中山醫學大學附設醫院
Chung Shan Medical University Hospital

Evidence Based Laboratory Medicine

實證檢驗醫學之應用

中山醫學大學附設醫院檢驗科
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資料參考來源

1 edition (2009)

AACC Press; 2nd edition (2007)

大綱

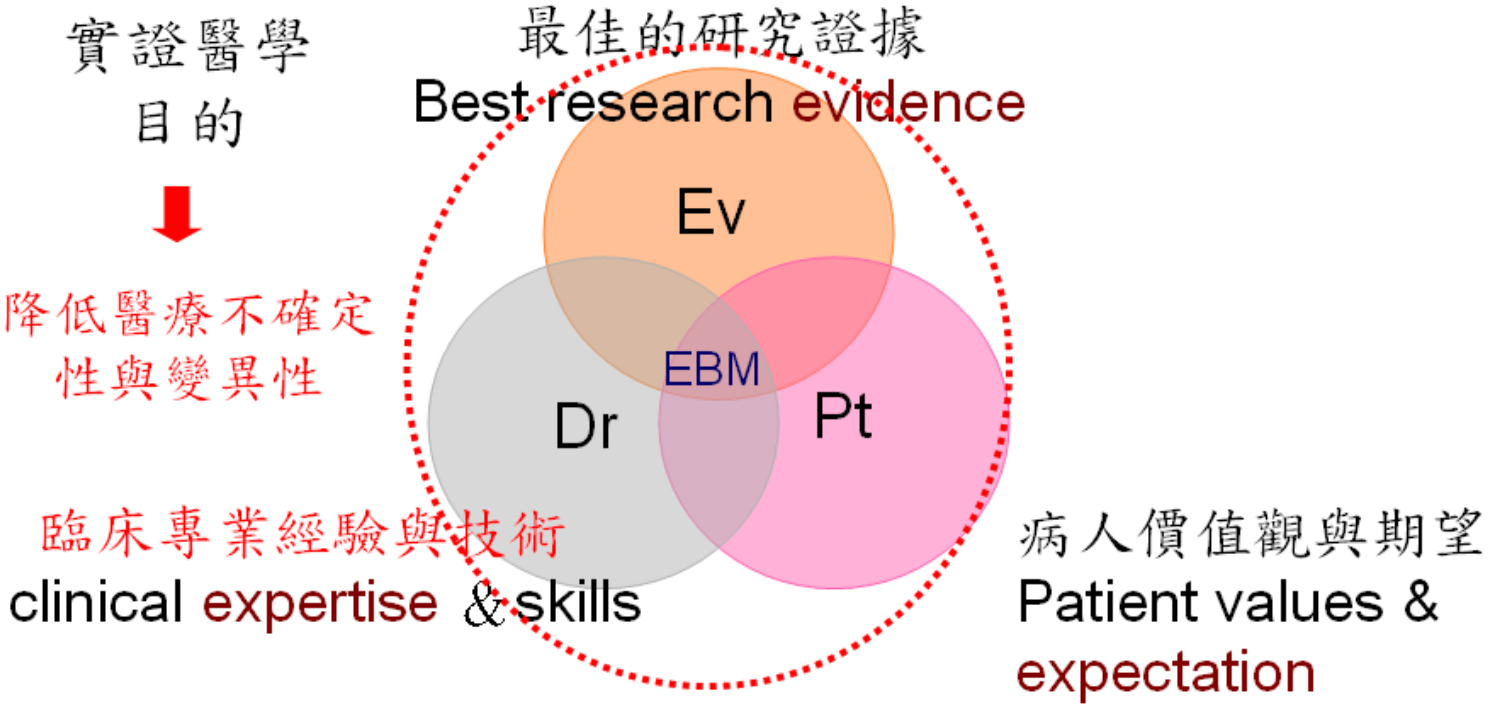
- EBM vs. EBLM
- 進行實證醫學的五大步驟介紹(問.查.評.用.審)
- 實證資源類型

1. 提問→PICO結構
2. 資訊檢索概念
3. 如何評讀文獻
4. 將實證整合並應用在病人身上
5. 評估執行的成效

何謂實證醫學

EBM (Evidence-Based Medicine)

- 取得現有最佳的研究證據，並與醫護人員的專業經驗及病患的期望相結合，制定出一套最佳的**臨床醫療決策**。



EBM (Evidence-based Medicine)
--以證據為基礎的醫學

- 實證醫學乃是從龐大的醫學資料庫中搜尋相關文獻，並以流行病學及統計學方法過濾出值得信賴的文獻，再經過嚴格評讀及綜合分析後，將所獲取之最佳研究證據(evidence)、臨床經驗(experience)及患者期望(expectation)相互整合，配合診療情境後制定出一套最佳的臨床醫療決策，並可用來協助醫護人員進行終身學習。

何謂實證檢驗醫學

EBLM (Evidence-Based Laboratory Medicine)

- 按照實證醫學“以當前最佳證據為基礎”的原則，規範檢驗醫學的研究、設計和文獻評價。
- 目的是向臨床提供有效檢驗的證據、提供最有利於醫患雙方的診斷試驗的診斷效能、成本-效果分析等資訊。
- 醫檢師不僅要向臨床醫師解釋檢驗項目的意義，而且要幫助他們合理地選擇檢驗項目。

進行實證檢驗醫學的五大步驟(5A)

- Ask (PICO): Formulate an answerable question
  - 提問: 由實際的臨床資料提出可回答的臨床問題
- Acquire: Track down the best evidence
  - 尋找最佳的實證文獻[各種文獻資料庫，包括發表及未發表資料〕
- Appraise: Critically appraise the evidence for validity, importance, and practicability
  - 嚴格評讀文獻的可信度、臨床重要性以及可應用性
- Apply: Integrate with clinical expertise and patient values
  - 整合並應用於患者的檢驗決策〔臨床應用〕以病人可以聽懂的語言告知各種處置之可能利益與風險
- Audit: Evaluate our effectiveness and efficacy
  - 評估效果，新檢驗方法執行成效與臨床效益

步驟一：Ask the Question

- 將臨床需求轉換成可回答的臨床問題

臨床問題的種類

- Therapy / Prevention：治療/預防的問題
  - 研究治療或預防方法的有效性
  - 例如：服用“阿斯匹林”是否可以預防中風？
- Diagnosis：診斷問題
  - 研究檢查方法或臨床表徵對疾病診斷的有效性
  - 例如：Troponin I診斷急性心肌梗塞的敏感性及特異性為何？
- Harm / Etiology：危害/病因問題
  - 研究暴露的危害或疾病的原因
  - 例如：停經婦女使用荷爾蒙治療是否會增加乳癌的機會？
- Prognosis：預後
  - 建立疾病預後的預測模式
  - 例如：利用Ranson’s criteria 預測急性胰臟炎死亡率為何？

建構完整的臨床問題

- “背景問題” (Background questions)
  - 詢問有關疾病或檢驗的一般知識
  - 問題根源6W (對象who、時間when、地點where、發生什麼事what 、如何發生how、為何發生why)
- “前景問題” (Foreground questions)
  - 詢問需特別知識或經驗的問題，有關使用何種檢驗/治療病人可增進病患健康
  - 利用**PICO**來形成前景問題

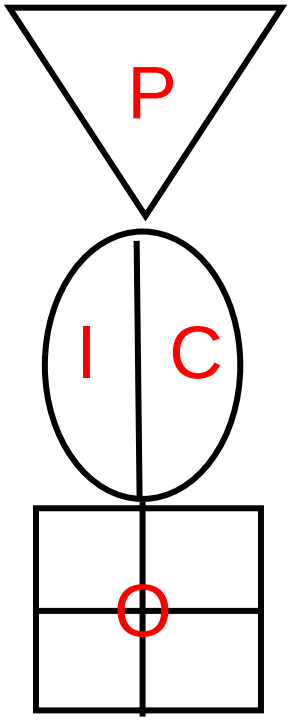
步驟一

將問題寫成PICO

PICO

Asking Answerable Clinical Question

- P: Patient / population
  代表問題所關心的病人族群或特質
- I: Intervention / test
  代表臨床介入處置(治療)或檢驗
- C: Comparator / control
  與臨床介入比較的對照介入
  (檢驗方法或reference standard)
- O: Outcome
  治療的效果或是診斷的正確率等



Formulate an Answerable Question

BNP in Urgent Care (A diagnostic question)

- Can I use the plasma BNP test (I) to rule-in or rule-out (O) decompensated heart failure in patients presenting with dyspnea to urgent care (P)?
- 針對急性呼吸困難者檢測B-Type Natriuretic Peptide來診斷DHF心力衰竭病人的效益是如何?

Comparison: gold standard diagnosis

Asking Answerable Clinical Question

(PICO) for A diagnostic question

Patient / Problem 病人問題	dyspnea patient with DHF
Intervention 介入檢查	BNP test or B-Type Natriuretic Peptide
Comparison 對照的處置	DHF Gold standard dyspnea patient without DHF
Outcomes 臨床結果	Diagnosis of DHF Stay in ER

臨床情境Scenario

- 一位腎臟科醫師最近讀了些有關腎衰竭病人偵測Cystatin C test的研究論文，打電話問檢驗科Cystatin C test 是否比傳統 serum creatinine，能更早偵測到腎移植病人因排斥造成的腎小球過濾速率變差。
- PICO???

Asking Answerable Clinical Question

(PICO) for A diagnostic question

Patient / Problem 病人問題	
Intervention 介入檢查	
Comparison 對照的處置	
Outcomes 臨床結果	

Asking Answerable Clinical Question

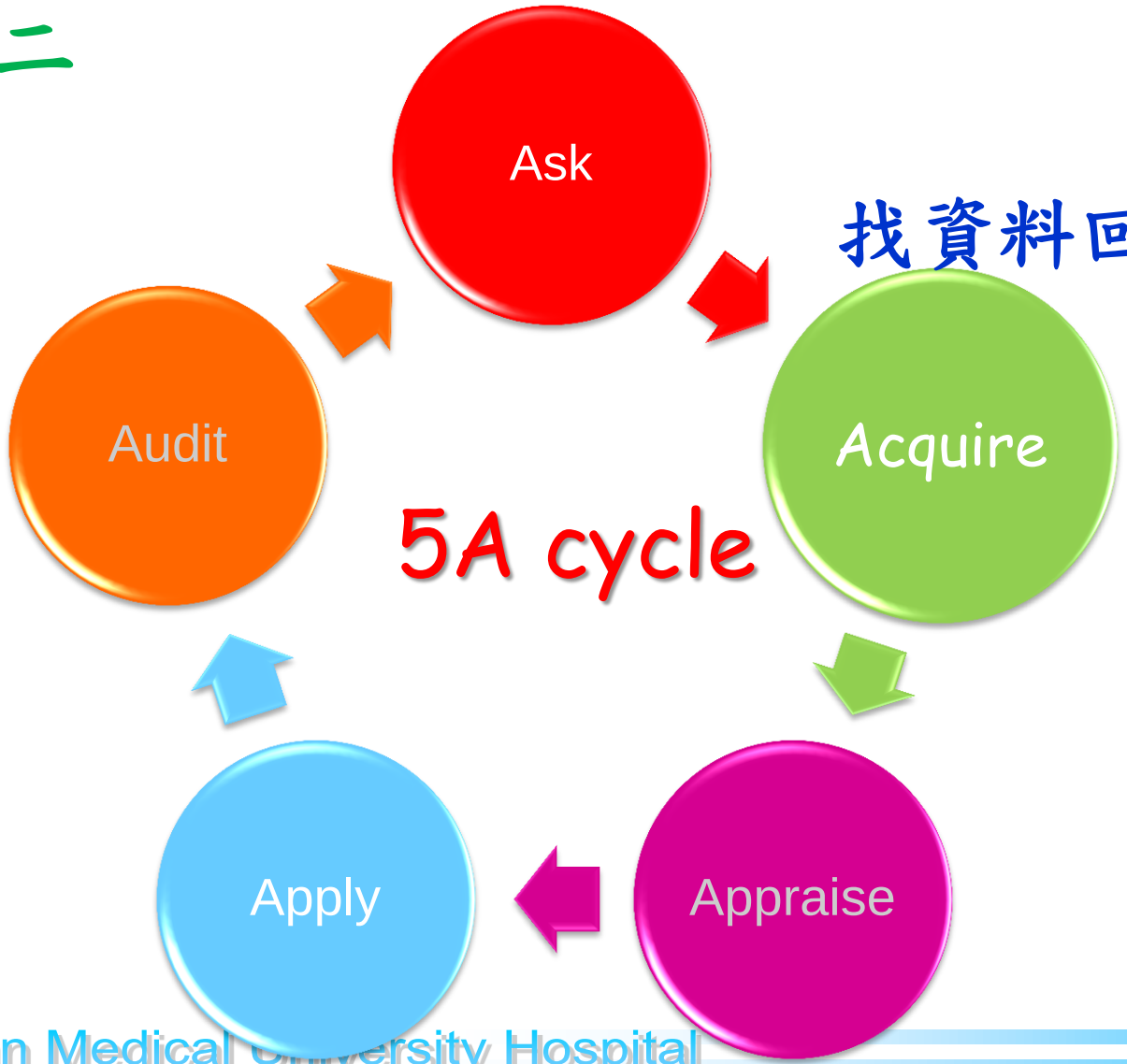
(PICO) for A diagnostic question

Patient / Problem 病人問題	Patient following kidney trans-plantation who develop a rejection episode
Intervention 介入檢查	Serum Cystatin C test
Comparison 對照的處置	serum creatinine
Outcomes 臨床結果	Change in concentration after operation Diagnosis accuracy against a reference method for GFR

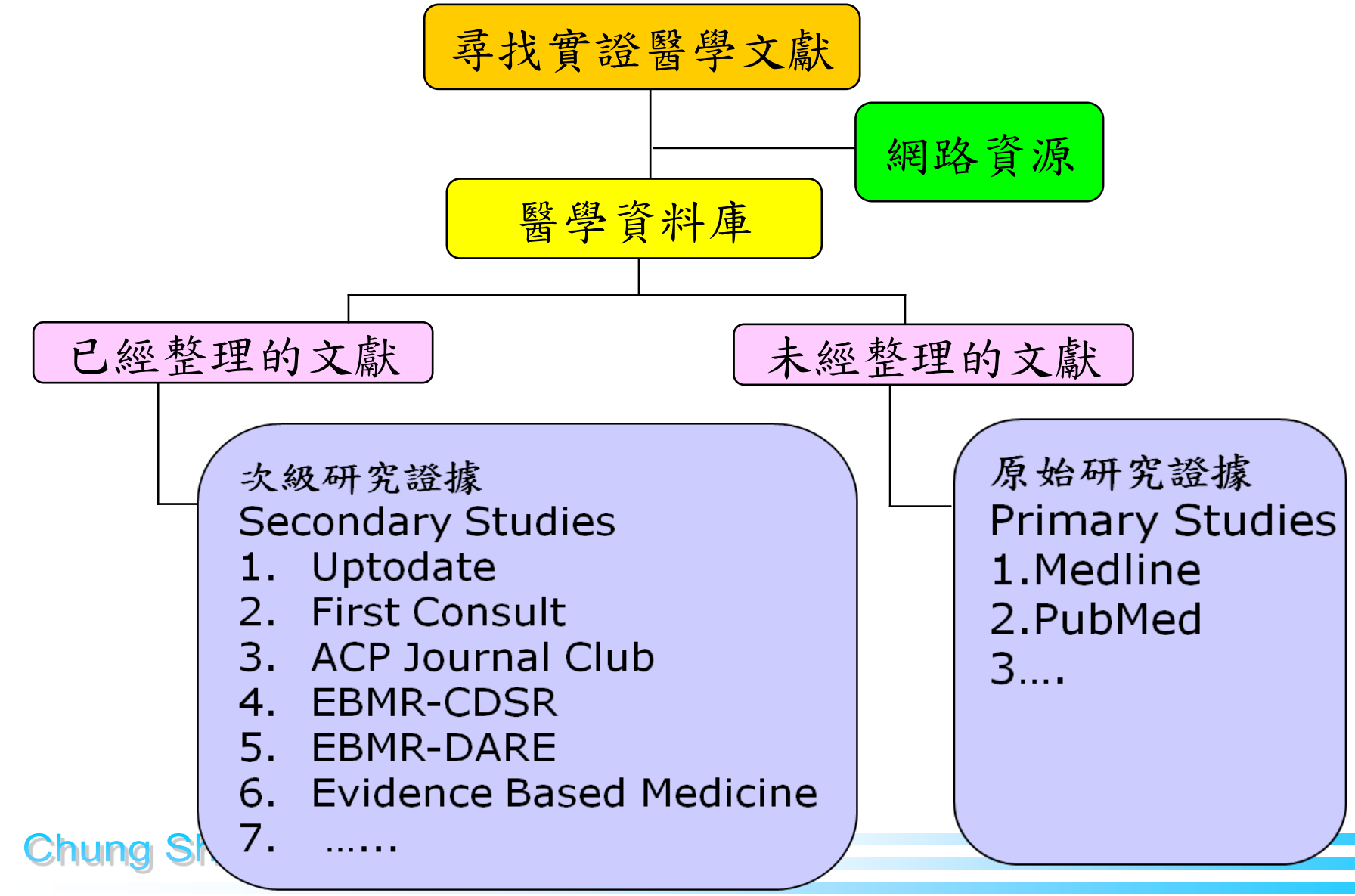
步驟二：Acquire the Information

- 搜尋最佳的醫學證據

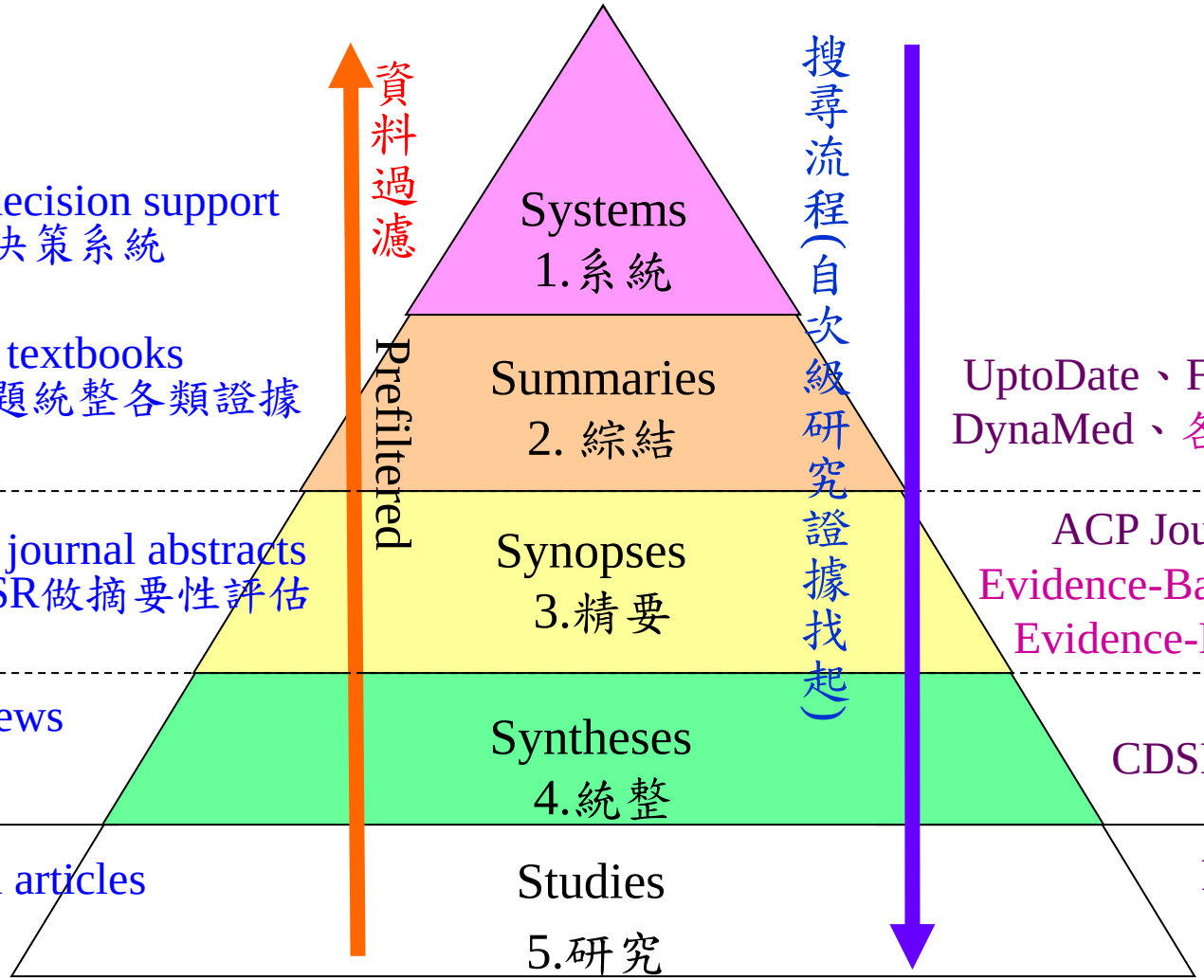
步驟二



常用實證醫學電子資源


尋找實證醫學文獻
網路資源
醫學資料庫
已經整理的文獻
未經整理的文獻
次級研究證據
Secondary Studies
1. Uptodate
2. First Consult
3. ACP Journal Club
4. EBMR-CDSR
5. EBMR-DARE
6. Evidence Based Medicine
7. ……
原始研究證據
Primary Studies
1.Medline
2.PubMed
3….

5S EBM Resources (非關證據強弱)



Computerized decision support
實証臨床資訊決策系統

Evidence based textbooks
針對某臨床主題統整各類證據以形成之概述

UptoDate、FirstConsult、DynaMed、各種Guidelines

Evidence based journal abstracts
對單篇研究及SR做摘要性評估

ACP Journal Club、Evidence-Based Medicine、Evidence-Based Nursing

Systematic reviews
系統性評論

CDSR、DARE

Original journal articles
原始研究文獻

PubMed、Medline

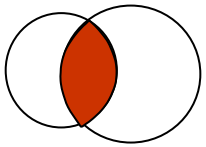
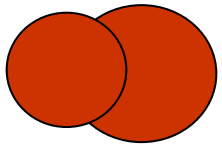
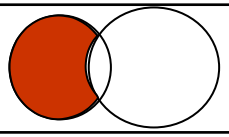
EBM Database

二次研究證據 (已經整理的文獻)	**1.System系統**	
	2.Summaries摘要 **- for背景知識**	(1) Evidence-based CPG (free) (2) Best Practice-Clinical Evidence (3) UpToDate (4) ACP Pier & ACP Medicine (5) FirstConsult (6) DynaMed (7) Medscape-eMedicine (free)
	3.Synopses精要 **(Article Review)** **- for背景知識**	(1) ACP Journal Club (2) Evidence-based Medicine (free) (3) Evidence based – xxx的期刊
	4.Syntheses統整 **(Systematic Review)** **- for證據評讀**	(1) The Cochrane Library - CDSR & Other Reviews (中文版摘要 free) (2) PubMed (free)-Clinical Queries之 systematic review (3) Medline之systematic review
原始研究證據 (未經整理的文獻)	**5.Studies** **- for證據評讀**	(1) The Cochrane Library- Clinical trials (2) PubMed (free)-Clinical Queries之Clinical study search (3) Medline (善用 more limit之功能)

搜尋流程（自二次研究證據找起）

中山醫學大學附設醫院實證醫學中心

布林邏輯 (Boolean logics)

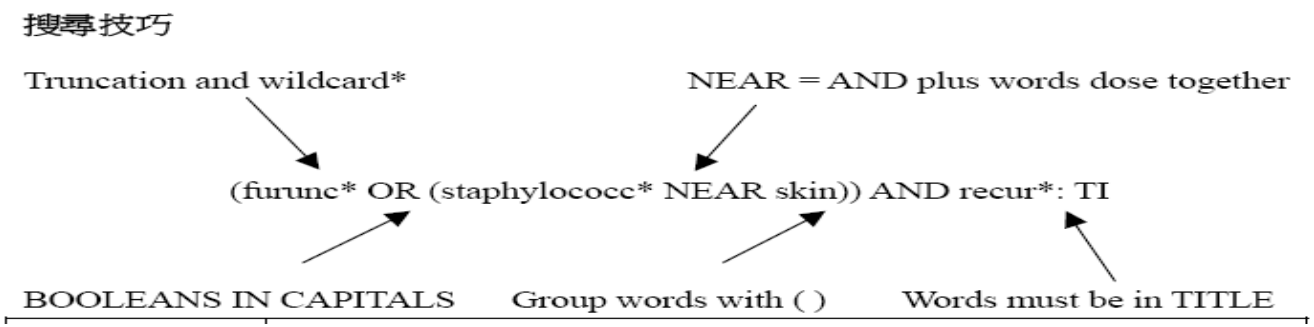
運算元	例舉	圖示	作用
AND	**H1N1 AND Tamiflu**		1.縮小檢索範圍; 2.用於相異概念詞彙
OR	**H1N1 OR Swine flu**		1.擴大檢索範圍; 2.用於相似概念詞彙
NOT	**H1N1NOT bird flu**		排除不相關的範圍

	Primary Term		Synonym 1		Synonym 2	
P	(Acute coronary syndrome	OR	unstable angina	OR	myocardial ischemia	) AND
I	(B-type natriuretic peptide	OR	NT-proBNP	OR		) AND
C	(	OR		OR		) AND
O	(Mortality	OR	death at 12 month	OR		

檢索策略

- 技巧
  - 布林邏輯運算(Boolean Logic) AND, OR, NOT
  - 位置運算(Adjacency)
    - A adjn B (A及B間可插入N個字,且順序可互換)
    - 如cerebral adj2 surgery會找到 “cerebral surgery”,”surgery cerebral”,”cerebral aneurysm surgery”, “cerebral comlications of surgery”等文章.
  - 截字(串字)查詢 (Truncation)
    - 在字尾加上萬用字元「*」依資料庫不同或以$?等表示
    - 如Flavor*會找到flavored, flavorful, flavoring etc.
  - 善用限制(Limit)功能：語言、年代、資料型態等
  - 特定欄位檢索(Search fields)

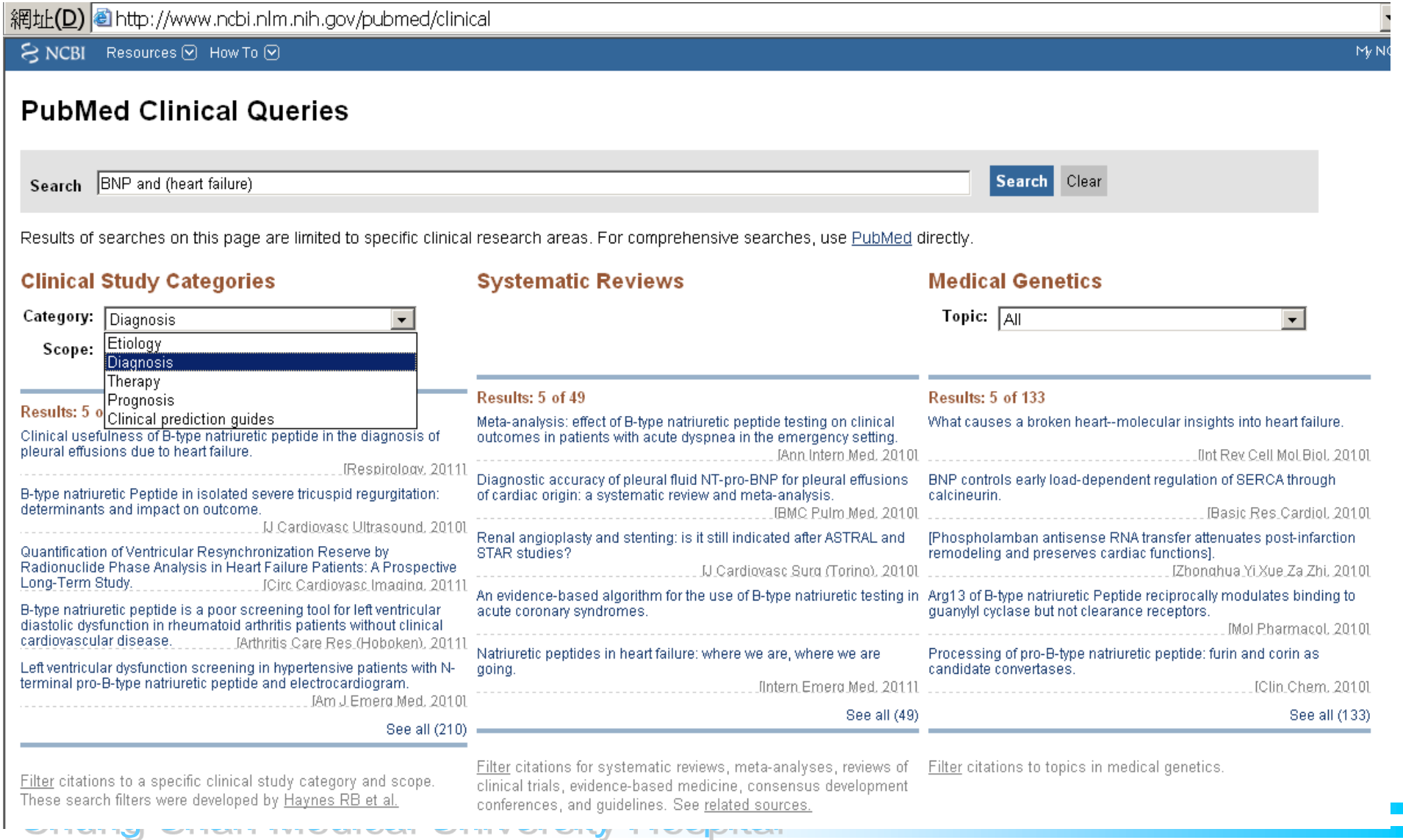
PubMed搜尋技巧



V	NEAR	類似 AND 的功能，必須同時包含兩個字，而且這兩個字中間的距離間隔，不能超過五個字。
	Limits	可以經由在某些方面加以限制，而找到想要找到的文章。如，日期、語言、及是否提供摘要等。
V	( )	利用括號組合文字。如，"(child OR adolescent) AND (hearing OR auditory)"，會找到包括"child"或"adolescent"以及"hearing"或"auditory"的文章。
	*	截斷字："*"爲萬用字元，代表任何字母。如，child* 爲 child 加任何字母，相當於(child OR child's OR children OR childhood)。
	[ti] or :ti	尋找標題中有該字眼的研究。如，hearing[ti] (in PubMed)及 hearing:ti (in Cochrane)會找到標題中有 hearing 這個字的研究。
	[so] or :so	尋找特定來源的研究，如，hearing AND BMJ [so] 會找到 BMJ 中與 hearing 有關的研究。
	MeSH	MeSH 爲 Medical Subject Headings 的縮寫，是關鍵字的特殊語彙，通常用在 PubMed 或 Cochrane。同時使用 MeSH 及內文(text words)，經常會很有用。

主標題詞

Question: Can BNP be used for guiding therapy in stable DHF patient?



NCBI Resources How To My NC

PubMed Clinical Queries

Search (heart failure and BNPand Guid*) and (meta-analysis) Search Clear

Results of searches on this page are limited to specific clinical research areas. For comprehensive searches, use PubMed directly.

Clinical Study Categories

Category: Diagnosis

Scope: Narrow

Results: 4 of 4

Biomarkers in heart failure--better than history or echocardiography? [Herz. 2009]

Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care. [Health Technol Assess. 2009]

[Differential diagnosis of dyspnea - significance of clinic aspects, imaging and biomarkers for the diagnosis of heart failure]. [Clin Res Cardiol. 2006]

Assessing the diagnostic test accuracy of natriuretic peptides and ECG in the diagnosis of left ventricular systolic dysfunction: a systematic review and meta-analysis. [Br J Gen Pract. 2006]

See all (4)

Filter citations to a specific clinical study category and scope. These search filters were developed by Haynes RB et al.

Systematic Reviews

Results: 5 of 63

Detection of silent myocardial ischemia in asymptomatic patients with diabetes: results of a randomized trial and meta-analysis assessing the effectiveness of systematic screening.

Vaginal misoprostol for cervical ripening and induction of labour. [Cochrane Database Syst Rev. 2010]

Meta-analysis of incidence, clinical characteristics and implications of stent fracture.

Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation.

Prophylactic implantation of cardioverter defibrillators in idiopathic nonischemic cardiomyopathy for the primary prevention of death: a narrative review. [Clin Cardiol. 2010]

See all (63)

Filter citations for systematic reviews, meta-analyses, reviews of clinical trials, evidence-based medicine, consensus development conferences, and guidelines. See related sources.

Medical Genetics

Topic: Diagnosis

Results: 1 of 1

Genetic variation in NOS1AP is associated with sudden cardiac death: evidence from the Rotterdam Study. [Hum Mol Genet. 2009]

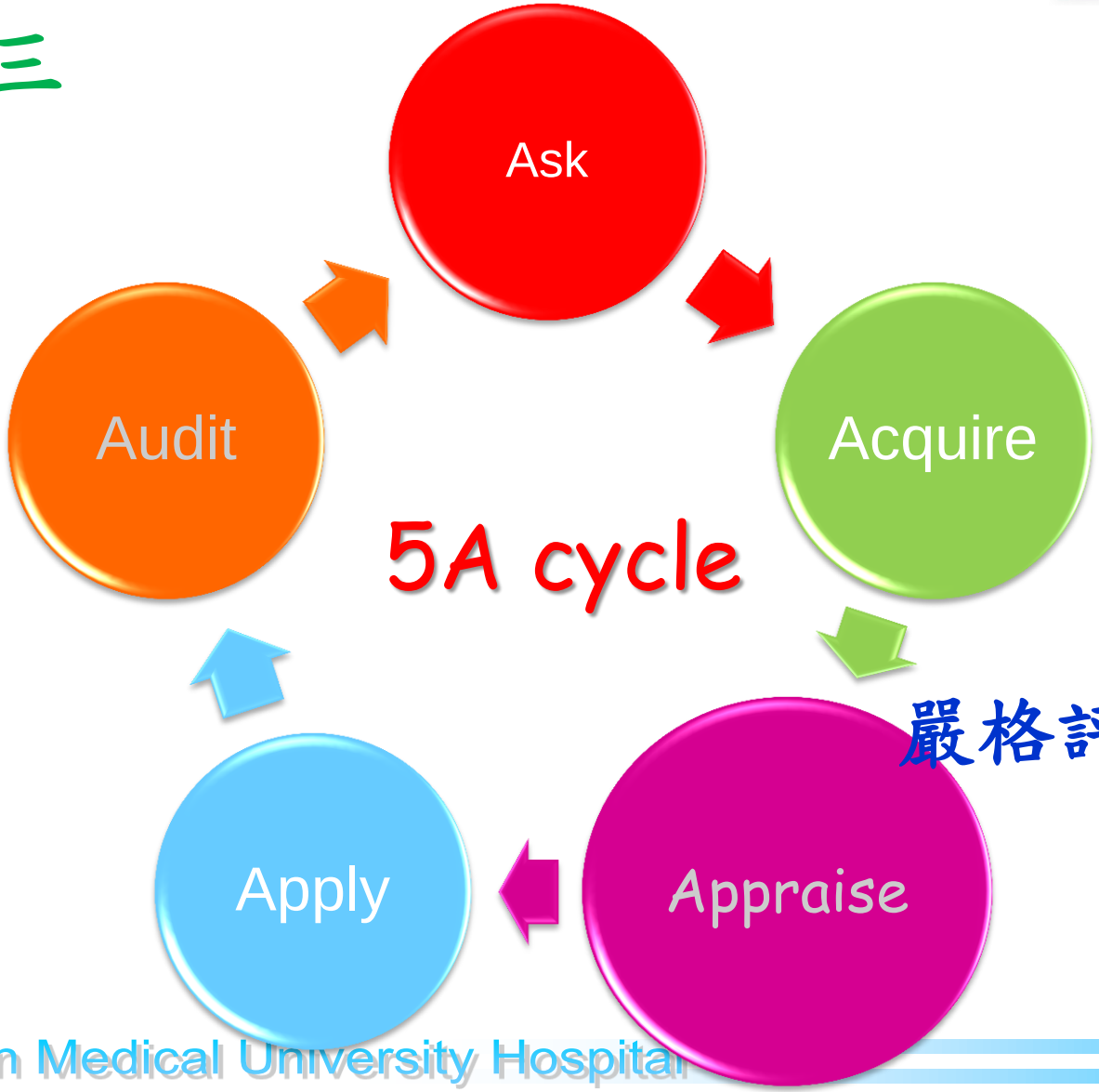
See all (1)

Filter citations to topics in medical genetics.

步驟三：Appraise the Evidence

- 嚴格的評讀文獻

步驟三



嚴格評讀文獻

Critical Appraisal 嚴格評讀文獻

Validity可信度: are the results of the study valid?

效度如何?
- Systematic review or diagnostic worksheet

Importance重要性: are test characteristics presented?

結果是甚麼?
- Impact, size of the effect

Practicability應用性: can we apply to our patients?

可以應用到我的病人嗎?
- Applicability and feasibility
- Usefulness in our practice

文獻評讀的重點

確認文獻"PICO"與臨床問題相符 ▶▶ 根據文獻類型選擇適當評讀工具 ▶▶ 開始評讀 ▶▶ 提供結論

- 這份研究的PICO與問題的PICO是否一致?
- 研究設計方法是否適當?
- 實驗的結果是否具不確定性(potential bias)
  - random隨機, spectrum具代表性, blinding 盲樣…
- Diagnostic test:
  - 是否能清楚的回答PICO問題?
  - 是否使用標準診斷方法？

偏差(Bias)

- 定義：在研究之設計與實施過程中，凡是會使數據**(data)**或結論朝向**(toward)**或偏離真實**(against truth)**之任何因子，稱之為偏差。
- 如果在研究之設計與實施過程中，忽略可預期之偏誤因素會使此研究之內部效度降低。

評讀方法比較

工具	類別	評比時間
Jadad Scale	級分別，共3項	~5分鐘
Cochrane risk of bias table	查核表，共7項	~10分鐘
RAMMbo	查核表，共7項	~10分鐘
CASP	查核表，共10項	~20分鐘
PRISMA	查核表，共27項	~1小時
Oxford CAT	查核表，共6項	~10分鐘

效度(Validity) - Appraisal checklist

- **RAMMbo**
- **R**ecruitment受試者招募
  - 研究樣本是否具有代表性(Representative)？
- **A**llocation試驗分組
  - 病人的治療是否隨機分派Random?隨機分配過程是否隱匿concealment?兩組在治療開始時的baseline是否相似？
- **M**aintenance維持
  - 對照組與實驗組是否被同等對待?是否所有的病人都被放到原先分派的組別中做分析?治療意向分析(Intention-to-treat analysis, ITT)
  - 是否追蹤夠久和完整**follow-up**
- **M**easurements結果測量
  - 病患、醫護人員、研究員是否對治療不知情(blinded)?
  - 測量是否客觀(**o**bjective)及標準化?

- **以上這些答案，通常可以在文章中的方法學(Method)部分和結果(Result)的第一、二段中找到**

解答不同類型臨床問題之研究設計

Question type (問題類型)	The best study design (研究設計)
Diagnostic test 診斷性檢驗	Prospective, blinded cross-sectional study comparing with gold (reference) standard test 前瞻性、盲法、與標準檢驗進行比較之斷面研究
Prognosis 預後	Cohort study 、 Case control study 世代研究、病例對照研究
Etiology 病因	Cohort study 、 Case control study 世代研究、病例對照研究
Therapy / Prevention 治療 /預防	Randomized control trial (RCT) 隨機對照試驗
Risk / Harm 風險評估	Randomized control trial (RCT)、Cohort study 隨機對照試驗、世代研究
Cost effectiveness 成本效益	Economic analysis 經濟分析

各類型問題原始文獻的證據等級

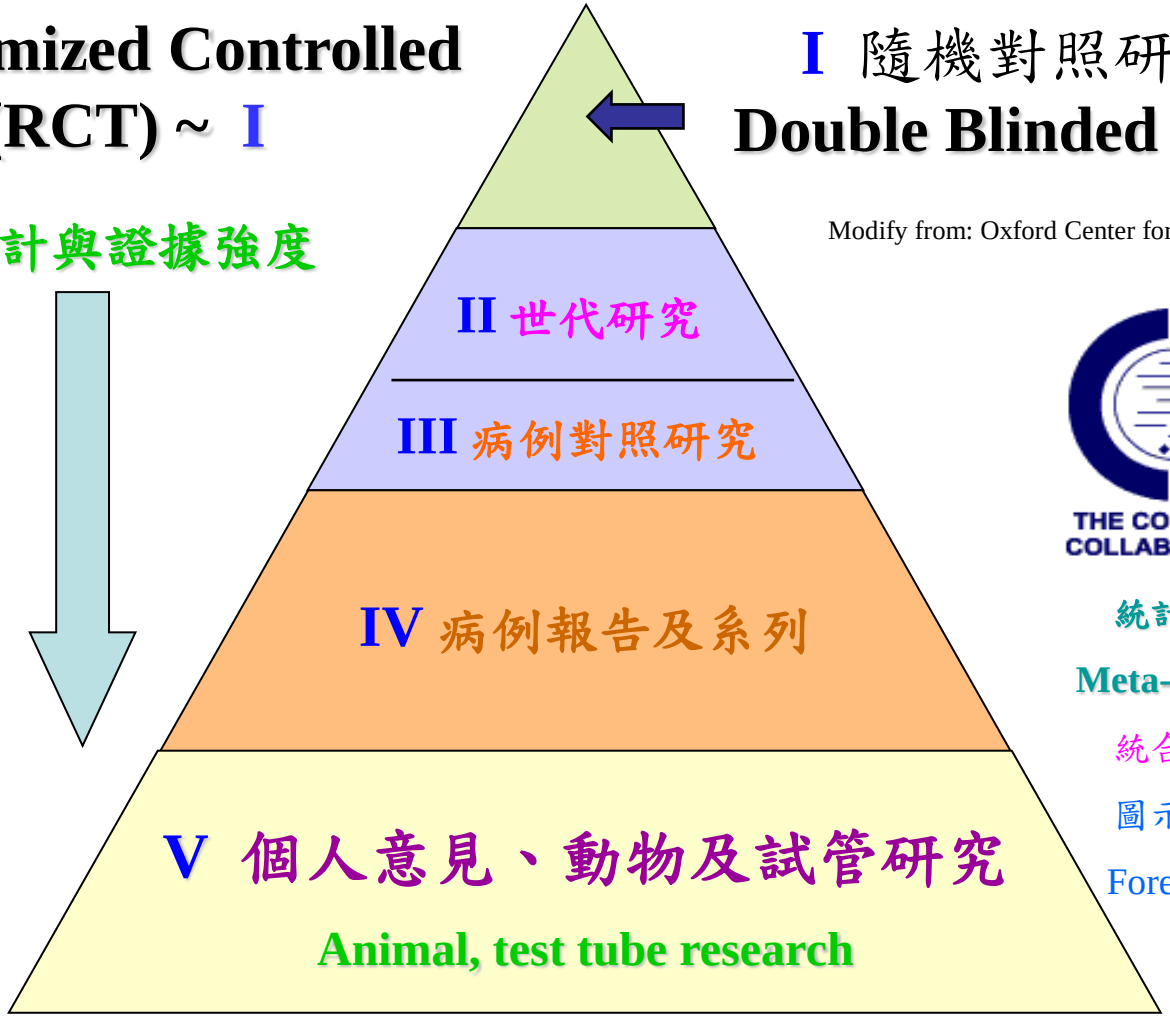
Type of Question	Suggested Best Type of Study
Diagnosis診斷	Prospective, blind comparison to a gold standard 前瞻盲法與黃金標準法比較橫斷性研究
Prognosis預後	cohort › case control › case series 世代研究>病例對照研究>病例系列研究
Etiology病因	cohort › case control › case series
Therapy治療	RCT› cohort › case control › case series 隨機對照實驗＞世代研究>
Prevention預防	RCT› cohort › case control › case series
Cost effectiveness 成本效益	Economic analysis經濟分析

Level of Evidence I~V

Randomized Controlled Trials (RCT) ~ I

I 隨機對照研究 Double Blinded RCT

研究設計與證據強度



Modify from: Oxford Center for EBM

THE COCHRANE COLLABORATION

統計方法

Meta-analysis

統合分析

圖示結果

Forest plot

Meta - analysis

研究設計與證據強度 **(Bias, Robust)**

Chung Shan Medical University Hospital

Hierarchy of evidence: arranges study designs by their susceptibility to bias. **(Robust)**

Study Design

Study Design			研究開始		(用途)
研究種類	時間性	過去	現在	未來	
Cross-sectional (prevalence)	橫斷性觀察				盛行率、診斷
Cohort (longitudinal)	縱向性(前瞻)		▼收集資料▼ Case & non-Case		發生率、病程預後、病因
Clinical Trial (experimental)	縱向性(前瞻)		定義世代並評估危險因子	觀察結果Y*N	藥物療效評估
			作治療〔治療組與對照組〕	觀察結果Y*N	
Case control (retrospective)	縱向性(回溯)	評估危險因子 Exposure: Y*N	界定病例組與非病例組		病因〔尤其罕病〕
Repeated cross-sectional	橫斷性觀察		收集資料▼	重複收集▼▼	隨時間改變

依不同問題的實驗設計區分證據等級

Level	Intervention	Diagnosis	Prognosis	Etiology
I		*A SR of level II studies*		
II	RCT	Cross-sectional study among consecutive or random presenting patients	Prospective inception cohort study	study
III	Pseudo-RCT or non-randomized experimental study Comparative observational study with concurrent control group (cohort study, case-control study)	Cross-sectional study among non-consecutive patients Diagnostic case-control study	Untreated control patients in a RCT Retrospectively assembled cohort study	A retrospective cohort study Case-control study
IV	Case series	Case series	Case series, or cohort study of patients at different stages of disease	Cross-sectional study

SR = Systematic Review; RCT = randomized controlled trial;

Systematic review

Most bias

證據等級

Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009)

http://www.cebm.net/index.aspx?o=1025

證據等級	與[治療/預防病因/危害]有關的文獻	與[預後]有關的文獻	與[診斷]有關的文獻	與[鑑別診斷/症狀/盛行率]有關的文獻	與[經濟/決策分析]有關的文獻
1a	用多篇 RCT[註1]所做成的綜合性分析 (SR[註 2] of RCTs)	用多篇世代研究所做成的綜合性分析(SR of inception cohort studies)	SR of level 1 diagnostic studies; CDR with 1b studies from different clinical centers	SR of prospective cohort studies	SR of level 1 economic studies
1b	單篇 RCT(有較窄的信賴區間)	Individual inception cohort study(追蹤完成>=80%)	有好的診斷參考標準之世代研究	Prospective cohort study with good follow-up	用臨床上明顯的成本項目來做綜合性的分析研究.
1c	All or none	All or none case-series	SpPin / SnNout	All or none case-series	Absolute better value or worse value analysis
2a	用多篇世代研	SR of	SR of level>2	SR of 2b and	SR of level>2

證據等級(續)

	究所做成的綜合性分析	retrospective cohort	diagnostic studies	better studies	diagnostic studies
2b	單篇 cohort 及低品質的 RCT	Retrospective cohort	Exploratory Cohort study with good reference standards	Retrospective cohort study or poor follow-up prospective cohort study	用臨床上明顯的成本項目所做成的有限度分析研究.
2c	Outcome research / ecological studies	Outcome research		Ecological studies	Audit or outcomes research
3a	SR of case-control studies		SR of 3b	SR of 3b	SR of 3b
3b	Individual case-control studies		Non-consecutive study	Non-consecutive study	用臨床上有限的成本項目所做成的分析.
4	Case-series(poor quality :cohort / case-control studies)	Case-series(poor quality prospective cohort studies)	Case-control study or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	沒有經過完整評讀醫學文獻的專家意見。	沒有經過完整評讀醫學文獻的專家意見。	沒有經過完整評讀學文獻的專家意見。	沒有經過完整評讀醫學文獻的專家意見。	沒有經過完整評讀醫學文獻的專家意見。

文獻評比: Importance

- 診斷 **Diagnosis**
  - Sensitivity 敏感性
  - Specificity 特異性
  - Predictive value (PPV, NPV)陽性預測值，陰性預測值
  - ROC curve
  - Likelihood ratio (LR+, LR-) 概似比

文獻評比: Importance

- 治療 Therapy
  - Relative risk reduction (RRR, 相對風險性降低度)
  - Absolute risk reduction (ARR, 絕對風險性降低度)
  - Number needed to treat (NNT, 益一需治數)
- 預後 Prognosis
  - Prediction model (Survival analysis, Hazard Ratio 風險比)
  - Event rate (事件發生率)
  - Odds ratio (OR, 勝算比)
- 危險因子 Risk factor
  - Cohort study (Relative risk, RR 相對風險比)
  - Case-control study (Odds ratio, OR 勝算比)
  - Number needed to harm (NNH, 害一需治數)--增加一位受試者產生因新治療所致醫源性傷害所需的治療病人數

評估檢驗效度的二維表

	Disease present	Disease Absent	Total
Index Test positive	True Positive (TP)	False Positive (FP)	TP + FP
Index Test negative	False Negative (FN)	True Negative (TN)	FN + TN
Total	TP + FN	TN + FP	TP + FN + FP + TN

評估檢驗效度的二維表

	Disease present	Disease Absent	Total
Index Test positive	True Positive (TP)	False Positive (FP)	TP + FP
Index Test negative	False Negative (FN)	True Negative (TN)	FN + TN
Total	TP + FN	TN + FP	TP + FN + FP + TN

Sensitivity = TP/(TP + FN)
Specificity = TN/(TN+FP)
*PPV = TP/(TP + FP)
*NPV = TN/ (TN + FN)

有病者 檢驗呈陽性的機率
無病者 檢驗呈陰性的機率
檢驗陽性者 有病的機率
檢驗陰性者 無病的機率

*Positive Predictive Value = PPV; Negative Predictive Value = NPV

評估檢驗效度的二維表

	Disease present	Disease Absent	Total
Index Test positive	True Positive (TP)	False Positive (FP)	TP + FP
Index Test negative	False Negative (FN)	True Negative (TN)	FN + TN
Total	TP + FN	TN + FP	TP + FN + FP + TN

Sensitivity = TP/(TP + FN)　有病者 檢驗呈陽性的機率

Specificity = TN/(TN+FP)　無病者 檢驗呈陰性的機率

*PPV = TP/(TP + FP)　檢驗陽性者 有病的機率

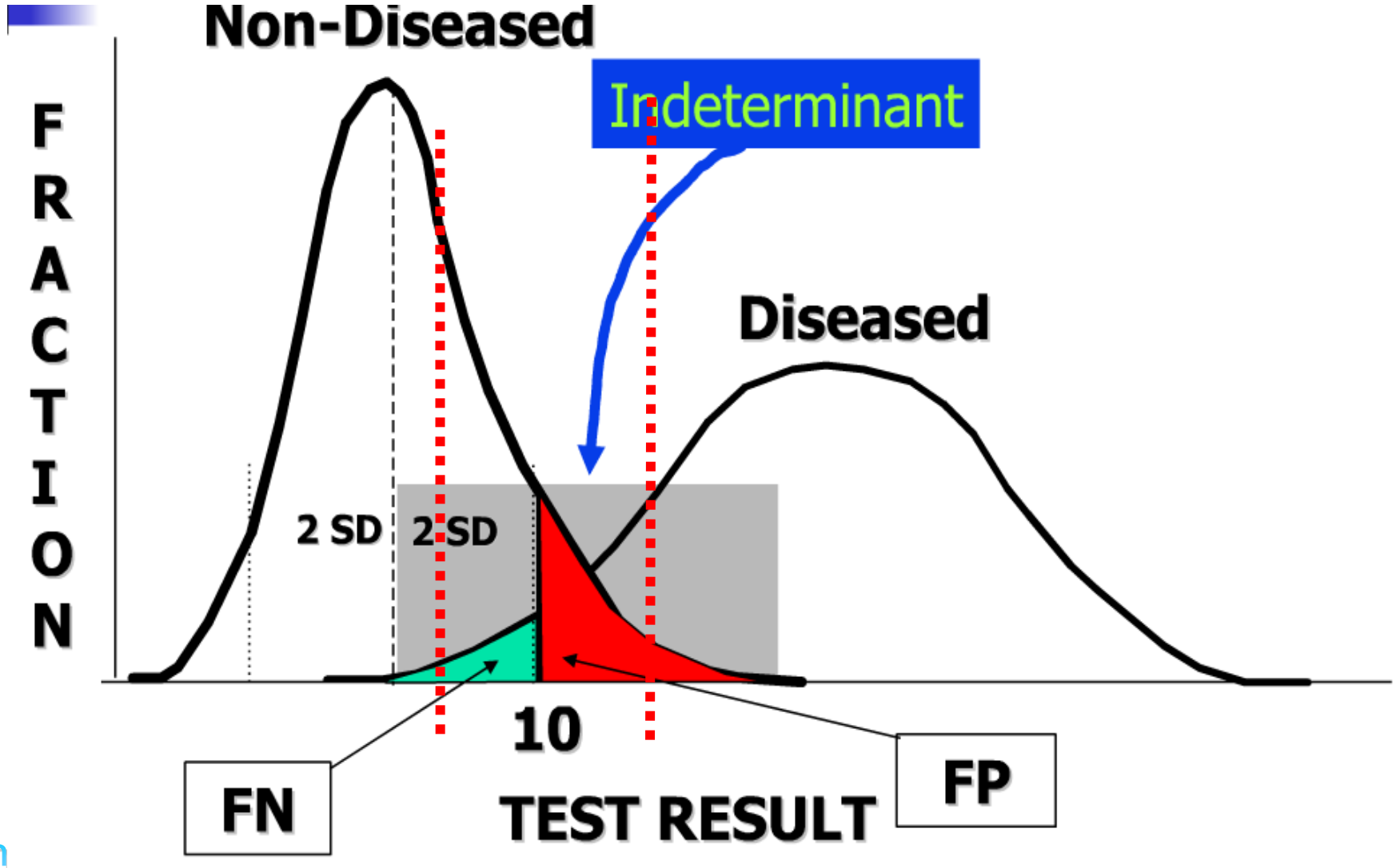
*NPV = TN/ (TN + FN)　檢驗陰性者 無病的機率

*Positive Predictive Value = PPV; Negative Predictive Value = NPV

篩檢效度和診斷效度

- 篩檢效度 SnNout (Rule out)
  - high Sensitivity test with Negative result rule out the diagnosis
- 當一個檢驗具有高度敏感度，若檢驗是陰性，則幾乎可以排除rule out那個診斷的可能性
  - 例如: HIV Ab screening (Sn H): Negative → Rule out
- 診斷效度 SpPin (Rule in)
  - high Specificity test with Positive result rule in the diagnosis
- 當一個檢驗具有高特異性，若檢驗是陽性，則幾乎可以確認rule in 那個診斷的可能性
  - 例如: HIV Ab WB (Sp H): Positive → Rule in

Comparison cut-off value



盛行率(不同族群)高低影響預測值

例:敏感度及特異性sen and spe = 95%

陽性預測值 隨著盛行率增加而升高

PPV	Prevalence
0.002	1/10000
0.02	1/1000
0.16	1/100
0.68	1/10

Prevalence (different clinical situations) affect predictive value

例： Ovarian cancer **CA-125** : PPV ~ 2% in screen vs. 97% in pelvic mass cases

- **同一診斷工具, 在不同盛行率情況下, 其 Predictive value 結果不同**

PPV

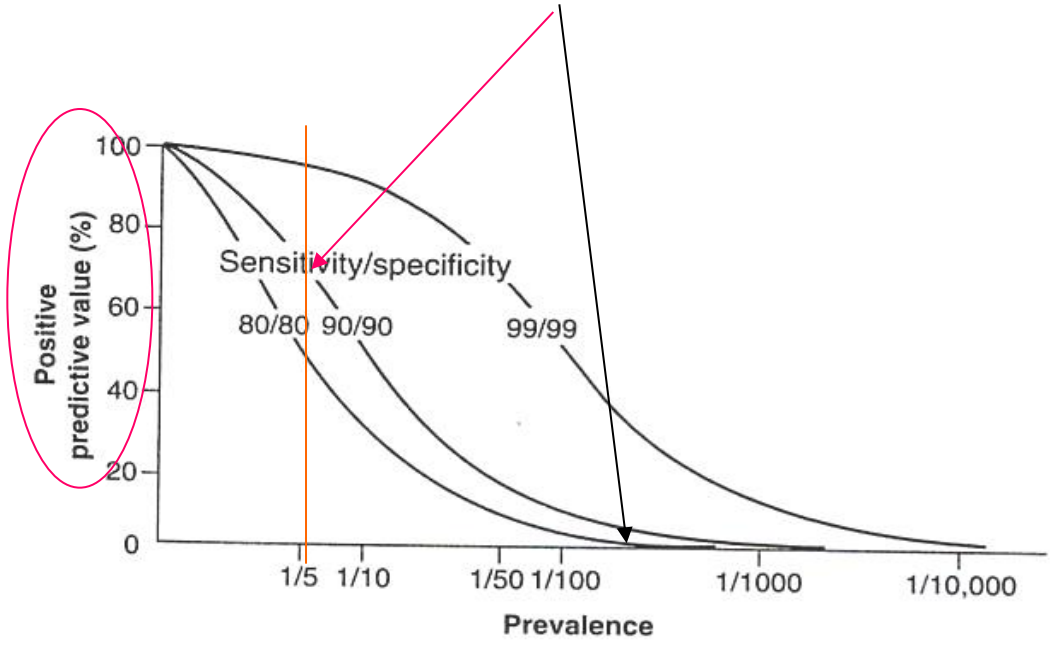


FIGURE 3.8 Positive predictive value according to sensitivity, specificity, and prevalence of disease

Prevalence affect the PPV

Community-wide HIV screening

Test: 90% sensitivity, 99% specific

Population: 10,000

Prevalence: **0.1%** = 10/10,000

PPV = 9/(9+100) = 0.08 = **8%**

NPV = 9890/(1+9890) = 0.9999 = 100%

DM screening

Population = 10,000

Prevalence = **10%** = 1000/10,000

Sensitivity = 900/1000 = 90%

Specificity = 8910/9000 = 99%

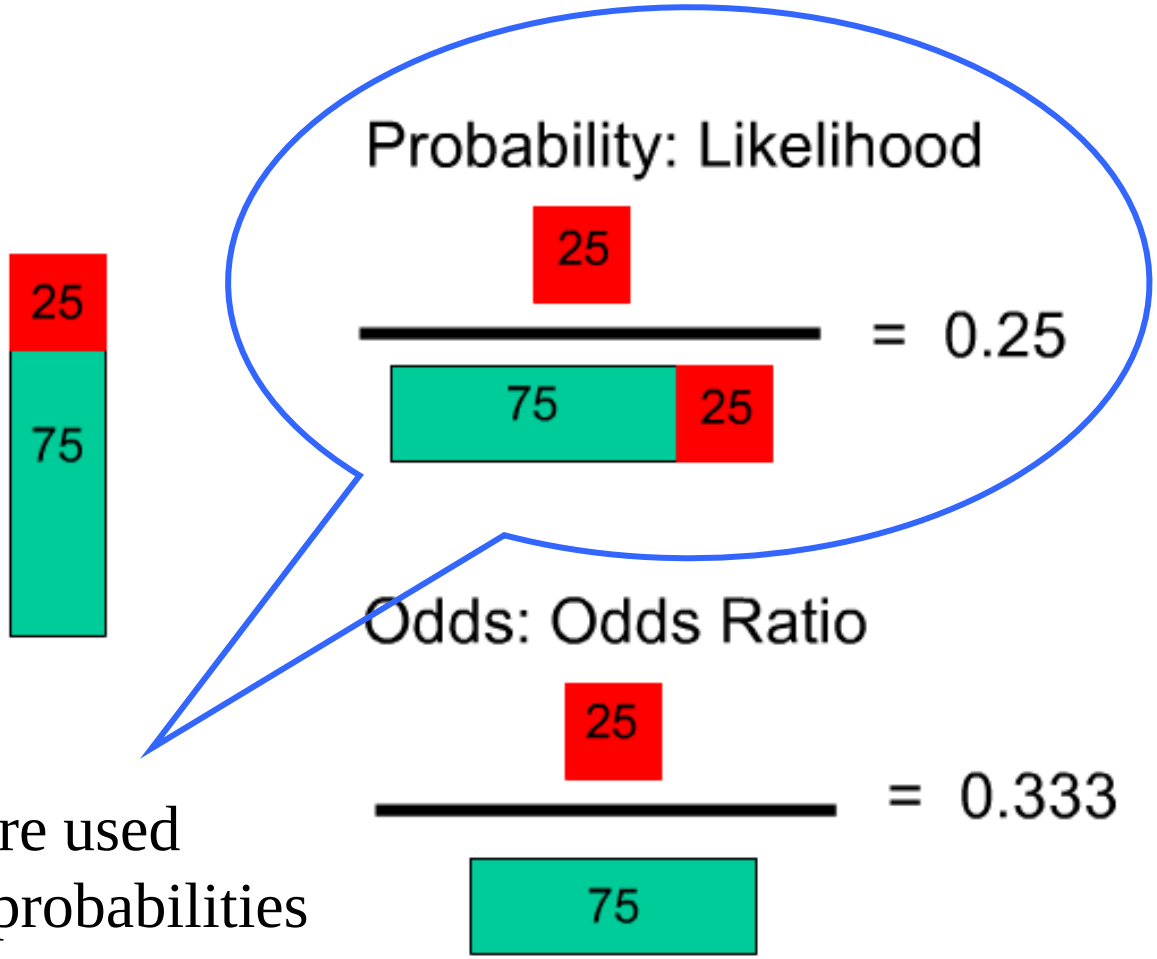
PPV = 900/990 = 0.91 = **91%**

NPV = 8910/9010 = 0.99 = 99%

Diagnostic test	Disease (HIV)	
	Present	Absent
Positive (陽性)	9 TP	100 FP
Negative (陰性)	1 FN	9890 TN

Test Result	Disease (DM)	
	Present	Absent
Positive (陽性)	900 TP	90 FP
Negative (陰性)	100 FN	8910 TN

Probability機率 vs. Odds勝算



Humans are used
To thinking in probabilities
rather than odds

Likelihood Ratios 概似比

Likelihood ratio is a very useful measure of diagnostic accuracy

有病者/無病者
檢驗呈陽性的比率

$$\text{Positive likelihood ratio} = \frac{\text{Prob. of positive result in patients } \textit{with disease}}{\text{Prob. of positive result in patients } \textit{without disease}}$$

$$\text{Negative likelihood ratio} = \frac{\text{Prob. of negative result in patients } \textit{with disease}}{\text{Prob. of negative result in patients } \textit{without disease}}$$

有病者/無病者
檢驗呈陰性的比率

Likelihood ratio

	Poor-fair	good	Excellent
Positive likelihood ratio	2.1-5.0	5.1-10.0	>10
Negative likelihood ratio	0.5-0.2	0.19-.1	<0.1

$$\text{Positive likelihood ratio} = \frac{\text{Sensitivity}}{(1 - \text{Specificity})}$$

Rule in

Ideally Big, >10

$$\text{Negative likelihood ratio} = \frac{(1 - \text{Sensitivity})}{\text{Specificity}}$$

Ideally Small, <0.1

Rule out

Diagnostic Odds Ratio勝算比

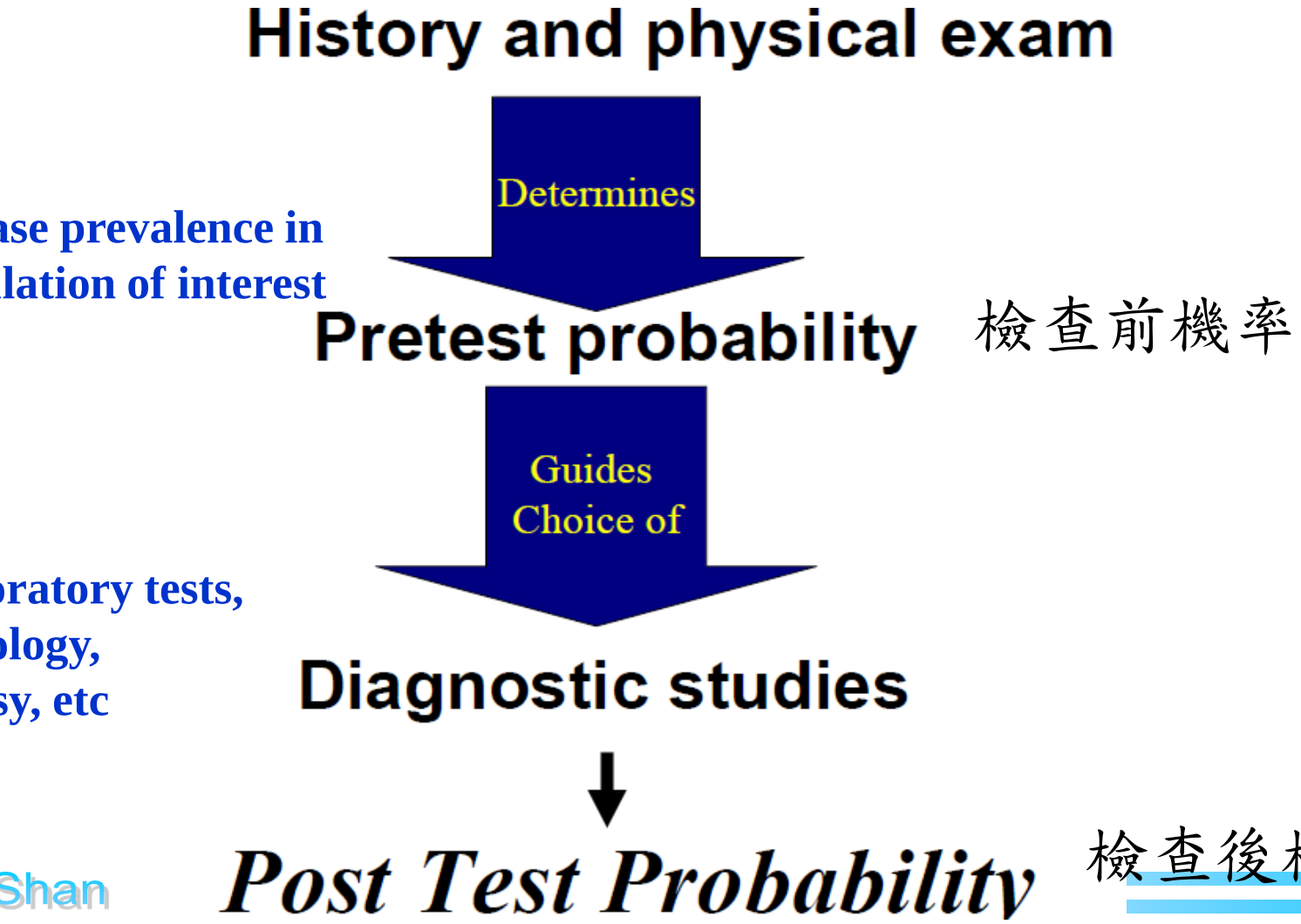
Single variable that indicates test performance

Calculation of diagnostic odds ratio

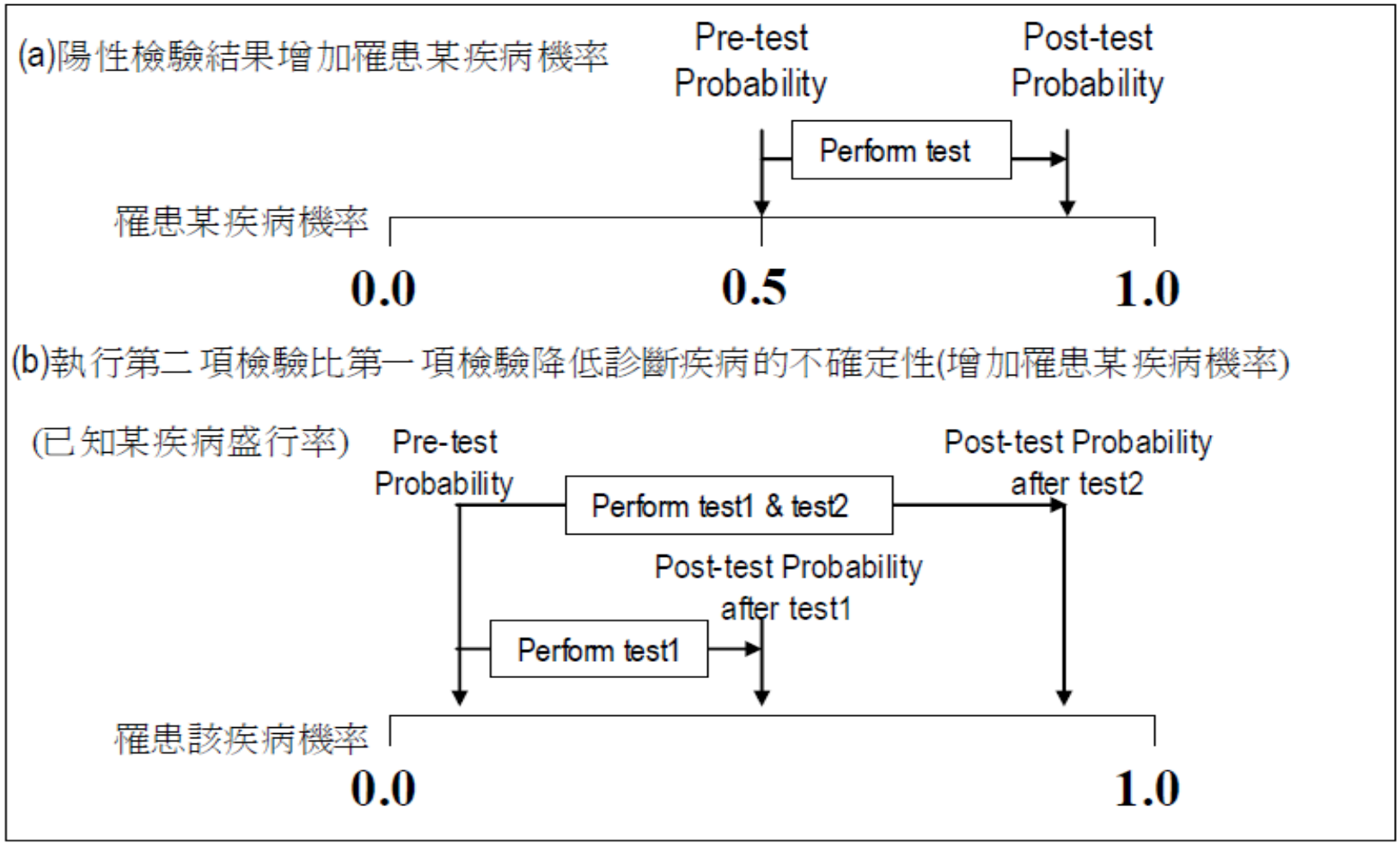
$$\text{Diagnostic Odds Ratio} = \frac{\text{Positive Likelihood Ratio}}{\text{Negative Likelihood Ratio}}$$

$$\text{Diagnostic Odds Ratio} = \frac{\text{Specificity}}{\text{1-Sensitivity}} * \frac{\text{Sensitivity}}{\text{1-Specificity}}$$

DIAGNOSTIC PROCESS



利用檢驗來降低診斷疾病的不確定性



【資料來源：Shortliffe & Perreault,1990〔8〕, p76】

Source: 臨床檢驗於實證醫學之應用。 高智雄(2007)，

因檢查結果陽性
有病機率由0.2增加至0.88的過程

- 檢查前機率　Pretest probability= Prevalence 0.2
- 檢查前勝算　Pretest odds = Prevalence / (1 – prevalence)

  0.2/0.8=0.25
- 陽(陰)性概似比Likelihood ratio of positive or negative

  LR (+) =30
- 檢查後勝算Posttest odds=pretest odds* LR (+)

  0.25*30=7.5
- 檢查後機率Posttest probability = Posttest odds/(1+Posttest Odds)

  7.5/(7.5+1)=0.88

因檢查結果陰性
有病機率由0.2減少至0.05的過程

- 檢查前機率　Pretest probability= Prevalence 0.2
- 檢查前勝算　Pretest odds = Prevalence / (1 – prevalence)

  0.2/0.8=0.25
- 陽(陰)性概似比Likelihood ratio of positive or negative

  LR (-) =0.22
- 檢查後勝算Posttest odds=pretest odds* LR (+)

  0.25*0.22=0.055
- 檢查後機率Posttest probability = Posttest odds/(1+Posttest Odds)

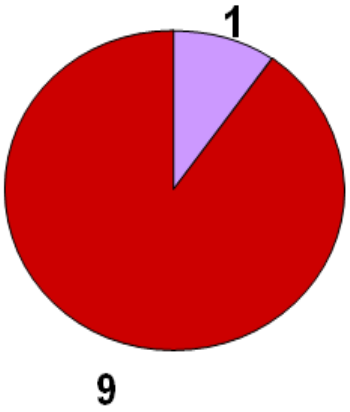
  0.055/(0.055+1)=0.05

Likelihood Ratios 概似比

- Pretest probability = prevalence of the target condition = $\frac{a+c}{a+b+c+d}$
- Pretest odds = $\frac{prevalence}{(1-prevalence)} = \frac{a+c}{b+d}$
- LR(+) = $\frac{sensitivity}{(1-specificity)} = \frac{a(b+d)}{b(a+c)}$
- LR(-) = $\frac{(1-sensitivity)}{specificity} = \frac{c(b+d)}{d(a+c)}$

Test result	Disease status	
	Present	Absent
Positive	True positive (a)	False positive (b)
Negative	False negative (c)	True negative (d)

- Posttest odds = pretest odds * LR(+)
- Posttest probability = $\frac{posttestodds}{(1+posttestodds)}$

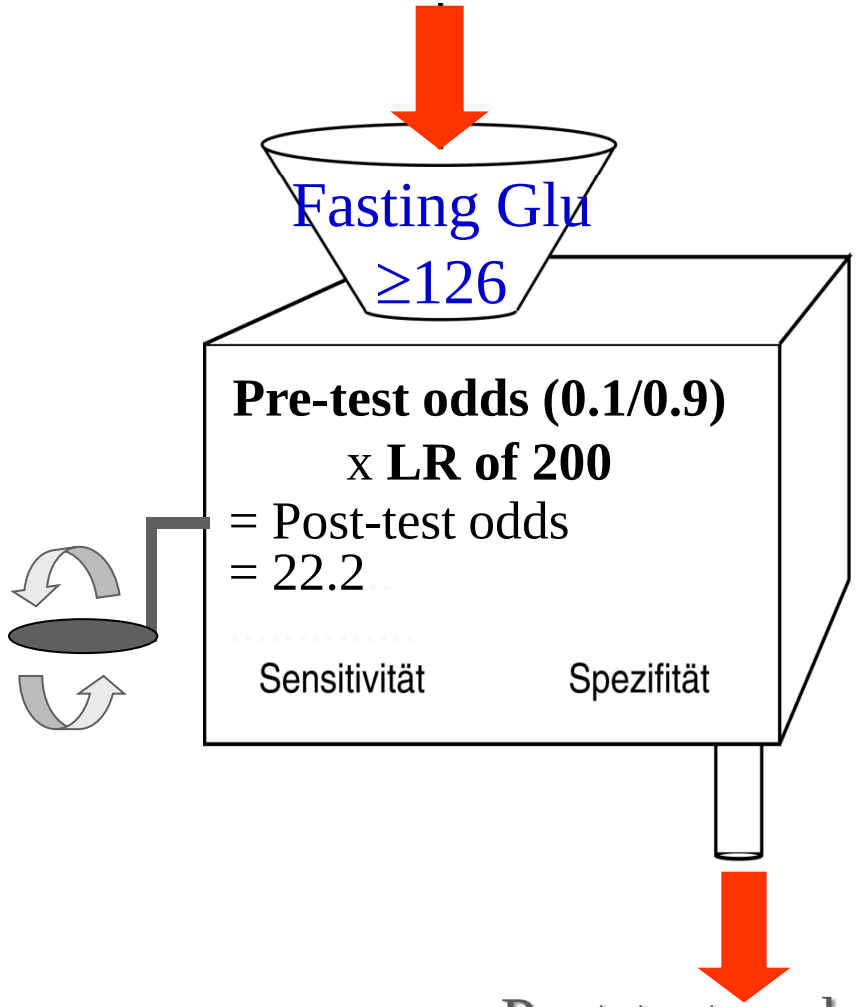


- probability (p): 1/10 = 0.1
- odds: 1/9
- odds = p/(1-p)
- p = odds/(1+odds)

Test as Probability Modifier

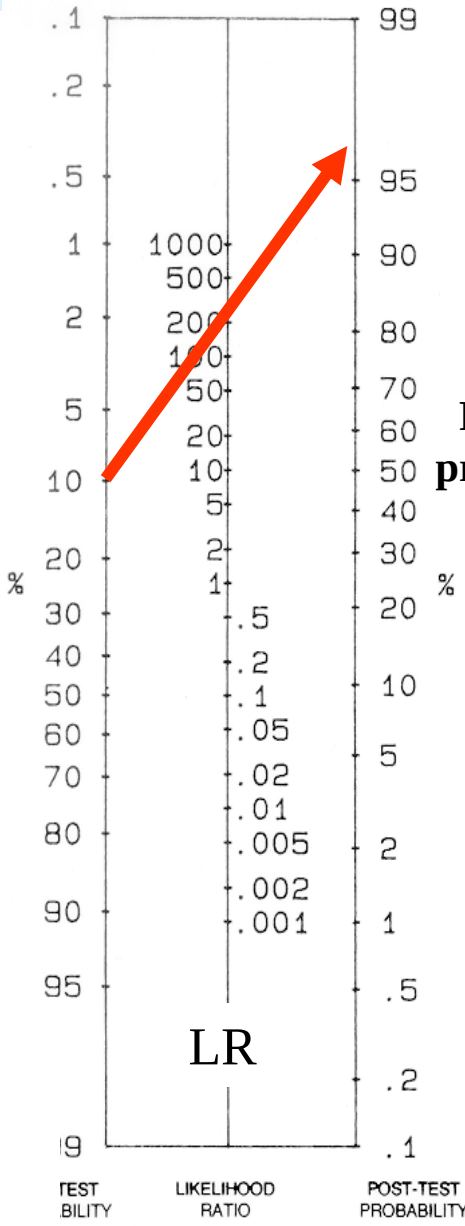
Fagan's Nomogram

DM Pre-test probability 10%



Post-test probability?

22.2/23.2 = 96%



Diagnostic test Summary

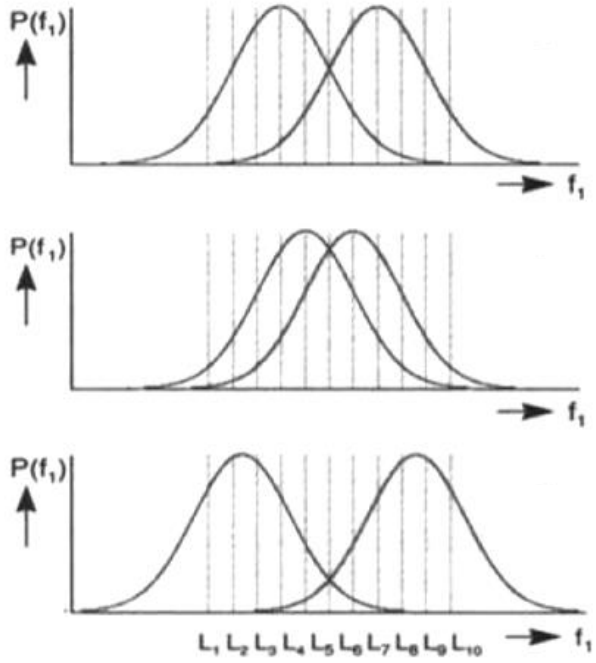
- Sensitivity, specificity, PPV, NPV (0-100)→100%最佳
- Positive Likelihood Ratio (陽性概似比) **LR+**
  - True positive rate / False positive rate
  - Sensitivity / (1－Specificity)
  - LR+ : 2-5 (fair), 5-10 (good), ≧10 → significant evidence
- Negative Likelihood Ratio (陰性概似比) **LR-**
  - False negative rate / True negative rate
  - (1－Sensitivity) / Specificity
  - LR- 0.2-0.5 (fair), 0.1-0.2 (good) ≦0.1 significant evidence
- ROC curve : AUC 0-1 > 0.8 good

Receiver Operating Characteristic (ROC) Curve

a

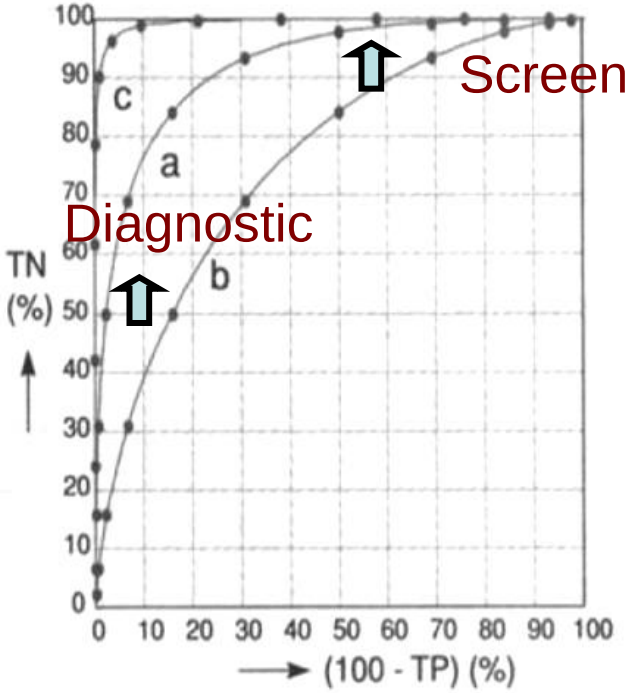
b

c



➤ 圖 15.7
在 (a) 中展現了圖 15.6b 裡的兩個主要族群，但現在我們指定 10 個不同的決策門檻 $L_1, L_2, \ldots L_{10}$ 並且計算每一個決策門檻的 FP 及 FN 百分比值。這十個合併的 (FP, FN) 可以被繪製成圖 15.8 的 ROC (a) 曲線。在 (b) 裡的兩個分布則相距更近（也就是說，在分布中有更多的重複）而 (c) 的分布則相距更遠。圖 15.8 即表現了本圖的 (b) 和 (c)。

Sensitivity (true positive rate)



1-specificity (false positive rate)

➤ 圖 15.8
圖 15.7 中的人口分布 ROC 曲線，FP 順著一軸而 FN（或是 1-TP）則順著另一軸（請參考圖例 15.7）。

AUC:c>a>b

Diagnosis

- Use of sensitivity test (高敏感度檢查的應用)
  - Treatable disease Screening
  - 未被檢查出來會有嚴重後果者
  - Rule out disease
- Use of specificity test (高特定度檢查的運用)
  - 當假陽結果會傷害患者身體、情緒或財物時
  - Rule in disease
- ROC curve
  - ROC下方的面積越大,診斷工具的準確度越好

catmaker

CATmaker

Use Control-C to copy selected text, Control-V to paste and Control-X to cut.

making a CAT diagnosis

Your Question | the Study Patients | the Study Evidence | the Bottom Line | the Other Stuff

Analysis 1 of 1

TEST		TARGET DISORDER: Present	TARGET DISORDER: Absent
	Positive	20 (a)	50 (b)
	Negative	40 (c)	60 (d)

			95% Confidence Intervals
SENSITIVITY	a / (a+c)	33 %	21 to 45
SPECIFICITY	d / (b+d)	55 %	45 to 64
Pre-test Probability ("Prevalence"):	(a+c)/(a+b+c+d)	35 %	28 to 42
Positive Predictive Value:	a / (a+b)	29 %	18 to 39
Negative Predictive Value:	d / (c+d)	60 %	50 to 70
LIKELIHOOD RATIO +	sens / (1 - spec)	0.73	0.49 to 1.11
LIKELIHOOD RATIO −	(1 - sens) / spec	1.22	0.95 to 1.57

Analyse another test in this same study

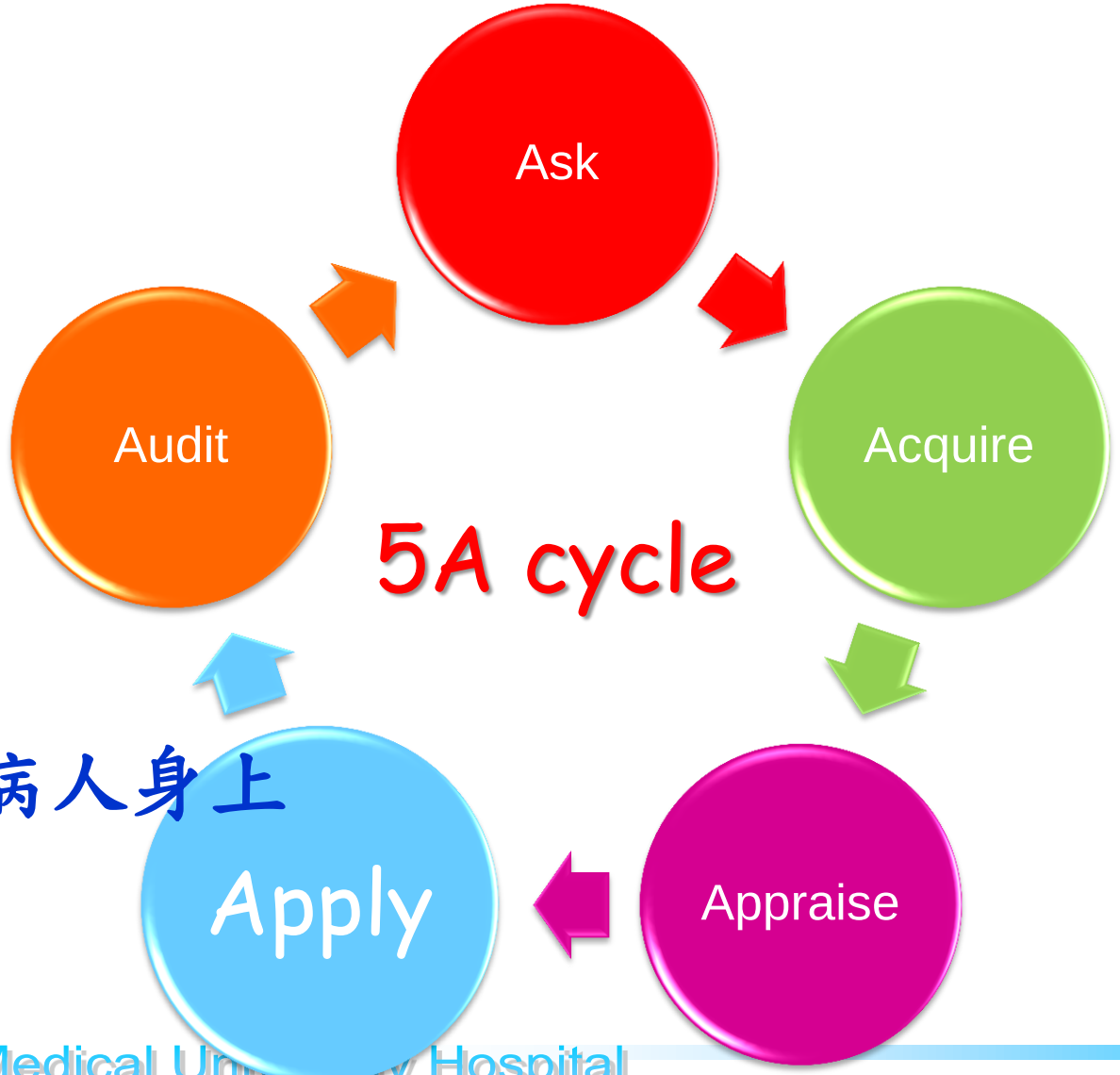
restart | show formulae | calc | previous | next

Please enter the numbers in each group for the diagnostic test in the study. When you're ready, click the CALC button to work out Sensitivity, Specificity, Likelihood Ratios, etc.

步驟四：Apply the Evidence

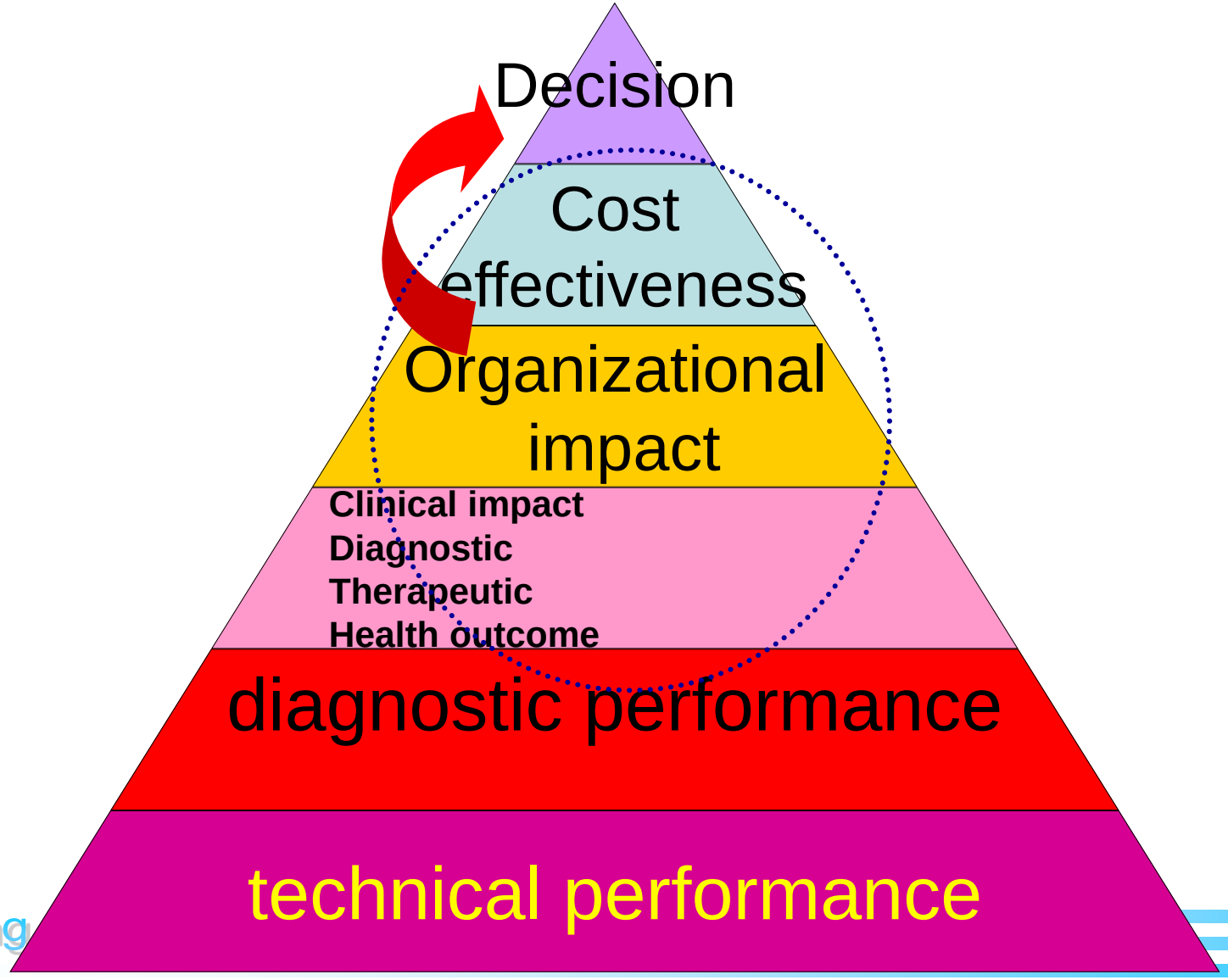
- 整合並應用於患者身上

步驟四



應用到病人身上

Apply:將實證整合並應用於患者身上



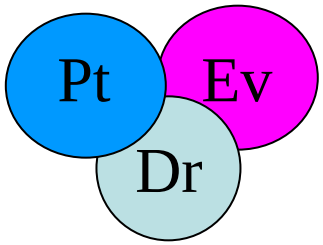
Apply：將證據與臨床專業經驗及病人期望結合

- 在你決定應用研究結果到你病人身上時，應該問的問題?
  - 您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？
  - 研究結果適用於您的病人嗎？
  - 您期望您的病人從研究結果中獲得多大的好處？病人的想法為何？
  - 還有哪些替代方案？
  - 建議的措施是否適用於我們所在的場所、診療環境？

Practice (Applicability) 臨床適用性

- EBM posits a hierarchy of evidence to guide clinical decision making. (Level of evidence)

- **Evidence alone is never sufficient to make a clinical decision. 3E:**
  - **Consider the patient's value (Expectation of the Patient)**
    告知 同意：用病人可以聽得懂的語言 (explain)
  - **Integrate clinical expertise (Expert opinion)**



步驟五：Assess or Audit

- 評估執行的成效

步驟五

評估實證之應用效度

評估執行效果及效用

Self–Evaluation (自我評估)

Step1:

1. 我有提出任何臨床問題嗎？Yes
2. 我提出的是結構完整的問題？Yes

Step 2:

1. 我知道在我的臨床領域中現有的最佳證據來源？Yes
2. 在搜尋方面我變得更有效率？Yes

Step 3:

1. 對我而言，應用此研究證據之評讀指引變得更簡單？Yes
2. 我可以更正確、更有效率的使用一些審慎評估度量工具，如LR？Yes

Step 4:

1. 我盡力將審慎評估之結果融入診療中？Yes
2. 為了適用於我的病人，我在調整一些嚴格評讀的度量值(機率、LR等)方面越來越精準及有效率？Yes

EBLM的應用方法和實施步驟

- EBLM的應用方法和實施步驟與EBM的基本一致，主要包括：
  - 診斷試驗技術品質評價：包括試驗方法的敏感度、特異度等。
  - 診斷試驗臨床診斷準確性評價：包括用於疾病診斷的檢驗項目的敏感度、特異度、概似比(likelihood ratio, LR)、機會比(odds ratio, OR)等。
- Jaeshke等認為，判斷一項診斷試驗是否有用的最終標準是：該試驗是否對診斷、治療和預後增加了有真正價值的信息，而現實是，由於製造商的熱情提供試劑、臨床醫師和檢驗人員的欣然接受，許多新檢驗專案在未被評價充分之前，就已被積極的推向臨床應用。


謝 謝 聆 聽
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