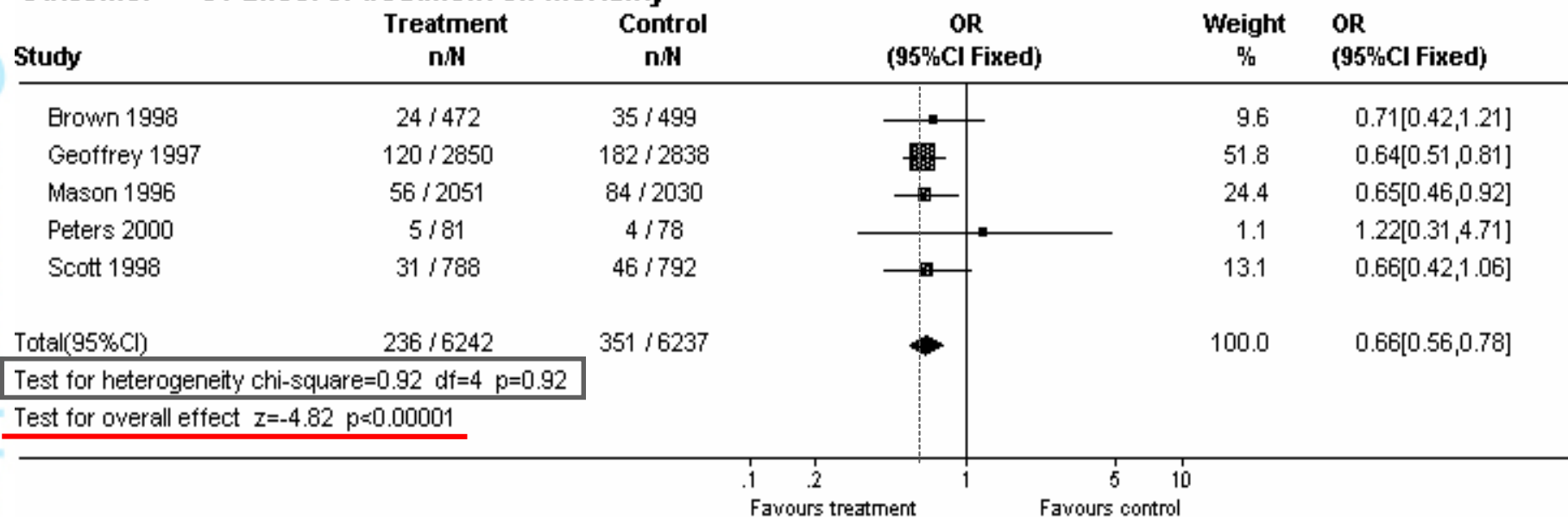
- Index test +ve
 - **Post-test odds = pre-test odds × LR+ =**
 $0.45 \times 6 = 2.7 = \{p/(1-p)\} \times \{Sn/(1-Sp)\}$
 - **Post-test odds = a/b = 731/270 = 2.7**
- Index test –ve
 - **Post-test odds = pre-test odds × LR– =**
 $0.45 \times 0.12 = 0.05 = \{p/(1-p)\} \times \{(1-Sn)/Sp\}$
 - **Post-test odds = c/d = 78/1500 = 0.05**

Post-test Probability

- Index test +ve
 - **Post-test probability = post-test odds / (post-test odds +1) = 2.7/(2.7+1) = 73% = $p \times Sn / \{p \times Sn + (1-p) \times (1-Sp)\} = PPV$**
 - **Post-test probability = $a/(a+b) = 731/1001 = 73%$**
- Index test –ve
 - **Post-test probability = post-test odds / (post-test odds +1) = 0.05/(0.05+1) = 5% = $p \times (1-Sn) / \{p \times (1-Sn) + (1-p) \times Sp\} = 1 - NPV$**
 - **Post-test probability = $c/(c+d) = 78/1578 = 5%$**
- +ve –ve: Sn 1-Sn; Sp 1-Sp

Meta-analysis: Forest plot

Comparison: 03 Treatment versus Placebo
 Outcome: 01 Effect of treatment on mortality



Eyeball test

Cochran Q

Impact size

步驟四：應用到病人身上 (將證據與臨床專業與病人價值結合)

- 你的病人是否與研究中的病人差別很大，以至於無法適用該研究結果？
- 你期望你的病人從研究結果中獲得多大的好處？
- 還有哪些替代方案？
- 研究結果適用於你的病人嗎？
- 病人的想法為何？

步驟四：應用到病人身上 (將證據與臨床專業與病人價值結合)

- 研究結果需要因應個別病人做調整
- 治療型研究的實際病人接受控制組療法的疾病發生率 **PEER(patient's expected event rate)** \neq 文獻中的 **CER** ,
NNT=1/RRRx**PEER**
- 診斷型研究真實群體盛行率 **$p \neq (a+c)/(a+b+c+d)$** , PPV、NPV、post-test odds & probability 要用會變的 **p** 和不變的 **S_n 、 S_p 、LR** 公式推導

步驟五：自我評估執行效果及效用

- 最後一個步驟來回顧：在實證醫學的執行過程中，你的表現如何？你可能要問自己下列幾個問題：
 - 你正在紀錄你的問題嗎？
 - 你是否正在廣大資源中找尋有用的外部證據？
 - 你搜尋及評讀證據的速度有多快？
 - 你有能力將這些證據應用在適當病人身上嗎？
 - 你是否依循這些新證據來改變你的診療習慣？

臨床底線(Clinical bottom line)

- Statement of best available answer(s) to the question
- 針對問題之最佳可獲得答案做精要陳述(不是文獻的結論，而是臨床應用的保守評估)

不同領域的文獻證據力分級

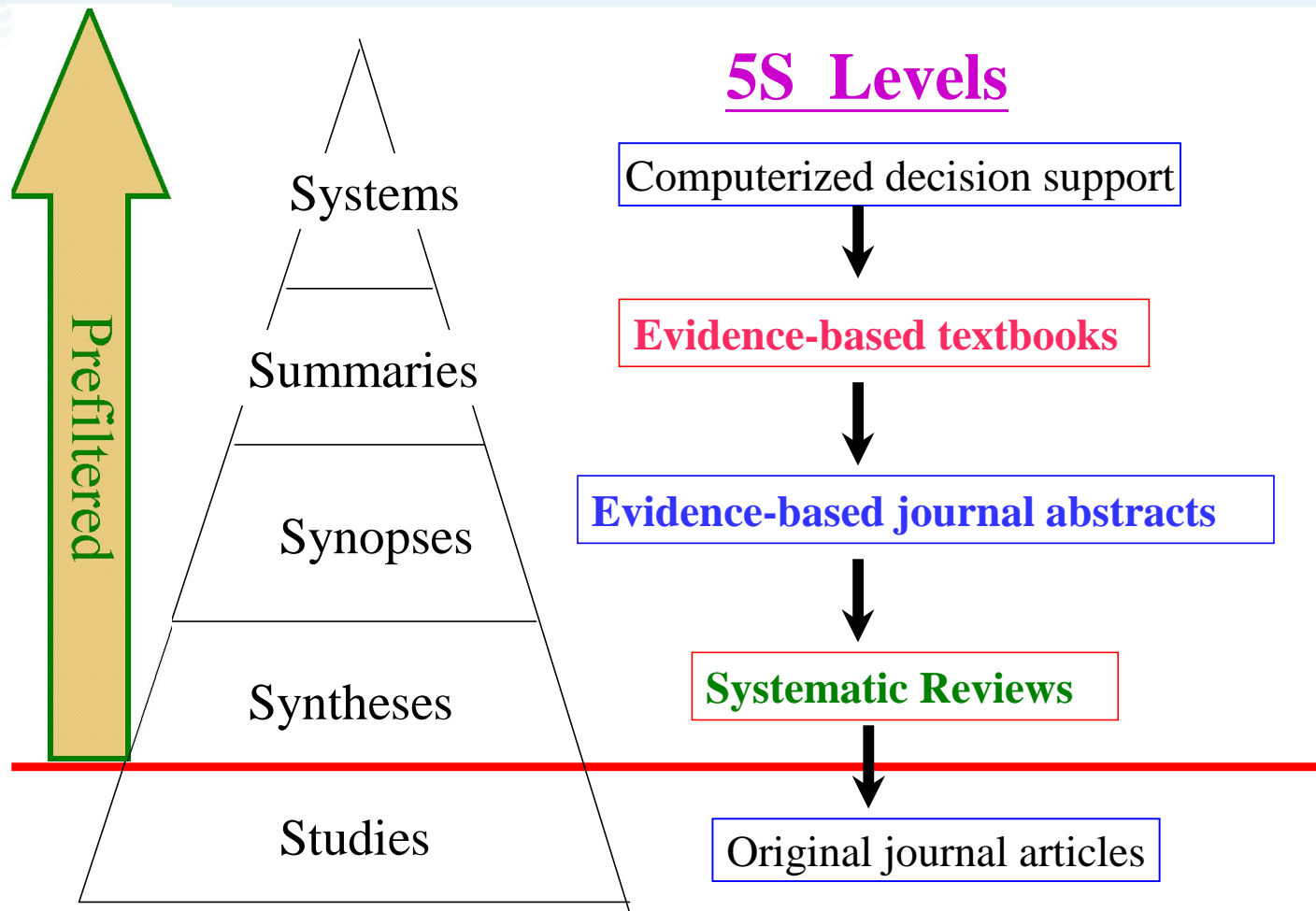
證據力等級	治療, 病因, 預防	預後	診斷	鑑別診斷, 症狀盛行率研究	經濟分析, 決策分析
Level 1	RCT ¹ 的系統性回顧; 或 Confidence Interval 窄的RCT	世代研究 ² 的系統性回顧; 或達到 80% 比例的世代研究; 或經驗證的臨床指引 ³	系統性回顧 Level 1 文獻; 或以公認標準驗證的世代研究; 或臨床指引	前瞻世代研究之系統性回顧; 或追蹤完整之前瞻世代研究	系統性回顧 Level 1 證據; 或比較好壞方向的研究
Level 2	世代研究 的系統性回; 或低品質的 RCT 或追蹤小於 80% ; 或預後研究 %	回溯性世代研究; 或追蹤 RCT 中未治療的對照組; 或由小族群推測或驗證的臨床指引; 或預後研究 ⁴	系統性回顧 Level 2 文獻; 或僅在小族群驗證的臨床指引	回溯世代研究之系統性回顧; 或追蹤不全之回溯世代研究; 或生態 (ecological) 研究	系統性回顧 Level 2 文獻; 或重要臨床方法或成本的單一研究; 或預後研究
Level 3	有對照組 (controlled study)		系統性回顧 Level 3 文獻; 或不連續或缺乏公認標準驗證的研究	不連續或小族群的世代研究	其他臨床方法或成本的研究, 包括敏感度 (sensitivity) 分析
Level 4	病例系列	病例系列	對照病例研究 (case-control study)	病例系列	未分析敏感度
Level 5	專家意見	專家意見	專家意見	專家意見	專家意見

國泰醫院劉致和醫師 2005 年根據牛津實證醫學中心 (Oxford Center for EBM, May 2001) 的列表摘譯 (網址為 http://www.cebm.net/levels_of_evidence.asp; 原出於 NHS R&D 團隊 Bob Philips and Chris Ball et al, since 1998)

Grades of Recommendation

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

- *"Extrapolations" are where data is used in a situation which has potentially clinically important differences than the original study situation*



Modified from R Brain Haynes et al.: ACP Journal Club Nov/Dec 2006 | Vol 145 • Number 34;A8-A9.

實行EBM的三種方式

- “Searching & appraising”
 - provides E-B care, but is expensive in time and resources
- “Searching only”
 - much, quicker, and if carried out among E-B resources, can provide E-B care
- “Replicating” the practice of experts
 - quickest, but may not distinguish evidence-based from ego-based recommendations

EBM的未來趨勢

- 協助臨床教學活動之進行
- 協助臨床服務共識的達成
- 協助臨床研究工作的進展
- 協助醫病關係的建構
- 建立自我學習的機制

EBM的未來趨勢

- 提供病情說明的學術根據
- 督促臨床工作者重視成效測量
- 從文獻搜尋的過程之中獲得關聯性學習
- 瞭解「臨床底線」之觀念以提供最佳服務
- 分享與運用網路上的醫學資源

典範的轉移(Paradigm Shift)

- 醫療執行由DOE (Disease-Oriented Evidence)轉移到POEM (Patient-Oriented Evidence That Matters)
- POEM就是結合最佳證據、臨床專業和病人偏好的實證醫學(EBM)，使我們能夠對病人做出最好的照顧

謝謝您的聆聽